Current trends in cancer treatment

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CURRENT TRENDS IN CANCER TREATMENT

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Preface

This book is based on Vth biennial conference of cancer chemotherapy held in Bombay in February, 1989. Research in cancer treatment strategies as well as related basic sciences is progressing at a rapid pace. This book crystallises the current understanding of conventional modalities of treatment while, exploring the possibilities for future. Pioneers and scientists of eminance have contributed to this book. Style of the contributors is maintained to emphasise the diversity in thinking.

We hope that this book will persuade the students of oncology to persue the art of creative research besides updating.

Dr. Nagraj G. Huilgol,

Dr. Ashok R. Mehta.

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OPTIMISATION OF CHEMOTHERAPY IN THE TREATMENT OF CANCER

Prof. J.M.A. Whitehouse

The era of cancer chemotherapy, although almost 50 years old might be said to have only just begun. The landmark discovery of the 1940's was of drugs capable of destroying certain cancer cells "in vivo" while causing damage to host normal cells which was largely reversible.

The refinements of local therapies which parallelled the first few decades of the development of chemotherapeutic agents reflected an unwillingness to acknowledge the increasing biological evidence that many cancers were unlikely to be cured by surgery or radiotherapy alone. Unfortunately expectations for the new anticancer drugs (foreshadowed almost a century earlier by Paul Ehrlich in his concept of the 'magic bullet') were unreaslistically high. Cure was the objective of every treatment and if one drug did not prove effective others were added, this justified by their different modes of action. The outcome was an inevitable trend towards discreditation of the treatment modality. Much of the blame for this perception of failure must lie with those on the periphery who felt that chemotherapy would be an easy answer to cancer treatment. It was viewed by many as a treatment which any clinician could use without special training or the need for special expertise. Such naivety is belied by the skills which are required by the surgeon or radiotherapist to maximise the benefits

of their own techniques.

The over-enthusiasm for chemotherapy which was fuelled during the 1970's became increasingly recognised as a precise science with all the requirement for discipline, accuracy, interpretation, documentation and monitoring which such a description entails. In order to exploit the achievements of this science, it is necessary to determine the impact it has had on the natural history of different cancers, but this cannot be done without first defining how such an effect can be assessed.

OUTCOMES OF TREATMENT

Reduction in tumour volume has long been equated with response. Unfortunately, the biological significance of a change in tumour volume has proved to be of dubious significance. A review by Warr et al., 1984 has also highlighted the problems of equating drug activity with 'response' since measurement of tumours is subject to high margins of error. The end points of therapy need scrutiny so that only those of real significance to the patient are retained.

'Complete eradication of cancer by all detectable means' reflects only the strength or weakness of detection techniques available to the investigator. The facilities and expertise vary both within and between institutions so that ''complete remission'' can only be regarded as a crude indicator of prognosis. Nevertheless it is now clear that complete remission does have biological significance in that his status sometimes confers prognostic advantage. The potential benefits to the patient include - improved quality of life resulting from absence of tumour burden or tumour derived effects; no requirement for additional therapy and therefore an absence of side effects; possible improvement in survival and in some cases a possibility of cure.

It is uncertain why there should be such a profound biological difference between complete and partial remission. Patients with a low tumour volume may be unaware of their tumours and may only become manifest. If the use of chemotherapy reduces the tumour burden substantially, the clinical state may parallel that of early pre-symptomatic disease, but once the damaged tumour tissue recovers, growth equates with that of the pre-treated tumour, but clinical evidence suggests that wide variations occur from a static state to one of accelerated growth. Partial remission does not appear to be associated with the substantial benefits seen with complete remission. This is emphasised in those conditions such as myeloma and breast carcinoma where partial remission can be converted by dose intensifi-

cation into a clinical complete remission (Selby, McElwain et al., 1987; Antman et al., 1988) bringing with it a definitive clinical advantage. It is as though complete remission restores the balance in favour of normal tissues - if tumour cells remian they may be switched to the dormant state and must await proliferation to a critical population before once again dominating that of the host tissue. Good evidence for the concept of tumour dormancy has come from animal studies. Cell suspensions of whole lungs from animals having a distant primary tumour which did not give rise to overt pulmonary metastases were made one week after excision of the primary. Injection of this suspension into the peritoneal cavity of nontumour bearing animals resulted in tumours indistinguishable from those of the original primary (Alexander et al., 1983). Dormant tumour cells can also be demonstrated in the kidney following intracardiac injection of sarcoma cells (Murphy et al., 1985). The role played by host immunity, host tissue effects and tumour products at this critical stage is the subject of intense research efforts.

What is now evident is that complete remission may in some patients represent complete eradication of disease, in others a state of prolonged tumour dormancy, but in others only temporary respite from disease.

In 1981 we set up a study to determine the role of surgery after initial chemotherapy for localised small cell carcinoma of the lung (Williams et al, 1987). A consequence of this study was that we were able to evaluate the difference between radiologically and surgically determined complete remission. 189 patients over a 4 year period were assessed for surgery after an initial 3 cycles of chemotherapy with daunorubicin etoposide and cyclophosphamide. 57 were found to have limited disease and of these 19 were unfit or ineligible for surgery. Of the 38 remaining 84% had objective responses to the chemotherapy and after restaging 25 were accepted for surgery. At operation 4 were inoperable, 9 had a lobectomy and 12 a pneumonectomy. Viable small cell lung cancer was found in the tissue from 16 patients, no tumour in 4 and a separate focus of poorly differentiated squamous cell carcinoma in another. In the 21 patients who underwent tumour resection, median survial was restricted to those with no evidence of viable tumour at surgery. Removal of residual tumour bearing lung did not appear to confer an advantage. Therefore only those patients who had microscopically proven complete remission enjoyed a substantial increase in expected survival a situation which was not influenced by surgery.

With available detection techniques, cure can only be predicted even in the most responsive tumours on the basis of overwhelmingly good prognostic factors (and even then not with certainty) or defined retrospectively on the basis of prolonged disease free survival. The duration of disease free survival required to define cure varies between tumours. Relapse from complete remission following chemotherapy of many solid tumours such as breast, ovarian cancer or lung cancer is virtually inevitable. Recovery occurs following majority of complete remission in acute myelogenous leukaemia and some lymphomas, but is less common in large cell lymphoma, Hodgkin's disease and teratoma.

The ten commonest cancers in the United Kingdom are those of lung, skin, prostate, female breast, bladder, colon, stomach, ovary, rectum, cervix/uterus. Anti-cancer drugs have very little activity in cancers of the rectum and colon but some activity in the remainder. Indeed complete remission following chemotherapy has been reported in cancers of the lungs, skin, female breast, stomach, ovary and cervix, but in none of these conditions does complete remission following chemotherapy equate with disease eradication. Following

Table 1 Categories of Response

Eradication	Type I	Total	
(= 'Cure')	Type II	Complete	(No detectable disease but subsequent relapse)
	Type III	Major	(Microscopic detectable disease only)
No Eradication	Type IV	Minor	(Measurable reduction)
	Type V	Symptomatic	(± stabilisation)
	Type VI	Nil	

Table 2 Conditions in which Complete Response is Reported

Type I	Type II
Hodgkin's Disease	Acute Leukaemias
Germ Cell Tumours	Lymphomas
Seminoma	Neuroblastoma
Choriocarcinoma	Soft Tissue Sarcomas
Histiocytic Lymphoma	Myeloma
Childhood—	Plasma Cell Leukaemia
Acute Lymphoblastic Leukaemia	Melanoma
Rhabdomyosarcoma	
Ewing's Tumour	Squamous Cell Carcinoma of Head and Neck
	Osteosarcoma
	Childhood Brain Tumour
	Carcinomas of Lung ovary Breast

chemotherapy, it is therefore possible to identify a number of different types of response. Table - 1. lists the categories of response.

Table II shows conditions in which chemotherapy has potential clinical benefit without necessarily resulting in cure are of course numerous. The benefits result from substantial but incomplete elimination of the tumour cells and a consequent control of tumour growth. Some drugs used alone are capable of producing complete remission in certain cancers but it is rare for cure to result with a single dose even in conditions where the tumour is exquisitively sensitive such as choriocarcinoma. It is the greater vulnerability to damage of the cancer cell when compared with its normal counterpart which results in a reduction in tumour volume. In untreated patients, other factors such as haemorrhage or macrophage infiltration may contribute to rapid and unexplained changes in tumour volume. The phenomenon of spontaneous regression is well documented particularly in follicular lymphoma (Krikorian et al. 1980), These changes may confuse the intepretation of chemotherapy effect, but inevitably the immediate assessment of anti-cancer effect depends upon changes in tumour volume.

The addition of two or more drugs with different modes of action at maximum tolerated doses may in sensitive tumours produce an effect greater than additive. It is the exploitation of this advantage which has occupied many oncolgists over the last decade-the challenge in terms of tumour control. Greater numbers of complete remissions have been obtained in certain tumours by dose intensification. For single agents this is most apparent in multiple myeloma (selby, McElwain et al., 1987).

Table 3 Selection of Tumours

	Chemotherapy Response Rates (%)		
Tumour	**CR**		**PR**
Lung (NSC)	0-10	6H	13-55
Lung (SC)	20-30		25-40
Skin		9-40	
Prostate		11-69	
Breast	9-20		33-61
Bladder		16-61	
Colon/Rectum		0-18	
Stomach	0-9		15-55
Ovary	17-33		30-44
Cervix	0-29		15-89

(deVita, Hellman, Rosenberg, 2nd Edition)

Better management and the use of newer agents such as cisplatin and etoposide have increased not only the CR rate of patients with germinal tumours, but also the proportion enjoying prolonged disease free survival (Einhorn et al., 1986). Those tumours for which combination chemotherapy is appropriate should be readily identifiable but distinction must be made between tumours which respond by reduction in size and those patients who benefit either from a reduction in symptoms or the achievement of disease free status with or without prolongation of survival, all of which should bring an improvement in quality of life. There is thus a cascade of benefit which may result from effective chemotherapy. Clearly reduction in tumour size alone may bring no benefit, but if accompanied by an improvement in quality of life (Slevin et al., 1984) it represents part of the significant value, this must be durable. Effective palliation may or may not be associated with improved survival, but where disease free survival is very prolonged this may equate with cure.

In order to derive the maximum benefit from available anti-cancer drugs, a process of selection is essential.

1. SELECTION OF TUMOURS

A wealth of well documented studies allows us to identify tumours which are responsive to chemotherapy and to categorise these on the basis of anticipated outcome following treatment. (Table 3). Clearly it is reasonable to select for active treatement patients with tumours known to achieve type I or type II responses. Indeed patients with types III, IV and V responses may enjoy an improvement in the quality and or duration of life. Unfortunately it is not always possible to predict type VI effects (no response), although it is more likely that colonic carcinoma or melanoma (where only 10-20% of response are reported), will be unresponsive than a breast or ovarian tumour where response rates may exceed 50%. It is the inability to select responding patients with accuracy, which means that substantial numbers of patients with different cancers are still treated without significant benefit. However, it is increasingly possible to define histological subtypes, with a broad tumour type, which are granulosa cell carcinoma of the ovary; large, squamous and adenocarcinoma of the lung, larger cell lymphoma with sclerosis etc., In addition the degree of differentiation of a tumour and its grade also give some indication on the likelihood of response. With current knowledge it it thus easier to predict those tumours unlikely to respond to chemotherapy than those in whom the response may be sub-optimal.

2. SELECTION OF PATIENTS

For any group of patients with a particular tumour, it is possible to define prognostic features based on anticipated response to therapy, known adverse features, irrespective of tumour bulk, advanced stage and the presence of constitutional symptoms. In Hodgkin's disease adverse features have been identified (Tubiana et al., 1985; Sutcliffe et al., 1985; Haybittle et al., 1985; Devita et al., 1980; Carde et al., 1983).

Identifying patients for whom chemotherapy is not appropriate isolates a heterogenous majority comprising those who may respond well and others with lesser responses. The identification of prognostic subgroups is essential if chemotherapy is to be used with greater precision. An example of such sub categorisation is apparent in the non Hodgkin's, intially be observed without treatment (Mead et al., 1984). Patients with follicular mixed lymphoma are reported to require more intensive treatment in order to achieve complete remission, but when obtained this is more durable than in straightforward follicular lymphoma (Gallagher et al., 1986). Different forms of treatment have been identified for intermediate and high grade lymphoma (Klimo et al., 1985; Shipp et al., 1986; Harrisworth et al., 1986).

Furthermore, optimum staging of patients with radiosensitive tumors permits the exclusion of patients from those identified for chemotherapy. The role of radiotherapy in apparently localised disease is currently being reexamined in Hodgkins disease. Already chemotherapy has supplanted radiotherapy in the management of teratoma and would appear to have curative potential in early stage Hodgkin's disease (Longo et al. 1987) and large cell lymphoma.

3. SELECTION OF DRUGS

There is an abundance of literature documenting response to different agents given singly or in combination. Although of variable quality the information is sufficient to indicate drugs with activity against tumours of a particular histological type. It is the need to derive this information in a stuctured way which led to the design of phase I, II and III studies. Phase I, to determine the maximum tolerated dose at the schedule and route chosen and to determine if human toxicity is predictable, reversible and treatable, Phase II to eliminate drugs which have low probability of therapeutic activity. Phase III to define the role of a new drug in therapeutic practice. These trials are randomised

comparative studies between the regimens and standard therapy. The final choice of drugs must be based on their efficacy, the side effects they cause, and should take into account both cost and long term side effects.

The need to compare cheap easy to administer therapies with drug combinations requiring hospital admission is emphasised by the heightened awareness of quality of life as an important end point.

In order to examine the two philosophical approaches to the therapy of ovarian cancer we set up a study to test whether the apparently improved responses to combination chemotherapy with cisplatin, adriamycin and cyclophosphamide (PACe) justified the major toxicity of this type of treatment and whether there was a prolongation of survival when compared with single alkylating agent therapy (Williams et al., 1985). Between 1979 and 1983, 89 patients with a histologically confirmed FIGO stage III and IV ovarian cancer aged between 15 and 69 were randomised to receive either PACe (Cisplatin 80 mg per M^2 iv on day 1. Daunorubicin 40 mg per M^2 iv on day 1. Cyclophosphamide 1 gm per M^2 iv on day 1. Courses were administered at 28 day intervals, minimum 5 cycles.) Or chlorambucil (10mg daily for 14 consecutive days followed by a 14 day rest period without treatment, minimum 2 years). 85 were available for analysis and at the time of analysis 72 of these had died.

The majority of patients were of poor prognosis having bulky disease after their initial laparotomy, but despite this, the overall response rate (CR + PR) for the combination was 68%. This was significantly higher (p=.0004) than for those receiving chlorambucil (26%). Those achieving surgically documented CR were 26% (PACe) and 15% (Chlorambucil). The major differences between the two treatments were the substantially greater number of PRs achieved by the combinations (42% versus 11%).

Despite the significantly greater response rate achieved by PACe, the median survival was not improved (PACe 13 months; chlorambucil 11 months), and the survival curves are not significantly different. (Log rank test = .25). Those patients receiving PACe experienced substantially more morbidity than those receiving chlorambucil.

Where a level of palliative benefit can be so clearly defined there is a need to define the minimum treatment required to achieve this result.

4. SELECTION OF ROUTE OF ADMINISTRATION

While all administration of drugs may avoid the need for hospital

attendance either as an outpatient or inpatient, it is an insecure method of treatment. It depends upon patient compliance and the vagaries of absorption. Parenteral administration, properly supervised guarantees that the total prescribed doses are received by the patient. Where repeated intravenous administration or sampling is required, an indwelling silastic catheter tunnelled beneath the skin to the brachial vein and positioned to lie within the superior vena cava can be maintained readily for a period of months. Fewer complications are seen than with a Hickman line and in addition the catheter can be readily maintained by the patient himself. For those ambulant patients receiving continuous infusions via a portable pump, a tunnelled catheter is essential. Some drugs can conveniently be given via the subcutaneous route e.g. cytosine arabinoside. This may permit self administration by the patient but often requires medical or nursing supervision. Intra arterial therapy has been proposed for certain tumours confined to a well localised anatomical site. The difficulties with this procedure appear to out-weigh any benefit. Small polymer pellets which can be injected subcutaneously via a large bore needle have been developed for LHRH analogue administration. These can easily be excised if necessary. Such techniques seem likely to be applied to certain anti-cancer drugs and might well be used for the administration of anti emetics.

5. SELECTION OF DOSE

The choice of drug dosage is critical and yet in any individual is subject to many variables. The pharmaco-kinetics of drugs differs substantially between patients. The levels achieved in blood, different tissues, the tumour and different parts of the tumour, the duration of sustained levels, the availability of active compounds, the rate of metabolism and excretion are some of the factors important in determining the ratio of therapeutic benefit to toxicity. Both are dose dependent and it is therefore likely that for any tumours and any drug there is an optimal dosage level. About this level the anti-tumour effect is compromised by toxicity to the host and below it maximum anti-tumour effect is not achieved. For any currently available drugs, the dose limiting toxicities are well known as are the broad range of maximum tolerated doses. Irreversible damage to vital organs is an unacceptable consequence of dose escalation so that upper limits are recognised for total dose administered of drugs such as adriamycin (cardiotoxicity) cisplatin (renal and neurotoxicity).

Bone marrow suppression is a consequence of the majority of anti-cancer drugs. The duration of suppression determines the extent to which this side effect is life threatening. Better supportive care has reduced the seriousness of this complication and allowed doses of some drugs to be escalated.

The effect has been to increase overall responses and in some conditions to convert partial to complete responses. This increase in response is however confined to those tumours where anti-cancer drugs have been shown to have some effect. The threshold response has been advanced by increasing the threshold of tolerability. The studies by Mac-Elwain et al using high dose melphalan have demonstrated that a significant CR rate can be achieved in myeloma in a selected group of patients (Selby et all., 1987). In this study a dose of melphalan of 180mg per M^2 was used. Increasing this dose resulted in unacceptable gastrointestinal toxicity which became the dose limiting factor. In certain other tumours, high dose therapy has raised the response rate but unlike myeloma where the duration of CR also appears to have been improved the benefits have been less evident. The concept of dose intensification has aroused much interest (Haynink et al., 1988). A study by Tannock et al involved a randomised trial of two dose levels of cyclophosphamide methotrexate and 5-fluorouracil in patients with metastatic breast cancer, lent support to the need to define a practical therapeutic dose. Patients receiving the high dose chemotherapy had greater toxicity in the immediate post treatment period but also a trend to improvement in general health and some disease related indices. The authors concluded that better palliation is achieved by using full dose chemotherapy.

One of the most exciting developments which is likely to have impact on modern cancer chemotherapy, has been the isolation of genetically engineered human colony stimulating factors. There are now a number of reports suggesting that either GCSF or GM-CSF can be used to produce sustained granulocyte levels so reducing infective episodes in patients receiving otherwise myelosuppressive therapy. A consequence of the introduction of the colony stimulating factors is likely to be that higher doses of treatment may be used with greater safety and possibly without the need for autologous bone marrow transplantation. There is already an indication that high dose single agents may achieve a higher CR rate in certain tumours. While the G and GM-CSF's may protect against the neutropenic effects of higher dose therapy, profound thrombocytopenia remains a problem. Current laboratory studies suggest that other CSF's such as IL-3 may have a

role given in combination with GCSF's in providing a broader stimulus to marrow progenitor cells, but this hypothesis will have to be tested in clinical practice. (Refer Table 4)

It is likey that dose escalation and dose intensification will result in a higher CR rate in some cancers and that this may equate with prolongation of survial in a few. The gains, however, seem unlikely to exceed those which we have already seen with improvements in supportive care. It will require new drugs to impact on cancers which are currently unresponsive to chemotherapy.

Table 4 List of studies evaluating CSF & rhG

No. of patients	Tumour	CSF	Ref
27	Bladder	rhG-CSF	Gabrilove et al. 1988
15	Various	G-CSF	Morstym et al. 1988
19	Breast, Melanoma	GM-CSF	Brandt et al. 1988
12	Lung (SC)	G-CSF	Bronchud et al. 1987

6. SELECTION OF SCHEDULE

It is not my intention to review here the evolution of those schedules which are now accepted to hold a place at the forefront of treatment for different cancers. The acronyms are well known. It is unfortunately still true that for any one condition, the choice of combination often remains a matter of personal preference. Thus, even in a condition such as Hodgkin's disease where treatement has been so carefully evaluated the choice lies between MOPP, MVPP, CHVPP, ABVD or variations of a hybrid of these. Examples of a choice of schedules in other diseases are all too common. Any schedule which is to be included among those accepted for practice, should have emerged in a well structured clinical trial to be that showing the greatest benefit to the patients. Many new schedules often appear having been tested in a pilot study and then an unrandomised study without the scrutiny and comparison with the treatment previously regarded as the "best" treatment.

The principles which determine the composition of a schedule are that it includes active agents with additive or anti tumour effect but less

than additive toxicity. The interval between treatments is designed to achieve maximum tumour damage, but to allow recovery of normal tissues that it is convenient for the patient and easily administered. Of fundamental importance is that it contributes to an improvement of the patient's quality of life.

If one uses the selection criteria identified above it is possible to define the best possible practice for the management of common cancers. Thus in non small cell lung cancer, those patients able to proceed to operation do so and those unfit for operation would receive no treatment unless symptomatic. There is no place for routine chemotherapy in their management and palliative radiotherapy is given in the fewest possible fractions. By contrast patients with small cell lung cancer where the tumour is chemosensitive, may receive combination chemotherapy with CAV.

For FIGO Stage II and IV ovarian cancer, the choice lies between cyclophosphamide ($2 per treatment) chlorambucil ($ 10 per 2 week treatment), PACe ($53 per treatment) and carboplatin ($150 per treatement). Cyclophosphamide has not been compared in a randomised study with PACe, but is unlikely to be significantly different in effect from chlorambucil which appears equally effective.

In the Non-Hodkin's lymphomas, some patients with nodular lymphoma require no initial treatment, but there is certainly no advantage in using CHOP (cost per treatment $61) or CVP (cost per treatment $20), over chlorambucil (cost per treatment $10), Randomised studies are currently in progress comparing. CHOP with some of the newer combinations used in the treatment of intermediate and high grade lymphomas. Currently patients with low volume disease who are asymptomatic are likely to respond well to CHOP alone (cost per treatment $61) while others may require more intensive therapy such as PEACe BOM or MACOP-B (cost per treatment $122). In Hodgkin's disease chlorambucil VPP appears well tolerated and in a study of 350 patients with 13 year follow-up the results appear as good as MOPP. Chlorambucil VPP (cost per treatment $13) until supplanted by a better treatment would seem to have the advantages of ease of administration limited toxicity but with equal activity to more toxic regimens. Loss of fertility caused by chlorambucil VPP is the major reason for seeking change.

The foundations for precision chemotherapy using available resources to their best effect are well known to all of us. There is however, a very real need to identify a treatment for any one condition which can be regarded as standard. This "best documented practice"

whose efficacy and toxicity is well known can then be used as a standard for comparison, against which any new compound or new schedule can be evaluated. Attempts have been made by consensus groups to identify optimum practice but their conclusions have tended to suffer where consensus groups are self appointed and their conclusions have therefore only been regarded as guidelines. However, the information is available in the world literature to enable us to select for any one clinical situation a management which combines efficacy, ease of administration, limited morbidity where availability and costs of the treatment are known, but most important of all where the likely benefit to the patient is predictable. Only if we begin to define best documented practice can we make the very best use of the treatments and resources at out disposal. If we take this initiative, we can then offer to those whose care lies in our hands, chemotherapy at its most precise.

REFERENCES

1. ALEXANDER P. Multi-Cellular origin of cancer. In:Theories of carcinogensis. Ed. Olav Hilmar Iversen. Hemisphere Publishing Corporation, Washington, 287-300, 1988.
2. ALEXANDER P. Dormant metastases - studies in experimental aniamals Pathology 141 : 379, 1983.
3. BRABDT SJ, PETERS WP, ATWATER SK, KURTZBERG J. BOROWITS MJ, JONES RB, SHPALL EJ, BAST RC, GILBERT CJ & OETTE DH. Effect of recombinant human granulocyte-macrophage colony-stimulating factor on haematopoietic reconstitution after high-dose chemotherapy and autologous bone marrow transplantation. New England Journal of Medicine, 318 (No 4, April):869-876, 1988.
4. BRONCHUD MH, SCARFFE JH, THATCHER N, CROWTHER D, SOUZA LM, ALTON NK, Granulocyte colony-stimulating factor in patients receiving intensive chemotherapy for small cell lung cancer. Br. J. Cancer 56 : 809-813, 1987.
5. GABRILOVE JL, JAKUBOWSKI AW, SCHIER H, STERBERG C, WONG G, Groups J, YAGODO A, FAIN K, MOORE MAS, CLARKSON B, OETTGEN HF, ALTON K, WELTE K & SOUZA L. Effect of granulocyte colony-stimulating factor on neutropenia and assoicated morbidity due to chemotherapy for transistional-cell carcinoma of the urothelium. New England Journal of Medicine, 318 (June): 1414-1422, 1988.
6. GALLAGHER CJ, EASTERLING MJ, BENNETT MH, VAUGHAN HUDSON B, HAYHOE FGJ, JELLIFFE AM VAUGHAN HUDSON G & MACLENNAN KA. Hospital Practice: Review of British national lymphoma investigation studies of Hodgkins disease and development of prognostic index. Lancet 27 (April):967-972, 1985.
7. HARRISHWORTH JD, WOLF SN, STEIN SS, GREER JP, CONSAR JB, GRECO FA. Effects of Mega COMLA (Cyclophosphamide, cytosine, vincristine and methotrexate followed by leucororin and predinsolone) plue CHOP (cyclyphosphamide, doxorubicin, vincrisine and predinsolone) in the treatment of lymphoid neoplasms with very poor prognosis. Cancer Treat. Rep. 70: 953, 1986.
9. LONGO D. GLATSEIN E, YOUNG R. DUFFEY P, HUBBARD S, DEVITA V. Randomized trial of MOPP Chemotherapy vs subtotal nodal radiation therapy in patients with laparotomy documented early stage HD. Proc. An. Assoc. Clin. Oncol. 6 : 206. 1987
10. MOERTAL CG, THYNNE GS. Cancer Medicine

(2 ed). HOLLAND JF er al (eds): PHILADELPHIA, LEA and FEBIEGER, 1982.

11. MORSTYN G, SOUZA LM, KEECH J, SHERIDAN W, CAMPBELL, ALTON NK, GREEN M, METACALF D & FOX R. Effect of granulocyte stimulating factor on neutropenia induced by cytotoxic chemotherapy, Lancet (March):67-672, 1988.
12. MURPHY P, TAYLOR I, ALEXANDER P, Organ distribution of metastases following injection of syngeneic rat tumour cells into the arterial circulation via the left ventricle. In: Hellman K & Eccles S (eds) Treatment of Metastasis: Problems and Prospects PP191-1985.
13. SELBY PJ, MCELWAIN TJ, NANDI AC, PERREN JJ. POWLES R et al. Mutiple Myeloma treated with high dose melphalan. Br. Haematol 66 : 55, 1987.
14. TANNOCK IF, BOYD NF, NANDI AC, PERREN JJ, POWLES R et al. Multiple Myeloma treated with high dose melphalan. Br. J. Haematol 66 : 55, 1987.
15. TANNOCK I, MURPHY K, Reflections on medical oncology: An appeal for better clinical trials and improved reporting of their results. J. Clin Onc 1:66-70, 1983.
16. WARR D. McKINNEY S & TANNOCK I. Influence of Measurement Error on Assessment of Response to anticancer chemotherapy: Proposal for new criteria of tumour response. Journal of Clin Onc 2 (No. 9 September) :1040-1046, 1984.
17. WATSON JV. What does "response" in cancer chemotherapy really mean? Br. Med. J. 283 : 34-37, 1981
18. WILLIAMS CJ, McMILLIAN I, LEA R, MEAD G. THOMPSON J, SWEETENHAM J., HERBERT A, JEFFREYS M. BUCHANAN R & WHITEHOUSE JMS. Surgery after initial chemotherapy for localized small-cell carcinoma of the lung. Journal of Clin Onc, 5 (No. 10 October):1579-1588, 1987.
19. WILLIAMS CJ, MEAD GM, MacBETH FR, THOMPSON J, WHITEHOUSE JMA, MACDONALD H, HARVEY V.J, SELVIN ML, LISTER TA, SHEPHERD JH & GOLDING P. Cisplatin combination chemotherapy versus chlorambucil in advanced ovarian carcinoma : mature results of randomized trial. Journal of Clin Onc 3 (No. 11 November):1455-1562, 1985.

2

AN OVERVIEW OF THE 1964-1988 EUROPEAN TRIALS FOR HODGKIN'S DISEASE AND DISCUSSION OF THE PRESENT STRATEGY

J.M. Cosset

The history of evolution of the treatment for Hodgkin's disease is a testimony of what a carefully designed clinical research can achieve. The following pages will describe the European experience in evolving the treatment strategies since 1964. All the efforts of the Lymphoma Group of the EORTC (European organisation for Research and Treatment of Cancer) since 1964, have been devoted to optimization of the treatment of Hodgkin's disease (HD) for any given patient (6, 36, 39, 40, 41, 42, 43, 44, 46).

First briefly a review of the results of four controlled studies conducted by the group from 1964 to 1988 for stages I and II HD, and then the results of the trial conducted from 1981 to 1986 for stages III B and IV will be presented.

Recently activated H7 controlled trial for stages I, II HD and, the basic guidelines for the discussion of the future European trial for stages III and IV will then be discussed.

I-The 1964-1988 EORTC TRIALS A/Stages I and II

1579 such patients were enrolled in four successive trials by 27 hospital centres from 1964 to 1988. All slides were reviewed by a ad-hoc pathology committee.

The H1 trial (1964-1971) included 288 patients with supra and infra-diaphragmatic stage I-II HD (43).

No laparotomy was performed at that time. Mantle field radiotherapy (RT) and inverted Y RT were then considered to be main therapy. The question in 1964 was : ''Could a monochemotherapy - namely, weekly velban for two years-improve the results achieved by extended field irradiation alone ?''. Thus all patients received first a regional RT (mantle field irradiation of inverted Y). They were then randomly assigned to one of two groups : a, no further treatment or b, a weekly injection of Velban (VLB) for 2 years.

The 15-year results show a definite advantage with combination RT-VLB over RT alone in terms of disease-free survival (DFS) : 60% for RT-VLB versus 38% for RT alone ($p<0.001$). However, this DFS advantage was not translated into any survival benefit; 15-year survival was 65% for RT-VLB and 58% for RT alone (No significant difference-NS). These findings suggest that salvage treatment was more efficient in the RT alone group than in the group of patients who had received the association RT-Velban. In addition, the incidence of relapse in the unirradiated paraaortic (PA) region was high, suggesting a need to explore and/or to systematically treat this area in the next study.

The H2 trial (1972-1976) included 300 patients with Supradiaphragmatic stages I and II HD (40, 43). The trial was designed on the basis of the preliminary results of the H1 trial and of the data which were available in the literature at that time.

The evaluation of staging laparotomy and splenectomy could not be avoided in 1972 (32). As mentioned above, the preliminary data from the H1 trial indicated that the paraaortic region should be either explored or treated. Thus patients were randomized to undergo a, staging laparotomy and splenectomy, then mantle field RT and finally paraaortic RT, or b, mantle field RT, then paraaortic (PA) and spleen RT (subtotal nodal irradiation : STNI). The trial actually compared splenectomy and splenic irradiation but also permitted an assessment of the prognostic significance of the information provided by the exploratory lapartomy.

In addition, based on preliminary data drawn from the H1 trial, patients with mixed cellularity (MC) or lymphocytic depletion (LD) histologic subtypes were randomly assigned to a, VLB alone or b, VLB + Procarbazine, for 2 years.

At 12 years, the DFS was 68% for STNT alone, and 76% for laparotomy-STNI (NS). Survival was 77% for STNI, and 79% for laparotomy-STNI (NS).

A positive laparotomy was very predictive of a subsequent relapse. Disease-free survival was 83% after a negative laparotomy (lap-) and only 56% after a positive exploration (lap +) ($p<0.001$). But this advantage did not yield any survival benefit. It was 80% for lap negative patients and 76% for lap positive (NS), due to the efficacy of salvage treatments.

Patients with MC and LD histologic subtypes who had received chemotherapy (CT) experienced a better DFS (85% at 12 years), than patients who were not given any CT (65% DFS) ($p<0.001$). However, here again, no difference in survival was detected between the two groups; 75% for the CT group, 80% for the no-CT group (NS).

The H5 (1977-1982): The trial included 494 patients with stages I and II supra-diaphragmatic HD (6). To further adapt the management strategy, two groups, ''favourable'' and ''unfavourable'' were selected, according to prognostic, indicators which were drawn from a preliminary analysis of the H1 and H2 trials.

For the ''favourable'' group of patients, it was postulated that a ''limited'' treatment (RT alone) could be considered once the definite evidence of non infra diaphragmatic involvement was obtained. Thus all the patients in this group (trial H5F) first underwent a laparotomy and splenectomy; if negative, the patients were assigned to a, Mantle field irradiation alone or b, Mantle RT + PA irradiation. If the laparotomy detected an abdominal extension of the disease, the patients were referred to the ''unfavourable'' trial (H5U - see infra). In the H5F subgroup the 9-year DFS was 69% for Mantle RT, and 70% for Mantle + PA RT (NS). Nine-year survival was 94% and 91% respectively, in the two subsets (NS).

Laparotomy was not performed for the ''unfavourable'' group of patient since extensive treatment was thought to be necessary anyway. Patients were randomly assigned to either a, total nodal irradiation (TNI) or b, combined modality treatment : 3 MOPP-Mantle RT-3 MOPP. Nine-year DFS was significantly better in the combined treatment group : 83%, versus 66% for TNI ($p<0.001$). Overall results for survival showed for MOPP-RT-MOPP; 88% versus 73% for TNI ($p = 0.06$). However, in patients below 40 years of age, no difference in long term survival could be detected between MOPP-RT-MOPP and TNI.

The H6 trial (1982 - November 1988) : It included 559 patients with stage I-II supra diaphragmatic HD. Only the 497 patients entered between 1982 and 1987 will be considered in the present study. The analysis of the previous trials allowed further refinements of prognostic

factors, and patients were selected on this basis to be entered in a favourable (H6F) or unfavourable (HGU) trial.

The favourable trial addressed the question of the need for laparotomy and splenectomy. Thus in a first arm a, the patients underwent a laparotomy, followed by a treatment which was adapted to the pathology findings; if it was lap negative : Mantle field RT (+ PA if MC or LD histologic subtypes); if lap positive: CT-RT combination (see unfavourable subgroup below) were adopted.

In the second arm b, patients, without any prior surgical exploration, directly received Mantle RT, paraaortic + spleen RT (STNI).

In this pragmatic trial, aimed at evaluating the long-term usefulness of laparotomy, the end point was survival and not DFS. At 4-year follow-up, as expected, DFS was slightly lower in the STNI group (75%) than in the laparotomy (+ adapted treatment) group (85%) ($p = 0.02$). However, due to the efficacy of salvage procedures, 4-year survival was similar in the two groups (89% for STNI, 93% for laparotomy and adapted treatment (NS)).

The ''unfavourable'' trial H6U was based on the preliminary results of H5U trial, which showed an advantage for the CT-RT combination over TNI in terms of DFS. Patients were randomly assigned either to arm a, 3 MOPP-Mantle RT-3 MOPP (23) or to arm b, 3 ABVD-Mantle RT-3 ABVD-Mantle RT-3 ABVD (31). DFS was slightly lower in the MOPP group (75%) than in the ABVD group (89%) but the difference was marginally significant ($p = 0.07$). There was no difference in survival (MOPP : 91%, ABVD : 89% (NS)). One of the main point of interest of this study will be the evaluation of toxicity in the two arms; however it would be premature to try to compare the late toxicities in those two groups at this point in time.

B/STAGES IIIB : IV

Apart from previous pilot studies which will not be reported here, between 1981 and 1986 the EORTC Lymphoma Group conducted a randomized trial for stages IIIB and IV HD, including 192 patients (35).

In 1981, one of the main questions was whether or not an alternation of MOPP and ABVD was superior to MOPP alone in terms of DFS and survival (4). Moreover, the EORTC Lymphoma Group was interested in evaluating the value of a complete response after 2 and 4 cycles of chemotherapy, as a possible predictor for a favourable longterm outcome.

Thus all the patients with stage IIIB-IV first received 2 cycles of MOPP. They were then submitted to an extensive clinical and radiological evaluation; if no progression was detected, patients were assigned either to a, 6 additional cycles of MOPP + initially involved field (IF) RT or to b, a subsequent alternation of 2 ABVD-2 MOPP-2 ABVD + IFRT.

A significantly higher rate of progression was observed in the MOPP group (22%) than in the MOPP/ABVD group (9%) ($p = 0.02$). For those patients who achieved a complete remission at the end of the treatment, DFS was not significantly different in both groups. The 5-year overall survival was marginally better in the MOPP/ABVD group (70%) than in the MOPP group (59%) ($p=0.12$).

Interestingly by multivariate analysis, the best predictor of a favourable outcome was the achievement of a complete remission (CR) after the first four cycles of CT : 5-year survival was 73% for patients who experienced a CR after 4 cycles of CT, and only 59% for patients who did not ($p=0.014$) (update November 88).

II - THE PRESENT STRATEGY A/ Stages I and II, supra diaphragmatic

The ongoing H7 trial (activated November 1988) is based on the results of the previous EORTC trials, on a detailed analysis of the prognostic factors in the EORTC cohort of 1,579 patients, and on the more recent data reported in the literature (2, 3, 13, 18, 19, 21, 25, 27, 30, 31, 33, 38).

Patients with supra diaphragmatic stage I-II HD are assigned to one of three prognostic groups.

1° / A first ''very favourable'' group represents a small subset; only 6% of the patients in the EORTC experience. It is very restrictively defined, and only includes patients with clinical stage (CS) I (42) and below 40 years of age, and without systemic symptoms (A) and Erythrocyte Sedimentation Rate (ESR) <50 mm (37), and of female gender, and with lymphocytic predominance or nodular sclerosis histologic subtypes, and without bulky mediastinal involvement (9, 27).

For these very selected patients, the EORTC data indicates that it is possible to test prospectively the use of a ''minimal radiotherapy'' (Mantle field RT alone) with overall survival as the end point. The small number of patients to be included in this group does not permit randomization.

At the other end of the scale the ''unfavourable'' group comprises

about 40% of the patients. The presence of only one of the following prognostic factors is sufficient for a patient to be included in this group : age > 50 years, or (A) with ESR > 50, or systemic symptoms (B) with ESR > 30, or 4 more involved sites (CSII4 or more) or mediastinal/thorax ratio > 0.35.

For those patients, data gathered by the EORTC as well as by other groups, clearly show that a combination of chemotherapy and radiotherapy is superior to radiotherapy alone for long term survival (31, 44).

The question now is to find out what would be the "best" CT-RT combination. In ongoing H7 trial, it was decided that the following two schedules be compared : a) 6 EBVP (17, 48) + IF RT and b) 6 MOPP/ABV (7, 23) + IF RT.

Acute and late toxicities as well as relapse and survival rates, are to be carefully evaluated in both arms (8, 10, 11, 12, 14, 15, 16, 20, 22, 24, 28, 29, 45, 47).

The intermediate or "favourable" group represents about 54% of the patients in the EORTC experience. It includes all the patients who were not entered in the two previous groups.

For those patients, satisfactory long-term survival rates can be achieved either by irradiation alone (STNI) or a CT-RT combination. Only a difference in long-term toxicity would result in preference being given to one of these two treatment schedules.

Thus, the ongoing H7 EORTC trial chose to compare a) STNI to b) 6 EBVP + IF RT. Acute and late toxicities are to be carefully recorded in both arms of this controlled study.

B/STAGES III IV

The future EORTC controlled study for stages III-IV HD is still under preparation; we will only report here the main guidelines for this next trial.

The study will be based on the use of an alternating chemotherapy schedule, based on the results of the 1981-1986 EORTC trial (35) and on those of recent series in the literature (3, 4, 5). The chosen scheme is the MOPP/ ABV, according to the description of the Vancouver group (7, 23).

The general strategy of the trial will be to adapt the treatment to the response which will be achieved after the first four cycles of CT, according to the findings of the previous EORTC study. If a complete response (or a good partial response - to be discussed-) has been

obtained, the same GT will be continued with two additional MOPP/ABV. If patient is still in complete remission at the end of the 6 chemotherapy courses, randomization is planned between a) involved field irradiation and b) no further treatment (since the definite value of such a complementary irradiation has never been evaluated when a CR has been achieved).

On the other hand, if a complete remission cannot be achieved after the first four MOPP/ABV courses, a treatment intensification would appear necessary; the use of a "classical" second line chemotherapy or of an intensified CT program followed by an autologous bone marrow graft is still under consideration in the Group.

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APPENDIX

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REFERENCES

1. ADRIEU J.M., CASASSUE P., DESABLENS B., HAROUSSEAU J.L., BRIERE J., TOURANI J.M., LEMEVEL A., IFRAH N., DANA M., COSCAS Y., JAQUILLAT C. Chemotherapy plus radiotherapy for Hodgkin's disease: clinical stages IA and IIA, in Salmon SE (ed) : Adjuvant Therapy of Cancer V.. Orlando, Grune & Stratton 1987, p763-772
2. BERGSAGEL D.E., ALISON R.E., BEAN H.A., BROWN T.C., BUSH R.S. CLARK R.M., CHUA T., DALLEY D., DEBOER G., GOSPODAROWICZ M., HASSELBACK R., PERRAULT. D., RIDEOUT. D.F. Results of treating Hodgkin's disease without a policy of laparotomy staging. Cancer Treat. Rep., 66: 717-731, 1982
3. BONADONNA G., SANTORO A., VIVIANI S., VALAGUSSA P. Treatment strategies for Hodgkin's disease. Seminars in Hematology, 25:2, suppl. 51-57, 1988.
4. BONADONNA G., VALAGUSSA P., SANTORO A. Alternating non-cross-resistant combination chemotherapy or MOPP in stage IV Hodgkin's disease : a report of 8 year results. Ann. of Int. Med., 104: 6, 739-746, 1986.
5. CANELLOS G.P., PROPERT K., COOPER R., NISSEN N., ANDERSON J., ANTMAN K.H., SANTAMAURO B., GOTTLIED A.J. MOPP vs ABVD vs MOPP alternating with ABVD in advanced Hodgkin's disease : a prospective CALGB trial. Proceedings of ASCO vol. 7, p 230, Abstract 888, 1988
6. CARDE P., BURGERS J.M.W., HENRY-AMAR M., HAYAT M., SIZOO W., VAN DER SCHUEREN E., MONCONDUIT M., NOORDIJK E.M., LUSTMAN MARECHAL J., TANGUY A., DE PAUW B., COSSET J.M., CATTAN A., SCHNEIDER M. THOMAS J, MEERWALDT J.M., SOMERS R., TUBIANA M. Clinical stages I and II Hodgkin's disease : a specifically tailored therapy according to prognostic factors. The 1977-1982 H5 controlled trials program. J. Clin. Oncology, 6; 239-252, 1988.
7. CONNOERS J.M., KLIMOP. MOPP/ABV hybrid chemotherapy for advanced Hodkin's disease. Semin. Hematol., 24-35, 1987
8. COSSET J.M., HENRY-AMAR M., BURGES J.M.V., NOORDIJK E.M., VAN DER WERF MESSING B., MEERWALDT J.H., VAN DER WERF MESSING B., MEERWALDT J.H., VAN DER SCHUEREN E. Late radiation

injuries of the gastro-intestinal tract in the H2 and H5 Hodgkin's disease trials : emphasis on the role of exploratory laparotomy and fractionation. Radiother. Oncol., 13;61-68, 1968

9. COSSET J.M., HENRY-AMAR M., CARDE P., CLARKE D., LE BOURGEOIS J.P., TUBIANA M. The prognostic significance of large mediastinal masses in the treatment of Hodgkin's disease. The experience of the Institute Gustave Roussy, Hematol. Oncol., 2;33-43, 1984
10. DA CUNHA M.F. MEISTRICH M.L., FULLER L.M., CUNDIFF J.H., HAGEMEISTER F.B., VELASQUEZ W.S., McLAUGHLIN P., RIGGS S.A., CABINILLAS F.F., SALVDOR P.G. Recovery of spermatogenesis after treatment for Hodgkin's disease: limiting dose of MOPP chemotherapy. J. Clin. Oncol., 2;5711-577, 1984
11. DIXON D.O., MCLAUGHLIN P., HAGEMEISTER F.B., FREIREICH E.J., FULLER L.M., CABANILLAS F.F., GEHAN E.A. Reporting outcomes in Hodgkin's disease and lymphoma. J. Clin. Oncol., 5;1670-1672, 1987
12. GREEN D.M., GENERAL R.L., PEARCE J., PANAHON A.M. GHOORAH J. The effect of mediastinal irradiation on cardiac function in patients treated during childhood and adolescence for Hodgkin's disease. J. Clin. Oncol., 5;239-245, 1 87
13. HAYDITTLE J.L., HAYHOE F.G., EASTERMING M.J., JELLLIFFE A.M., BENNETT M.H., VAUGHAN HUDSON G., CAUGHAN HUDSON B., MaCLENNAN K.A. Review of British National Lymphoma Investigation of Hodgkin's Lancet 1;967-972, 1985
14. HANCOCK S.L., HOPPE R.T., HORNING S.J., ROSENBERG S.A. Intercurrent death after Hodgkin's disease therapy in radiotheray and adjuvant MOPP trials. Ann. Int. Med., 109;183-189, 1988
15. HENRY-AMAR M. Quantitive risk of second cancer in patients in first complete remission from early stages of Hodgkin's disease. N. Cancer Inst. Monogr., 6;65-72, 1988
16. HENRY-AMAR M., PELLAE-COSSET B., BAYLE-WEISGERBER C., HAYAT M., COSSET J.M., CARDE P., TUBIANA M. Risk of secondary acute leukemia and preleukemia after Hodgkin's disease. The Institute Gustave Roussey experience, in V. Diehl, M. Pfrevndschuh, M. Loeffear (eds) : New Aspects in the Diagnosis and Treatment of Hodkin's disease. Rec. Cancer Res. 1989 Koln, FRG, Octobre 1-3, 1987 (in press).
17. HOERNI B., ORGERIE M.B., EGHBALI H., BLANC C.M., DAVID B., ROJOUAN JZITTOUN R. Novelle association d'Epirubicine, Bleomycine, Vinblastine et Prednisone (EBVP II) avant radiothrapie dans les stades localises de Maladie de Hodgkin. Essai de phase II chez 50 malades. Bull, Cancer, 8;789-794, 1988
18. HOPPE R.T. The contemporary management of Hodgkin disease. Radiology, 169;297-304, 1988
19. HOPPE R.T., HORNING S.J. ROSENBERG S.A. The concept, evolution and preliminary results of the current Stanford clinical trials for Hodgkin's disease. Cancer Surveys, 4;459-475, 1985
20. HORNING S.J., HOPPE R.T., KAPLAN H.SS., ROSENBERG S.A. Female reproductive potential after treatment for Hodgkin's disease. N Eng. J. Med., 304;1377-1382, 1981
21. HORWICH A., EASTON D., NOGUEIRA-COSTA R., LIEW K.H., COLMAN M., PECKHAM M.J. An analysis of prognostic factors in early stage Hodgkin's disease. Radiother. Oncol., 7;95-106, 1986
22. KALDOR J.M., DAY N.E., BAND P., CHOI N.W., CLARKE E.A., COLEMAN M.P., HAKAMA M., KOCH M., LANGMARK G., NEAL F.E., PETTERSON F., POMPPE-KIRN V., PRIOR P., STORM H.H. Second malignancies following testicular cancer, ovarian cancer and Hodgkin's disease : an international collaborative study among cancer registers. Int. J. Cancer, 391571-585, 1987
23. KLIMO P., CONNORS J.M. An update on the Vancouver experience in the management of advanced Hodgkin's disease treated with the MOPP/ABV hybrid program. Sem. in Hematology, 25, 2 suppl2, 34-40, 1988
24. LE BOURGEOIS J.P., MIGNAN M.,

PARMENTIER C., TUBIANA M. Renal consequences of irradiation of the spleen in lymphoma patients Brit J. Radiol., 52;56-60, 1979

25. LEE C.K.K., AEPPLI D.M., BLOOMFIELD C.D., LEVITT S.H. Hodgkin's disease : a reassessment of prognostic factors following modification of radiotherapy. Int. J. Radiat, Oncol, Biol. Phys., 13;983-991, 1987
26. LONGO D.L., YOUNG R.C., WESLEY M., HUBBARD S.M., DUFFEY P.L., JAFFE E.S., DEVITA V.T. Jr Twenty years of MOPP therapy for Hodgkin's disease. J. Clin. Oncol., 4, 1295-1306, 1986
27. MAUCH P., GORSHEIN D., CUNNINGHAM J., HELLMAN S. Influence of mediastinal adenopathy on site and frequency of relapse in patients with Hodgkin's disease. Cancer Treatment Rep., 66;809-817, 1982
28. PEDERSEN-BJERGAARD J., SPECHT L, S. Q. ERSBOLL, J. STRUCK J., HANSEN H.H., NISSEN N.I. Risk of therapy related leukemia and preleukemia after Hodgkin s disease. Relation to age, cumulative dose of alkylating agents, and time form chemotheray. Lancet, 2;83-88, 1987
29. POHJOLA-SINTONEN S., TOTTERMAN K.J., SALMO M., SILTANEN P. Late cardiac effects of mediastinal radiotherapy in patients with Hodgkin's disease. Cancer, 60;31-37, 1987
30. RICHARDS M.A., GREGORY W.H., LISTER T.A. Prognostic factors in lymphoma IN : Pointers to Cancer Prognosis. Stoll BA (ed) Dordrecht Martinus Nijhoff Pub.; 333-340, 1987
31. ROSENBERG S.A. Editorial : Exploratory laparotomy and splenectomy for Hodgkin's disease : a commentary. Hematol. Oncol., 2;61-63, 1984
32. ROSENBERG S.A. Editorial : Exploratory laparotomy and splenectomy for Hodgkin's disease : a commentary. J. Clin., Oncol., 6;574-575, 1988
33. ROSENBERG S.A., KAPLAN H.S. The evolution and summary results of the Stanford randomised clinical trials of the management of Hodgkin's disease : 1962-1984 Int. J. Radiat. Oncol. Biol. Phys., 11;5-22, 1985
34. SANTORO A., BONADONNA G., VALGUSSA P., ZUCALI R., VIVIANI S., GVILLANI F., PAGNONI A.M., BONFANTE V., MUSUMECI R., CRIPPA F., TESORO TESS J.D., BANFIA. Long term results of combined chemotherapy-radiotherapy approach in Hodgkin's disease : superiority of ABVD plus radiotherapy versus MOPP plus radiotherapy. J. Clin. Oncol., 5;27-37, 1987.
35. SOMERS R., HENRY-AMAR., CARDE P., NAJMAN A. MOPP vs alternating 2 MOPP/2 ABVD in advanced Hodgkin's disease Proceedings of ASCO, vol. 7, p. 236, abstract 914, 1988
36. SOMERS R., TUNIANA M., HENRY-AMAR M. EORTC Lymphoma cooperative group studies in Hodgkin's disease in V. Diehl, M, Pfrevndschuh, M. Loeffear (eds) : New Aspect in the Diagnosis and Treatment of Hodgkin's disease. Rec. Res. cancer Res. 1989 (in press).
37. SUTCLIFFE S.B., GOSPODAROWICS M.K., BERGSAGEL D.E., BUSH R.S., ALISON R.E., BEAN H.A., BROWN T.C., CHUA T., CLARK R.M., CURTIS J.E., DEMBO A.J., FITZPATRICK P.J., HASSELBACK R.H., RIDEOUT D.F., STURGEON J.F.G., QUIRT I., YEOH L., PETERS M.V. Prognostic groups for management of localized Hodgkin's disease. J. Clin. Oncol., 3;393-401, 1985
38. SUTCLIFFE S.B., GOSPODAROWICZ M., BUSH R.S. Mediastinal involvement by Hodgkin's disease and the implications for management for those patients with local or locoregional disease. Hematol Oncol., 2;74-76, 1984
39. TUBIANA M., COSSET J.M., CARDE P., HENRY-AMAR M., HAYAT M., AMIEL J.L. The contribution of clinical trials to the treatment of patients with early stages of Hodgkin's disease. Drugs Exp. Clin. Res., 12;105-112, 1986
40. TUBIANA M., HAYAT M., HENRY-AMAR M., BREUR K., VAN DER WERFMESSING B., BURGERS M. Five year results of the EORTC randomized study of splenectomy and spleen irradiation in clinical stages I and II of Hodgkin's disease. Europ J. Cancer, 17;355-363, 1981
41. TUBIANA M., HENRY-AMAR M.,

BURGERS M., VAN DER WERF-MESSIN B., HAYAT M. Prognostic significance of erythrocyte sedimentation rate in clinical stages I-II of Hodgkin's disease. J. Clin. Oncol., 2;194-200, 1984

42. TUBIANA M., HENRY-AMAR M., BURGERS M., QASIM M., SOMERS R., SIZOO W., VAN DER SCHUEREN E. Prognostic significance of the number of involved areas in the early stages of Hodgkin's disease. Cancer, 54;885-894, 1984
43. TUBIANA M., HENRY-AMAR M., HAYAT M., BURGES M., SOMERS R., SIZOO W., VAN DER SCHUERENE E. The EORTC treatment of early stage of Hodgkin's disease. The role of radiotherapy. Int. J. Radiat. Oncol. Biol. Phys., 10;197-210, 1984
44. TUBIANA M., HENRY-AMAR M., VAN DER WERF-MESSING B., HENRY J., ABBATUCCI J., BURGERS M., HAYAT M., SOMERS R., LAUGIER A., CARDE P. A multivariate analysis of prognostic factors in early Hodgkin's disease. Int. J. Radiat. Oncol. Biol. Biol. Phys., 11;23-30, 1985
45. TUCKER M.A., COLEMAN C.N., COX R.S., VARGHESE A., ROSENBERG S.A. Risk of second cancers after treatment for Hodgkin's disease. N. Engl. J. Med., 318;76-81, 1988
46. VANDER WERF-MESSING B. Morbus Hodgkin's disease, stage I and II trial of the EORTC. Hodgkin's disease Symposium, Stanford University, 1972. Natl. Cancer Inst. Monogr., 36;331-386, 1973
47. VAN RIJSWIJK REN, VERBEEK J., HAANEN C., DEKKER A.W., VAN DAAL WAJJ, VAN PEPERZEEL H.A. Major complications and causes of death in patients treated for Hodgkin's disease J. Clin. Oncol., 5;1624-1633, 1987
48. ZITTOUN R., EGHBALIH., AUDEBERT A., ROJOUAN J., DAVID B., BLANC C.M., HOERNI B., DEBRAY J., PIERRE ET MARIE CURIE GROUP. Assoiciation d'Epirubicine, Bleomycine, Vinblastine et Prednisone (EBVP) Bull. Cancer (Paris) 74;151-157, 1987

3

INTENSIVE CHEMOTHERAPY WITH PERIPHERAL BLOOD STEM CELL RESCUE IN OVARIAN CANCER

Davy M.L.J.

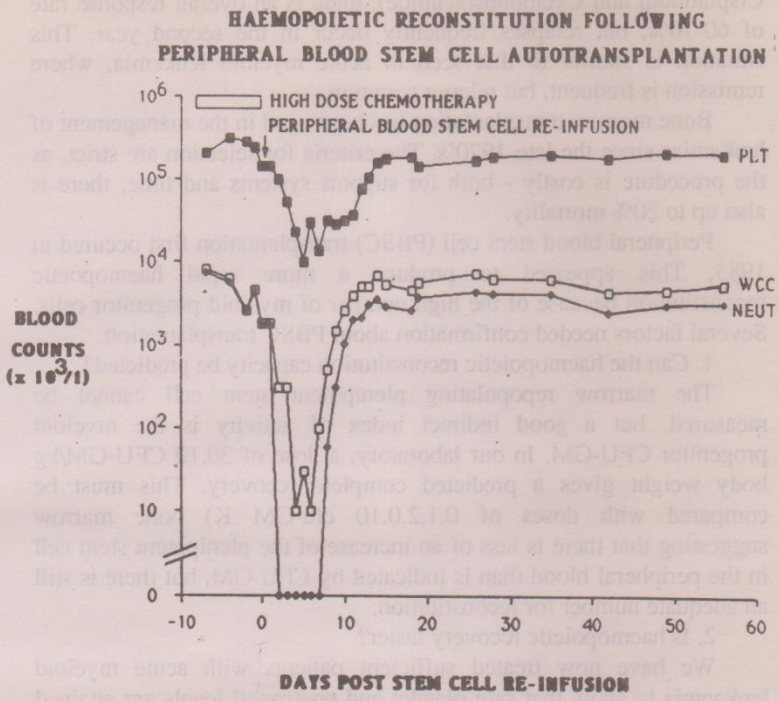
Ovarian cancer presents one of the greatest challenges in gynaecological oncology today. The majority present with late stage disease, and will ultimately die from this disease. Overall survival has not altered appreciably in the last 30 years.

The single most important prognostic factor for ovarian cancer is Stage 1. A meticulous surgical approach is needed. Despite careful surgical staging, with the exception of some cases of Stage I disease, surgical removal of all macroscopic disease is not sufficient to guarantee cure.

Therapies adjuvant to surgery have been explored over the last 20 years. Radiation, firstly to the pelvis, then later to the whole peritoneal cavity either by the moving strip or open field techinques has been used. Toxicity problems have prevented adequate dosage to sites of preference of metastasis-namely diaphragms and para-aortic nodes. The liver, kidneys and small bowel tolerate only small doses of radiation which are suboptimal for tumour kill.

The early 1970's and early 1980's saw the increased use of chemotherapy in ovarian cancer.

Alkylating agents produced some responses. Then a variety of drugs were added in an attempt to produce synergism of effect but with only additive toxicity. Responses were modest - but the price in



toxicity was high, some times even with death. Many researchers felt that it was only a matter of supporting the patient through the toxicity so that more drugs could be delivered, to achieve cure.

Cisplatinum then became available. Responses were seen not only in patients with good prognostic factors such as early stage, well differentiated tumours, but also in the bad prognostic groups.

In an attempt to verify these responses, second look surgery flourished; one needed proof of the completeness of the response in order to stop therapy. Even with negative second look surgery. patients have continued to relapse.

It has been shown that the Platinum response is dose-dependant. Dose limiting toxicity was renal but since the use of forced diuresis has protected against this, neurotoxicity is the major problem.

Second generation analogues do not have any wider spectrum of activity, but have differing toxicities, and it is here that we are seeking to capitalize on the newer technologies available today.

Using Platinum-based combinations (in our institution,

Cisplatinum and Cyclophosphamide), there is an overall response rate of 60-70%, but relapses frequently occur in the second year. This situation is similar to that seen in acute myeloid leukemia, where remission is frequent, but relapse common.

Bone marrow transplantation has been used in the management of leukamias since the late 1970's. The criteria for selection are strict, as the procedure is costly - both for support systems and time; there is also up to 20% mortality.

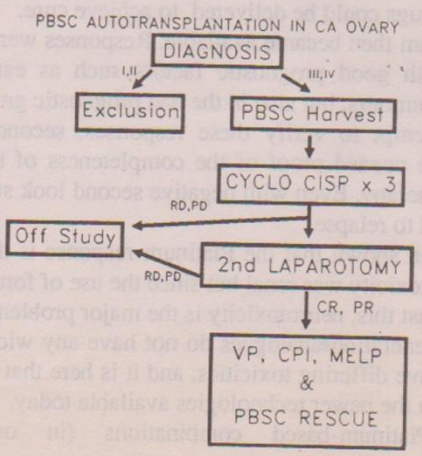
Peripheral blood stem cell (PBSC) transplantation first occured in 1985. This appeared to produce a more rapid haemopoetic reconstitution because of the high number of myeloid progenitor cells. Several factors needed confirmation about PBSC transplantation.

1. Can the haemopoietic reconstitution capacity be predicted?

The marrow repopulating plenipotent stem cell cannot be measured, but a good indirect index of activity is the myeloid progenitor CFU-GM. In our laboratory, a dose of 30.10 CFU-GM/kg body weight gives a predicted complete recovery. This must be compared with doses of 0.1.2.0.10 cfu-GM K) bone marrow suggesting that there is less of an increase of the plenipotent stem cell in the peripheral blood than is indicated by CFU-GM, but there is still an adequate number for reconstitution.

2. Is haemopoietic recovery faster?

We have now treated sufficient patients with acute myeloid leukaemia to show that safe platelet and neutrophil levels are attained 9-15 days faster than with bone marrow (Fig 1) thus reducing infection, haemorrhage and hospitalization.



3. Is immune recovery more rapid and complete?

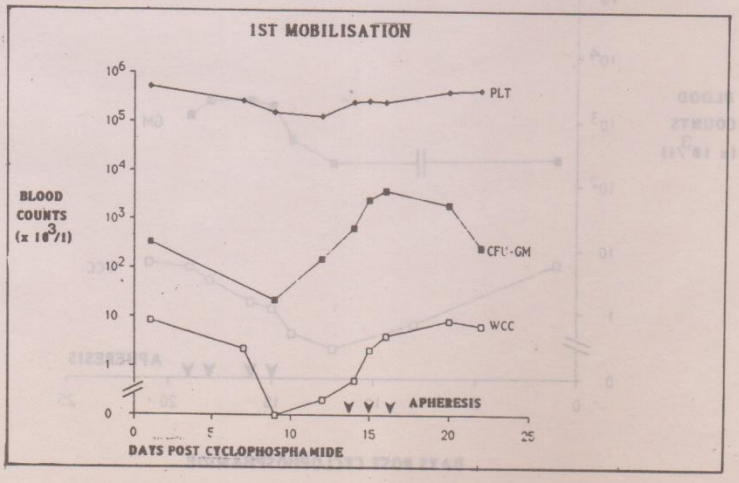
Several studies using bone marrow reconstituion have shown that the immune recovery is significantly delayed - both in vivo and in vitro. This leads to increasing opportunistic infections. even in the presence of normal neutrophil counts. PBSC autografts give much higher lymphocyte counts, suggesting that there is a different pattern of immune reconstitution, which may well follow the granulocyte pattern.

Thus PBSC transplantation has developed into a relatively simple procedure with stem cells collected by leukophoresis and haemopoietic reconstitution safer and more rapid than using bone marrow. The stage was therefore set for initiating studies in solid tumours.

There are many questions still to be answered and perhaps the most pressing is to know if we are asking the correct question.

This initial study was designed to answer the question whether dose intensification with appropriate supports could improve the survival chances for a patient whose tumour had already shown sensitivity to Platinum.

All women with Stages III and IV disease post surgery were considered. Documentation of all disease sites both surgically removed and remaining post surgery was vital. A priming dose of Cyclophosphamide 4gm/m with pre and post hydration was given and, leukaphoresis on 3-5 occasions was to take place after recovery from nadir values. The PBSC were stored and chemotherapy using the routine regimen of Cisplatinum and Cyclophosphamide for three courses given.



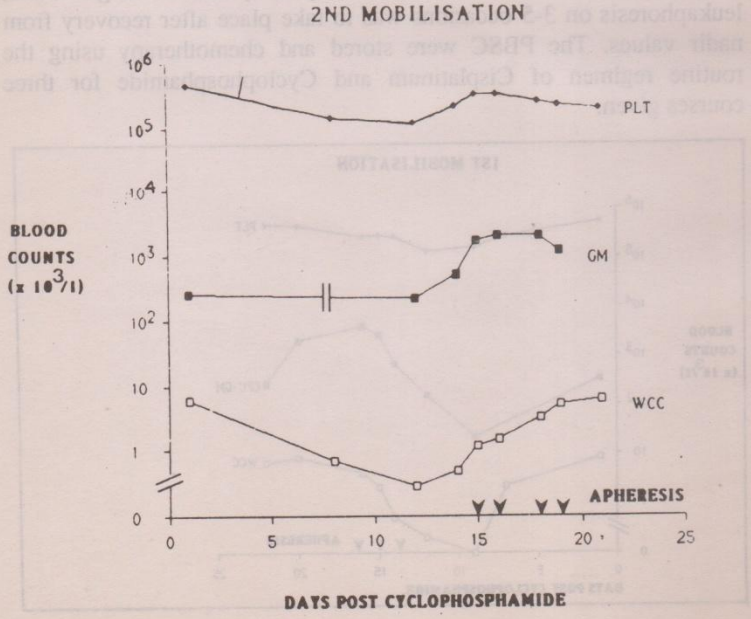
Cyclophosphamide was chosen for two reasons; it had activity in ovarian cancer - and it also had been shown in leukaemias that the more intense the chemotherapy with viogrous haemotological recovery, the better the PBSC harvest.

Recovery after the nadir usually occured on or about day 13.

After the third course, a decision would then be made regarding response. Clinical responders were then subjected to laparotomy to confirm this response. After surgery. intense chemotherapy using VP-16, Carboplatin and Melphalan was then given and PBSC transplantation occured two days post therapy Table 1.

To date, five patients have been entered on the study since April 1988. This report is about one of these five; the first one has completed therapy, the next two failed to show initial response, the fourth did not produce sufficient CFU-GM and the fifth is still being primed.

At initial surgery her tumour was extensive and an 8cm mass could not be resected from the pelvis. During her initial chemotherapy, this tumour mass decreased to about half its original size and she was thus considered to have been a partial responder. At second surgery, this fact was confirmed and the mass further resected. There were still widespread small deposits scattered throughout the abdominal cavity.



Chemotherapy was commenced on the eight post operative day after the sutures were removed. she received 5 units of blood and 2 of platelets in toto during her recovery phase. She also ran a fever of 39°C commencing on day 5 and was discharged from hospital on the 14th day post PBSC reconstitution. Figure 3 shows the pattern of haemopoietic reconstitution, illustrating also its persistence.

This study to date poses more questions than it answers:

Are we selecting the right cases to demonstrate any effect? Should we be restricting this study only to patients with minimal residual disease?

Should we be using higher doses of Cisplatin initially - or treating with more course before dose intensification?

More importantly - we need a success or two to keep going.

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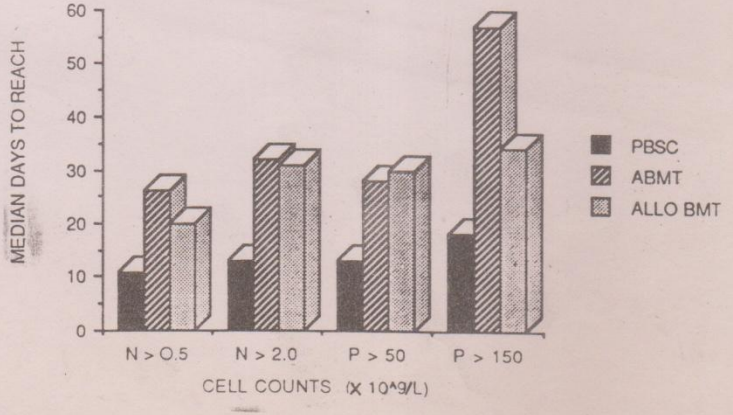


REFERENCES

1. Annual report on the Results of Treatment in Gynaecological Cancer PETTERSSON F. et al FIGO Stockholm 1984 Vol 19
2. OZOLS R.F., YOUNG R., High Dose Cisplatin therapy in Ovarian cancer Oncol Vol 12 p21 1985
3. To L.B., DYSON P.G. BRONOFORD. A.C., RUSSELL J.A., HAYLOCK D.N., HO J.Q.K. KIMBER R.J., JUTTNER C.A. et al A case Report: Peripheral Blood Stem Cells Collectedd in very Early Remission Produces Rapid and Sustained Autologous Haemopoietic Reconsitution in Acute Non-Lymphoblastic Leukaemia. Bone Marrow Transplantation Vol 2 p 103 1987
4. JUTTNER C.A. To L.B., HYCOCK D. et al Circulating Autologous Stem Cells Collected in Very Early Remission From Acute Non-Lymphoblastic Leukaemia Produce Prompt But Incomeplete Haemopoietic Reconstituion After High Dose Melphalan or Supra Lethal Chemo/radiotherapy. Br. J. Haematol Vol 16 p 739 1985.

4

STRATEGIES FOR CIRCUMVENTING RESISTANCE TO CYTOTOXIC DRUGS

Peter R. Twentyman

1. INTRODUCTION

At the most simplistic level, the expression, 'resistance to cytotoxic drugs' is a statement of the fact that most tumours cannot be eradicated by currently available chemotherapy. Although a few relatively uncommon cancers such as childhood acute leukaemia and testicular teratomas can now be permanently controlled by combination chemotherapy, treatment of most common solid tumors such as lung, colon and breast cancers is, at best, palliative and, in many cases, ineffective in any sense.

The basic reason for this situation is that currently available cytotoxic drugs do not provide a sufficiently good 'therapeutic ratio'. That is to say, the maximum dose which can be delivered without unacceptable normal tissue toxicity is not sufficient to reduce tumour cell survival to the level needed for permanent control. This problem has been approached by the use of drug combinations, so that most modern regimes include 3 or 4 different cytotoxics with different modes of action and non-overlapping toxicities. Despite advances brought about by this approach, however, the problem remains unchanced.

Virtually all the cytotoxic drugs in current use are either selectively toxic to proliferating cells or targeted towards some

biochemical process which is largely similar in tumour cells and one or more normal tissues. Recently, a number of strategies have been adopted to develop agents with a better 'therapeutic ratio'. At the primary screening level, the new NCI Drug Screen has been set up to discover agents which, in a large panel of human tumour cell lines, show striking specificity for particular tumour types [1]. A separate approach has been to target drugs, by conjugation to antibodies, to epitopes present only on the surface of tumour cells [21] whilst yet a different route has been to develop 'latent' drugs which are inactive in the parent form but which can be activated by enzymes known to be present in tumour cells but not in normal tissues [75].

Although promising early results have been obtained using such techniques, it is too early to say whether or not they will result in sufficient improvement in 'therapeutic ratio' as to produce advances in clinical therapy.

A quite different approach to the question of therapeutic resistance has been the investigation of the molecular basis of the relative sensitivity and resistance of tumour and normal cells to cytotoxic drugs. Harris [27] has however emphasised the point that to expect to control tumours with cytotoxic drug implies a requirement of particular drug sensitivity on the part of the tumour cells and we should not be surprised that this is generally not found to be the case.

In considering the mechanism of drug resistance it has been useful to think of clinical resistance as either 'inherent' or 'acquired'. Some tumour types, as previously stated, are inresponsive to chemotherapy from the time of initial diagnosis and are therefore said to demonstrate 'inherent' resistance. In other tumour types, however, such a small cell lung cancer and ovarian cancer, there is frequently a very good response to initial chemotherapy (complete response rate in small cell lung cancer is typically 50%) but almost always the disease recurs within months and displays a progressive resistance to further drug treatment. Such tumours are said to demonstrate 'acquired resistance'. It remains unclear whether the basic mechanisms of inherent and acquired resistance are the same. It could be that the development of acquired resistance represents the overgrowth of an inherently resistant subpopulation of cells present at the time of initial therapy. On the other hand, reduction in tumour burden may induce in some way a change in differentiation pathways leading to a resistant phenotype emerging as a result of regrowth from a surviving precursor population. Alternatively, mutations induced by the drugs themselves may result in a move towards therapeutic resistance.

To date, strategies for investigation of resistance to chemotherapy have largely been based on the production of drug resistant variants of tumour cell lines in the laboratory. A comparison of such sublines with their parent lines has allowed the elucidation of a variety of mechanisms operating in such model systems and the development of sensitive biochemical probes. These probes can then be applied both to cell lines showing inherent resistance and to clinical biopsy specimens in order to determine whether the operation of a particular mechanism can be reconciled with the degree of resistance observed.

The methods of development of resistant cell lines will not be dealt with in detail here. For this information, the reader is referred to a number of excellent reviews [4, 6, 44, 52]. Instead I will briefly describe the biological basis of a number of different types of resistance, comment upon their clinical signficance, and discuss strategies which may possibly be useful in the circumvention of such resistance.

2) TYPICAL MULTIDRUG RESISTANCE (MDR)

The phenomenon of 'typical' MDR (or 'pleiotopic drug resistance') occurs in the laboratory when cells are made resistant in vitro by exposure to increasing concentrations of one of a number of drugs [4, 6, 44, 52]. These drugs are all high molecular weight, lipophilic natural products and the group includes adriamycin (ADM), vincristine, vinblastine, actinomycin D, colchicine and etoposide (VP 16). In general induction of resistance to one of these agents leads to cross resistance to other agents within the group. Little or no resistance is usually seen, however, to alkylating agents [4, 52].

Pharmacological studies have revealed that MDR cells usually exhibit a reduced cellular accumulation of the MDER phenotype drugs and in most cases this can be due to an increased cellular efflux [19, 30, 72]. An example of modified drug accumulation is shown in figure 1. MDR cells also exhibit physico-chemical changes in their plasma membranes which can be demonstrated using techniques such as fluorescence polarisation and electron spin resonance [25, 49].

Although a number of different gene amplifications and protein hyperexpressions have been demonstrated in MDR cells [31, 34, 42, 73], the most commonly observed correlate is hyperexpression of a 170 KD molecular weight glycoprotein, (P-glycoprotein) in the plasma membrane [31]. The amino acid sequence of this protein is strongly

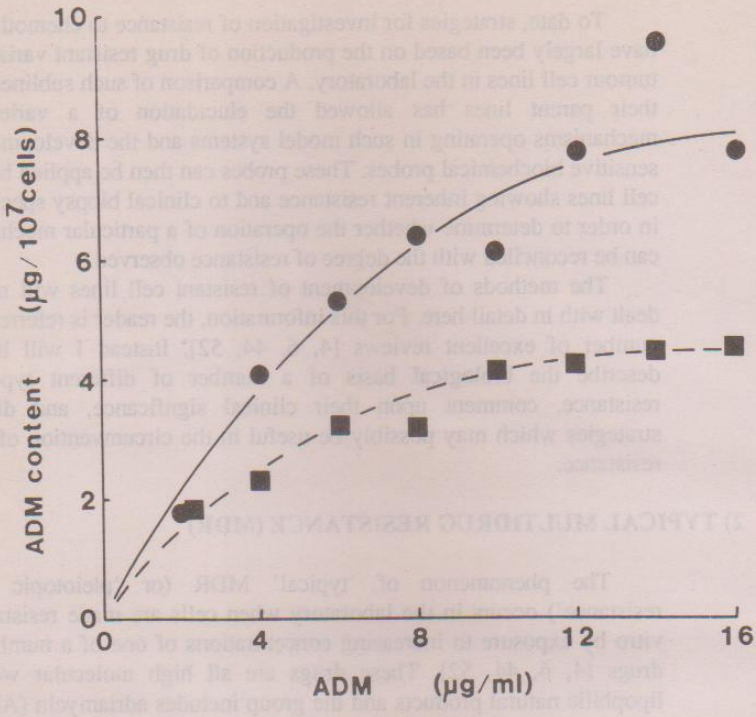


Figure 1

Accumulation of adriamycin by human small cell lung cancer cells. Parent line H69/P (●) or multidrug resistant subline H69/LX4 (■) cells were exposed to adriamycin in suspension for 1 hour. (For details see original paper by Twentyman et al, 1986, reference 72; reproduced with permission.)

homologous to the sequence of the haemolysin bacterial membrane transport protein suggesting a possible role in drug transport [8,24]. Studies using photoaffinity-labelled drug show that the P-glycoprotein molecule contains cytotoxic drug binding sites, thereby supporting this concept [13, 54].

Studies using either monoclonal antibodies to P-glycoprotein or cDNA probes for the gene have demonstrated the protein or mRNA in a number of human cancer types [3, 23, 35]. Additionally, however, several normal tissue types contain P-glycoprotein mRNA and the tumours with highest levels tend to be derived from such normal

tissues (Kidney, adrenals) [20]. On the other hand, however, studies on other types of drug-resistant cancers have failed to identify the presence of P-glycoprotein as a major component [20, 39].

A number of approaches have been used to circumvent the problem of MDR in laboratory models. Studies of crossresistance patterns have resulted in the identification of both analogues of known compounds and new structures where full activity appears to be mantained in MDR cells [28, 37, 71]. The most complete series has been amongst the anthracyclines and related compounds, where discrete changes in structure which lead to preserved activity are identified [10, 11, 28, 71]. Examples are shown in Figure 3. A second approach has been to use additional chemical compounds, "resistance modifiers" which, when co-administered with cytotoxics lead to a partial or complete restoration of sensitivity in resistant cells. The prototype compound is the calcium transport blocker, verapamil (VRP), first demonstrated as a RM by Tsuruo in 1981 [64, 65]. Since that time, many other compounds, particularly calcium transport blockers and calmodulin inhibitors have been shown to act as RMs [32, 48, 63, 66]. In general these compounds are able to reverse the reduced cytotoxic drug accummulation seen in resistant cells. The majority of studies have found that, as far as VRP is concerned, this occurs via an interference with the efflux process although changes in drug uptake have also been found [22, 25, 33]. Examples of VRP modification of ADM resistance are shown in Figure 3. It should also be noted from this figure that the combination of VRP with a 'low resistance' compound such as aclacinomycin A may be particularly effective strategy [68].

It seems very unlikely that the ability of VRP to act as an RM is mediated via its effect on calcium dependent voltage channels. Studies using labelled calcium chloride have failed to detect major changes in calcium fluxes brought about by VRP [5]. Furthermore, resistance modification has been observed in cells lacking voltage dependent channels [18].

Many calcium transport blockers are also calmodulin inhibitors. It does not appear, however, that a direct correlation exists between the ability of compounds to inhibit calmodulin-dependent functions and their resistance modification ability. We, for instance, have found that the highly specific calmodulin inhibitor, calmodizolium, is ineffective as a resistance modifier (unpublished data). Extensive structure-activity relationships by Ramu [47, 48] have shown that many RM compounds possess a range of biological activities including inhibition

of protein kinase C, binding to phospholipids and replacement of Ca++, direct membrane effects and induction of changes in lipid metabolism. The conclusion reached by Ramu from this work was that the mechanism of RM may involve alteration of the physicochemical properties of the cell membrane of drug-resistant cells or effects on lipid metabolism resulting in changes in membrane fluidity. It has very recently been demonstrated that VRP is able to bind to P-glycoprotein and in doing so competitively inhibits the binding of photo-affinity labelled vinca alkaloids [14]. Another extremely interesting observation is that in MDR cells of the mouse P388 line, there is an increase in the rate of membrane cycling and that this is reversed by VRP [55, 56]. In contrast, a study of ADM partitioning in 2 phase system in the test tube has demonstrated the ability of VRP to modify such partitioning [29]. This result could possibly be interpreted as evidence for some change in the chemical confirguration of the adriamycin molecules, brought about by VRP which results in an altered intracellular distribution. This wide variety of data currently available do not therefore conclusively indicate a single mechanism of action for VRP or for RMs in general.

An ideal RM would be a compound which greatly increased the cytotoxic drug sensitivity of tumour cells whilst leaving unchanged the sensitivity of the critical normal cells. In terms of experimental systems, this has often been equated to a requirement that the RM should sensitise a cell subline with acquired resistance whilst not sensitising the parent line. These requirements are clearly only equivalent if the resistance is due to a biological property absent from both normal cells and sensitive tumour cells. Very limited data on normal cells types indicate, however, that VRP, at clinically relevant concentrations, may not sensitise bone marrow colony-forming cells [60]. Furthermore, it is clear that 'parent' cells lines have a range of cytotoxic drug sensitivities and that the relatively insensitive cell lines may be regarded as showing 'inherent' resistance. Data on treatment of cell lines with cytotoxics plus or minus VRP would certainly indicate sensitisation of relatively resistant lines not previously exposed to drugs in vitro [40]. In our own laboratory, we find that sensitisation of the EMT6 mouse tumour cell line (parent) to ADM by VRP is at least as great as sensitisaion of the 40 fold ADM-resistant subline EMT6/AR1.0 [51]. Clearly, the question of differential sensitisation will be a major issue in the possible clinical usefulness of sensitisers.

A number of clinical trials of VRP as a RM have already been carried out or are in progress. From the in vitro data, it appears that

concentrations of 3-6 μM are necessary for major effects, although some effect is seen down to a dose of 0.5-1 μM [68]. For example in Figure 3. In early trials, achievement of a median plasma VRP level of 1.3 μg/ml was associated with unacceptable toxicity [45]. Using more complex schedules of VRP administration, however, more recent studies have achieved higher VRP levels with acceptable toxicity and early results indicate an advantage for patients with multiple myeloma receiving VRP in combination with standard chemotherapy [16].

The effective resistance modiffication potential of VRP may be

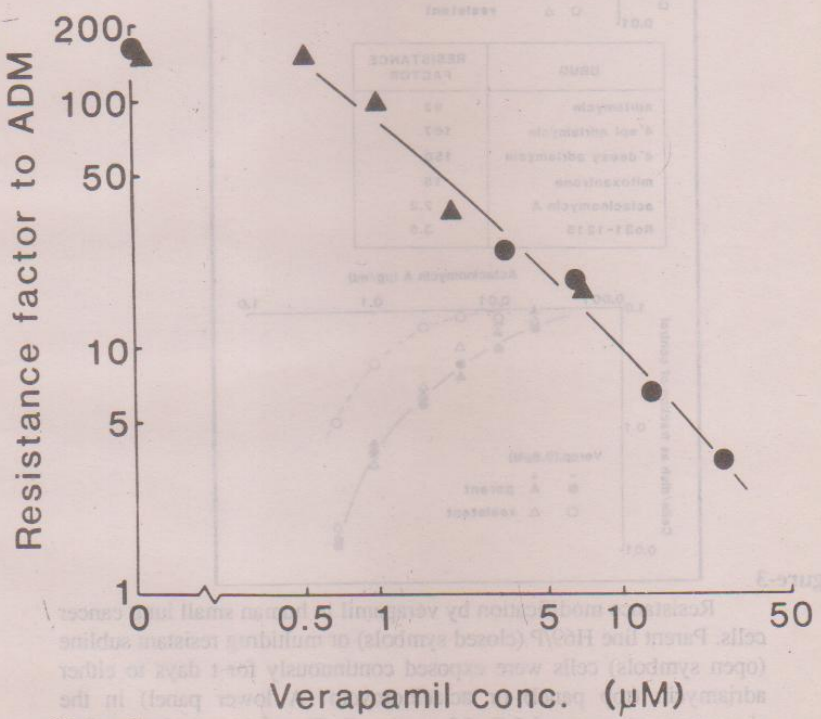
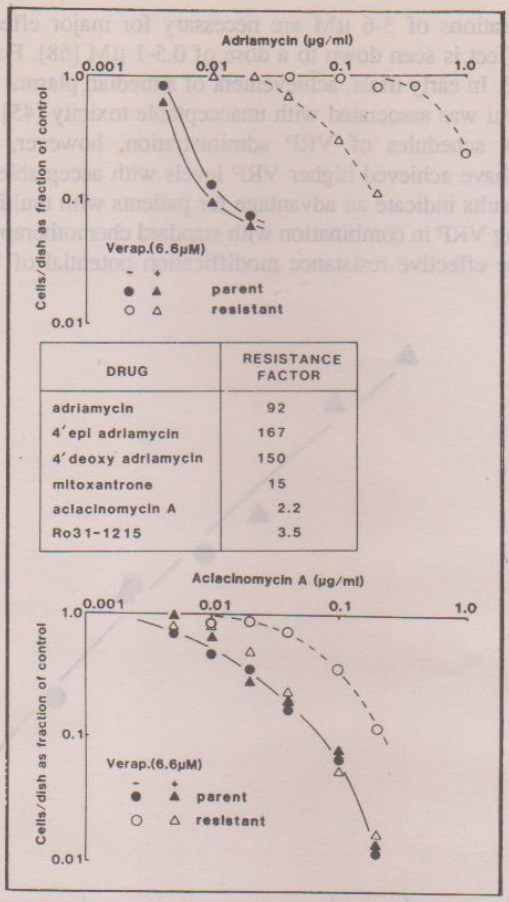


Figure-2

Dose-dependence of resistance modification for human small cell lung cancer cells exposed to adriamycin together with different concentration of verapamil. The resistance factor is the ratio of ID50S for adriamycin in the resistant subline H69/LX4 and the parent line H69/P. (For details see original paper by Twentyman et al, 1986, reference 68; reproduced with permission).



DRUG	RESISTANCE FACTOR
adriamycin	92
4'epi adriamycin	167
4'deoxy adriamycin	150
mitoxantrone	15
aclacinomycin A	2.2
Ro31-1215	3.5

Figure-3

Resistance modification by verapamil in human small lung cancer cells. Parent line H69/P (closed symbols) or multidrug resistant subline (open symbols) cells were exposed continuously for t days to either adriamycin (top panel) or aclacinomycin (A lower panel) in the absence or presence of 6.6 µM verapamil. The resistance factors (i.e. ratio of ID50S for resistant and parent lines) for a number for anthracyclines including adriamycin and aclaciomycin A are given in the centre panel. It is seen that whereas verapamil can only partly restore sensitivity of H69/LX4 cells to adriamycin, full restoration of sensitivity is seen with aclacinomycin A. (For details see Twentyman et al, 1986, reference 68.)

underestimated by measurement of plasma VRP. It has recently been shown that the major metabolite, norverapamil, is equally effective as a RM and appears in the circulation at approximately equal levels to the parent compound [41].

Several alternative calcium transport blockers have received attention as potential clinical RMs. Amioderone appears to be an effective RM in vitro at concentrations which are within the clinically achievable range [7] and this is also true of quinidine [63]. Clinical trials of these two compounds are in progress at the US National Cancer Institute.

Initially identified as a possible RM because of its interaction with calmodulin [12], the immunosuppressive agent cyclosporin A (CsA) has been the subject of studies in a number of laboratories. Although probably not related to its calmodulin inhibition, the RM properties of CsA have been demonstrated in both human and rodent cells in vitro [58, 59, 70] and also in mouse tumours in vivo (see Table) [59]. In my laboratory we have identified analogues of CsA which, whilst non-immunosuppressive, are more potent RMs than the parent compound [67] and one of these in particular (B3-243) is currently the subject of in vivo studies. Early results indicate that considerable potentiation of ADM effect is seen in mouse tumours at

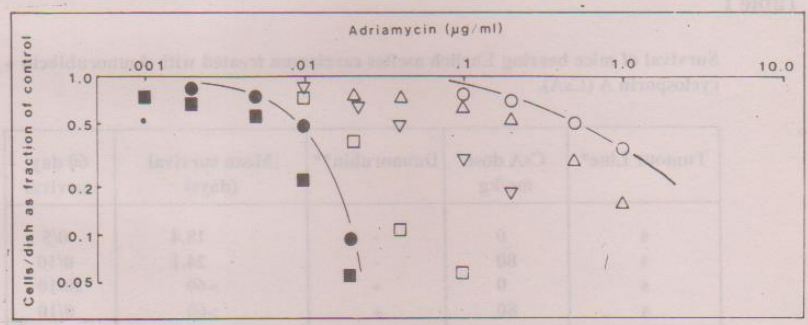


Figure 4

Response to adriamycin of human small cell cancer cells exposed continuously for 6 days in the absence or presence of different concentrations of cyclosporin A. Closed symbols - parent line H69/P; open symbols - multidrug resistant subline H69/LX4. Dose of cyclosporin A : circles = 0 μ g/ml; upright triangles = 1 μ g/ml; inverted traingles = 2 μ g/ml; squares = 5 μ g/ml. (For details see Twentyman et al, 1987, reference 70, reproduced with permission.)

B3-243 doses which are not themselves acutely toxic. Cellular pharmacokinetic studies indicate that the RM properties of the cyclosporins are closely related to their ability to modify cellular pharmacokinetics and to increase drug accumulation by cells showing the MDR phenotype [10, 11].

3) ATYPICAL MULTIDRUG RESISTANCE

The great majority of human and rodent cells lines assuming an MDR phenotype by in vitro treatment with one of the accepted range of drugs possess a clearly defined set of properties, namely

a. Cross resistance to an accepted range of agents (although this is qualitative rather than quantitative and the numerical resistance values may vary).
b. Hyperexpression of P-glycoprotein.
c. Reduced cellular drug accumulation which may be reversed by VRP.

There are, however, in the literature a number of cell lines which provide exceptions to the general case. For example, the H69/Ar human small cell lung cancer subline, shows a characteristic cross-

Table I

Survival of mice bearing Ehrlich ascites carcinoma treated with daunorubibcin + cyclosporin A (CsA).

Tumour Line*	CsA dose mg/kg	Daunorubin**	Mean survival (days)	60 day survival
s	0	-	18.4	0/5
s	80	-	24.1	0/10
s	0	+	>60	10/10
s	80	+	>60	0/10
R	0	-	19.0	0/5
R	80	-	24.0	0/10
R	0	+	21.1	0/10
R	80	+	>60	10/10
R	25	+	>60	10/10
R	5	+	51.2	4/10

*S = daunorubicin sensitive : R = daunorubicin resistant
** For details of treatment regimes see original reference (Slater et al, reference 59

resistance pattern but does not hyperexpress P-glycoprotein and shows little RM by VRP (9, 43). In our laboratory we have derived a subline of the human large cell lung carcinoma line COR-L23 which has similar properties (50). An ADM resistant variant of the human leukaemia HL60 cell line shows a MDR resistance spectrum, is defective in cellular drug accumulation but is devoid of P-glycoprotein (36). In this resistant cell line, three distinct phosphylated membrane proteins are seen which are not present in the parent cell line (38). A human leukemic cell line, CEM, made resistant by exposure to teniposide (VM-26) was cross-resistant to ADM but not to vincristine. Furthermore drug accumulation in these cells was unchanged.

It is presently unclear whether or not there is a common mechanism behind the 'atypical MDR' seen in these various cell lines. IN the CEM resistant line, lower levels of the enzyme, topoisomerase II are seen compared with the parent line (17). A modified activity of topoisomerase II has been independently reported in Chinese hamster cell line with cross-resistance to etoposide (VP16) and m-AMSA (46). This enzyme is involved in the breaking and reorganizing of DNA strands as part of normal cellular functioning. Available evidence strongly suggest that topoisomerase II is the target for the cytotoxicity for VP16 and possibly for other drugs (including ADM) (46). Clearly therefore there is a theoretical potential for resistance to be induced by modification of topoisomerase II activity interference. The topisomerase II activity would then be a possible approach to resistance modification. At the moment, however, there is no firm evidence that such a mechanism of resistance occurs in clinical cancer therapy.

GLUTATHIONE AND RELATED ENZYMES

The tripeptide glutathione (GSH) is the principal cellular non-protein thiol and is able to react with, and detoxify many of the reactive alkylating agents used in chemotherapy (2,53). This interaction is catalysed by the family of enzymes known as glutathione-S-transferases (GST) (2, 53). In addition, glutathione peroxidase (GPX), involved in the oxidation of GSH to the disulphide CSSG, can detoxify free radicals including those produced in DNA by a number of cytotoxic drugs including alkylating agents and ADM and also reduce toxic peroxides (2,53).

Amongst cell lines made drug-resistant by in vitro treatment,

there are a variety of examples in which GSH or its related enzymes are increased in concentration.For example an L1210 tumour cell line made resistant to melphalan showed increased GSH compared to the parent line [6]. Similarly a cell line with increased resistance to nitrogen mustards showed increased GST activity [74], and a human breast cancer cell line with resistance to ADM showed a 13-fold increase in GPX activity [57].

Strategies to reverse resistance due to increased GSH levels have included depletion of cellular levels by agents which directly inactivate GSH (such as diethylmaleate) or, alternatively the use of buthionine sulfoxamine (BSO) a synthetic amino acid which inhibits GSH synthesis [53]. The latter approach has been more successful at lowering GSH to the low level needed for sensitisation and has been shown to restore alkylating agent sensitivity to a number of cell lines with induced resistance [26]. Recently a number of agents with the ability to inhibit GST activity have been studied for their ability to restore sensitivity to nitrogen mustards in a rat breast carcinoma cell line in which resistance was accompanied by increased GST levels. The most effective compound was found to be ethacrynic acid [62]. Previously used as a diuretic in the clinic, this agent is about to enter clinical trial as a resistance modifier in the US.

There is very little evidence that changes in GSH or related enzymes as a component of clinical drug resistance. However, a recent study has demonstrated by immuno-histo-chemistry that colon tumours have higher levels of the mRNA for the isoenzyme of GST than surrounding colonic mucosa [44]. Further data obtained by a number of laboratories using cDNA probes for GST isoenzymes are expected to be published in the near future. In our laboratory we have demonstrated high levels of GSH in leukaemic lymphocytes from a patient with chronic lymphocytic leukaemia resistant to alkylating agents and radiation [69]. A series of leukemia patients is currently being studied with respect to their alkylating agent sensitivity and GSH levels.

OTHER MECHANISMS

In addition to these mechanisms which can account for cross-resistance to various spectra of drugs, these are numerous well-documented examples of other mechanism which are more drug-specific (summarised in reference 6). These include transport changes, alterations in drug activation or inactivation, modification in

target enzymes and increased activity of repair mechanisms. Indeed, the very multiplicity of possible resistance mechanisms presents a daunting prospect in terms of clinical appraoch. Perhaps the best documented example of this comes from an investigation by Curt et al [15] who determined the basis of methotrexate resistance in cell lines from 7 patients with small cell lung cancer whose tumours had become refractory to the drug. In 4 of them resistance was due to decreased ability to polyglutomate methotrexate, in another there was increased activity of dihydrofolate methotrexate, in another there was increased activity of dihydrofolate reductase and in two more there were very low levels of thymidylate synthetase.

The clinical relevance of almost all of these other 'single drug' mechanisms of resistance is quite unclear. It would, however, be suprising if the diversity shown in the example above methotrexate is not seen for other agents also.

CONCLUSION

We are still at a very early stage of understanding the way in which drug resistance occurs in the cancer patient and even further from knowing what to do about it. Although a very large volume of data has been generated in laboratory studies over the last 10 years, particularly with regard to the molecular basis of 'typical MDR', there are still very few examples of patients where this mechanism has been shown to be clinically relevant. Data are, however, accumulating rapidly and an 'explosion' of papers describing findings in large numbers of patients can be expected over the next few years. The position with regard to other types of resistance is even more unsatisfactory but again, data should emerge in the near future.

It is already clear from animal studies and from early clinical trials that successful circumvention of resistance using agents such as VRP or BSO will again depend upon improved 'therapeutic ratio'. Expression of P-glycoprotein appears to be a normal function of a variety of body tissues and therefore agents such as VRP may, in addition to possessing their own toxicity, potentiate cytotoxic drug effects in noraml tissues. Similarly, depletion of GSH by BSO can reasonably be expected to increase the sensitivity of all tissues to alkylating agents to a lesser or greater extent.

Clearly such approaches will have no benefit in patients where the drug resistance mechanism being 'circumvented' does not operate. An ideal clinical trial of any strategy should therefore include a

demonstration , prior to therapy, that the relevant mechanism operates in that patients. This is now feasible using either antibodies (probably together with multiparametric flow cytometry) or cDNA probes on tumour biopsy specimens. In addition, in some instance, it will be possible to test agents such as VRP in combination with cytotoxics using in vitro chemosensitivity tests. We are currently adopting this approach with blood sample from leukaemia patients.

It may be that cellular resistance mechanisms may prove to be so ubiquitous and diverse that no strategy will do other than 'switch' the target cell from one mechanism to another. Until, however, we understand more fully the genetic mechanisms controlling the expression of those genes which determine drug sensitivity and resistance, the current empirical approach to resistance circumvention is the best that can be offered in the face of a clinical problem requiring urgent action.

REFERENCES

1. ALLEY M C, SCUDIERO D, MONKS A, HUSEY M L, CZERWINSKI M J, FINE D L, ABBOTT B J, MAYO J G, SHOEMAKER R H, BOYD M R, Feasibility of drug screening with panels of human tumor cells lines using a microculture tetrazolium assay. Cancer Res 48 : 589-601, 1988.
2. ARRICK B A, NATHAN C F. GLUTATHOINE metabolism as a determinant of therapeutic efficacy : a review. Cancer Res 44 : 4224-4232, 1984.
3. BELL D R, GERLACH J H, KARTNER N, BUICK R N, LING V. Detection of P-glycoprotein in ovarian cancer: a molecular marker associated, with drug resistance. J Clin Oncol 3 : 311-314, 1985.
4. BRADLEY G, JURANKA P F, LING V. Mechanism of multidrug resistance Biochim Biophys Acta 948 : 87-128, 1985
5. CANO-GAUCI D F, RIORDAN J R. Action of calcium antagonists on multidrug resistant cells : specific cytotoxicity independent of increased cancer drug accumulation. Biochem Pharmacol 36 : 2115-2123, 1987.
6. CHABNER B A. The oncologic end game. J Clin Oncol 4 : 625-638, 1986.
7. CHAUFFERT B, REY D, CONDERT B, DURMAS M, MARTIN F. Amiodarone is more efficient than verapamil in reversing resistance to anthracyclines in tumour cells. Br J Cancer 56 : 119-122, 1987.
8. CHEN D J, CHIN J E, UEDA K, CLARK D P, PASTAN I, GOTTESMAN M M, RONINSON I B. Internal duplication and humology to bacterial transport proteins in the mdrl (P-glycoprotein) gene from multidrug-resistant human cells. Cell 47 : 381-389, 1986.
9. COLE P C, DOWNES H F, SLOVAK M L. Effect of calcium antagonists on the chemosensitivity of two multidrug resistant cell lines which do not overexpress P-glycoprotein. Br J Cancer 59 : 42-46, 1989.
10. COLEY H M, TWENTYMAN P R, WORKMAN P. Identification of anthracyclines and related compounds which retain preferential activity over adriamycin in multidrug resistant cell lines and further resistance modification by verapamil and cyclisporin A. Cancer Chemoth Pharmacol submitted for publication).
11. COLEY H M, TWENTYMAN P R, WORKMAN P. Improved cellular accumulation is characterisic of anthracylines retaining high activity in human and murine multidrug resistant cells with further enhancement by their

combination with verapamil and cyclosporin A. Manuscript in preparation.
12. COLOMBANT P.M., Robb A, Hess A D. Cyclosporin A binding to calmodulin: a possible site of action on T lymphocytes. Science 228 : 337-339, 1985.
13. CORNWELL M M, GOTTESMAN M M, PASTAN I. Increased vinblastine binding to membrane vesicles from multidrug resistant human KB cells. J Biol Chem 261 : 7921-7928, 1986.
14. CORNWELL M M, PASTAN I, GOTTESMAN M M. Certain calcium channel blockers bind specifically to multidrug-resistant human KB carcinoma membrane vesicles and inhibit drug binding to P-glycoprotein. J Biol Chem 262 : 2166-2170, 1987.
15. CURT G A, JOLIVET J, CARNEY D N. Determinants of the sensitivity of human small-cell lung cancer cell lines to methotrexate. J Clin Invest 76 : 1323-1329, 1985
16. DALTON W S, DURIE B G M, SALMON S E, GROGAN T M, SCHEPER R J, MELTZER P S. Multidrug resistance in multiple myeloma : detection of P-glycoprotein in clinical specimens and reversal of resistance with verapamil. Blood 70 : 834 (abstract), 1987.
17. DANKS M K, YALOWICH J C, BECK W T. Atypical multiple drug resistance in a human leukemic cell line selected for resistance to teniposide Cancer Res 47 : 1297-1301. 1987.
18. FINE R L, FINHEL M S, CURT G A, SCHEPARTZ S A, CHABNER BA. Reversal of adriamycin resistance in CHO/R cells by nitrendipine is not mediated by binding to calcium channel receptors. Proc AACR 25 : 14 (abstract), 1984.
19. FOJO A, AKIYAMA S, GOTTESMAN M M, PASTAN I. Reduced drug accumulation in multiple drug-resistant human KB carcinoma cell lines. Cancer Res 45 : 3002-3007, 1985.
20. FOJO A, UEDA K, SLAMON D F, POPLACK D G, GOTTESMAN M M, PASTAN I. Expression of a multidrug-resistance gene in human tumors and tissues Proc Nat Acad Sci USA 84 : 265-269, 1987.
21. FRANKEL A E. Antibody-toxin hybrids : a clinical review of their use J Biol Resp Mod 4 : 437-446, 1985.
22. GANAPATHI R, GRABOWSKI D. Enhancement : of sensitivity to adriamycin in resistant P388 leukaemia by the calmodulin inhibitor trifluorperazine. Cancer Res 43 : 3696-3699, 1983.
23. GERLACH J H, BELL D R, KARKOUSIS C, SLOCUM H K, KARTNER N, RUSTUM Y M, LING V, BAKER R M. P-glycoprotein in human sarcoma : evidence for multidrug resistance. J Clin Oncol 5 : 1452-1460, 1987.
24. GROS P, CROOS J, HOUSMAN D. Mammalian multidrug-resistance gene: complete cDNA sequence strong homology to bacterial transport proteins. Cell 47 : 371-374, 1986.
25. GUPTAS S, VAYUVEGULA B, SWEET P, STUPECKY M, MURRAY S, JACOBS R, SLATER L. M. Membrane potential changes associated with pleiotropic drug resistance. Clin Res 34 : 881 (abstract), 1986.
26. HAMILTON T C, WINKER M A, LOUIE K G, BATIST G, BEHRENS B C, TSURUO T, GROTZINGER K R, MCKOY W M, YOUNG R C, OZOLS R F. Augmentation of adriamycin, melphalan and cisplatin cytotoxicity in drug-resistant and sensitive human ovarian carcinoma cell lines by buthionine sulfoxamine mediated glutathione depletion. Biochem Pharmacol 34 : 2583-2586, 1985.
27. HARRIS A L. DNA repair and resistance to chemotherapy. Cancer Surveys 4 : 601-624, 1985.
28. HILL B T, DENNIS L Y, Li X T, WHELAN R D H. Identification of anthracyline analogues with enhanced cytotoxicity and lack of cross-resistance to adriamycin using a series of mammalian cell lines in vitro. Cancer Chemoth Pharmacol 14 : 194-201, 1985.
29. HINDENBURG A A, BAKER M A, GLEYZER E, STEWART V J, CASE N, TAUB R N. Effect of verapamil and other agents on the distribution of anthracyclines and on reversal of drug resistance. Cancer Res 47 : 1421-1426, 1987.
30. INABA M, KOBAYASHI H, SAKURAI Y, JOHNSON R.K, Active efflux of daunorubicin and adriamycin in sensitive and resistant sublines of P388 leukaemia. Cancer Res 39 : 2200-2203, 1979.

31. KARTNER N, SHALES M, RIORDAN J R, LING, V. Daunorubicin-resistant Chinese hamster ovary cells expressing multidrug resistance and cell-surface P-glycoprotein. Cancer Res 43 : 4413-4419, 1983.
32. KESSEL D, WILBERDING C. Promotion of daunorubicin uptake and toxicity by the calcium antagonist tiapamil and its analogues. Cancer Treat Rep 69 : 673-676, 1985.
33. KESSEL D, WILBERDING C. Mode of action of calcium antagonists which alter anthracycline resistance. Biochem Pharmacol 33 : 1157-1160, 1984.
34. KOCH G, SMITH M, TWENTYMAN P R, WRIGHT K. Identification of a novel calcium-binding protein (CP22) in multi-drug resistant murine and hamster cells. FEBS Letters 195 : 275-279, 1986.
35. MA D D, SCURR R D, DAVERY R A, et al. Detection of a multidrug resistant phenotype in acute non-lymphoblastic leukaemia. Lancet 1 : 135-137, 1987.
36. MARSH W, CENTER M S. Adriamycin resistance in HL60 cells and accompanying modifications of a membrane protein contained in drugsensitive cells. Cancer Res 47: 5080-5086, 1987.
37. McGOWN A T, EWEN C, SMITH D B, FOX B W. Preclinical studies of a novel anti-miotic agent, amphethinile. Br J Cancer 57 : 157-159, 1988.
38. McGRATH T, CENTER M S. Mechanism of multidrug resistance in HL60 cells: evidence that a surface membrane protein distinct from P-glycoprotein contributes to a reduced cellular accumulation of drug. Cancer Res 48 : 3559-3563, 1988.
39. MERKEL D, HILL S, FUQUA S, CLARK G, DRESSLER L, McGUIRE W. Multiple drug resistance P-glycoprotein gene amplification in human primary breast cancer. ASCO Proceeding 6 : 57 (abstract), 1987.
40. MERRY S, FETHERSTONE C A, KAYNE S B, FRESHNEY R I, PLUMB J A. Resistance of human glioma to adriamycin in vitro: The role of membrane transport and its circmvention with verapamil. Br J Cancer 53 : 129-135, 1986.
41. MERRY S, KERR D, FLANIGAN P, MILROY R, FRESHNEY R I, KAYNE S B. Inherent adriamycin resistance in a murine tumour line. I. Circumvention with verapamil and norverapamil. Br J Cancer 56 : 185 (abstract), 1987.
42. MEYERS M B, BIELDER J L. Increased synthesis of a low molecular weight protein in vincristine-resistant cells. Biochem Biophys Res Commun 99 : 228-235, 1981.
43. MIRSKI S E L, GERLACH J H, COLE P C. Multidrug resistance in a human small cell lung cancer cell line selected in adriamycin. Cancer Res 47 : 2594-2598, 1987.
44. MOSCOW J A, COWAN K H. Multidrug resistance. J Nat Cancer Inst 80 : 14-20, 1988.
45. OZOLS R F, CUNNION R E, KELCHER R W, HAMILTON T C, OSTCHEGA Y, PARRILLO J E, YOUNG R C. Verapamil and adriamycin in the treatment of drug-resistant ovarian cancer patients. J Clin Oncol 5 : 641-647, 1987.
46. POMMOER Y, KERRIGAN D, SCHWARTZ R E. Altered DNA topoisomerase II activity in Chinese hamster cells resistant to topoismerase II inhibitors. Cancer Res 46 : 3075-3081.
47. RAMU A. Structure activity relationship of compounds that restore sensitivity to doxorubicin in drug-resistant P388 cells. In: Resistance to Antineoplastic Drugs. Ed Kessel D. CRC Press 1988.
48. RAMU A, BALUBIGER D, FUKS Z. Reversal of acquired resistance to doxorubicin in P388 murine leukaemia cells tamoxifen and other triparanol analogues. Cancer Res 44 : 4392-4395, 1984.
49. RAMU A. GLAUBIGER D, MARGRATH I T, JOSHI A. Plasma membrane lipid structural order in doxorubicin-sensitive and resistant P388 cells. Cancer Res 43 : 5533-5537, 1983.
50. REEVE J G, RABBITTS P H, TWENTYMAN P R. Cellular concomitants of multidrug resistance in a human large lung carcinoma cell line. Lung Cancer suppl 4 : All, 1988.
51. REECE J G, WRIGHT K A, KOCH G, TWENTYMAN P R. Sensistivity of multidrug resistant EMT6 mouse tumour cells to the cytotoxic and chemosensitisation effects of verapamil and cyclosporin A. Br J Cancer (submitted for publication).

52. RIORDAN J R, LING V. Genetic and biochemical characterisation of multidrug resistance. Pharmac Therap 28 : 51-75, 1985.
53. RUSSO A, CARMICHAEL J, FRIEDMAN N, De GRAFF W, ZOCHNER Z, GLASTEIN E, MITCHELL J B. The roles of intracellular glutathione in antineoplastic chemotherapy. Int J Radiat Oncol Biol Phys 12 : 1347-1354, 1986.
54. SAFA A R, GLOVER C I, MYERS M B, BIEDLER J L, FELSTED R L. Vinblastine photoaffinity labelling of a high molecular weight surface membrane glycoprotein specific for multidrug-resistant cells. J Biol Chem 261 : 6137-6140, 1986.
55. SEHESTED M, SKOVSGAROD T, VAN DEURS B, WINTHER-NIELSEN H. Increase in non-specific absorptive endocytosis in anthracycline and vinca alkaloid resistant Ehrlich ascities tumour cell lines. J Nat Cancer Inst 78 : 171-179, 1987.
56. SEHESTED M, SKOVSGAROD T, VAN DEURS B, WINTHER-NIELSEN H. Increased plasma membrane traffic in daunorubicin resistant P388 leukaemic cells. Effect of daunorubicin and verapamil. Br J Cancer 47 : 1421-1426, 1987.
57. SINHA B K, KATKI A G, BATIST G, Differential formation of hydroxyl radicals by adriamycin in sensitive and resistant MCF-7 human breast cancer tumour cells: implication for the mechanism of action. Biochemistry 26 : 3776-3781, 1987.
58. SINHA L M, SWEET P, STUPECKY M, GUPTA S. Cyclosporin A reverses vincristine and daunorubicin resistance in acute lymphatic leukaemia in vitro. J Clin Invest 77 : 1405-1408, 1986.
59. SLATER L M, SWEET P, STUPECKY M, WETZEL M, GUPTA S. Cyclosporin A corrects daunorubicin resistance in Ehrlich ascites carcinoma. Br J Cancer 54 : 235-238, 1986.
60. SMITH M A, MERRY S, SMITH J G, KAYE S B. Clinically relevant concentrations of verapamil do not enhance the sensitivity of human bone marrow CFU-GM to adriamycin and VP16. Br J Cancer 57 : 576-578, 1988.
61. SUZUKAKA D, PETRO B J, VISTICA D T. Reduction in glutathione content of L-Pam resistant L1210 cells confers drug senstitivity. Biochem Pharmacol 31 : 121-124, 1982.
62. TEW K D, CLAPPER M L, HOFFMAN S J, BOMBER A M. Enhanced efficacy of nitrogen mustards (NM) in combination with glutathione S transferase inhibitors in alkylating agent resistant tumours. Proc AACR 24 : 31 (abstract), 1988.
63. TSURUO T, LIDA H, KITATANI Y, YOKOTA K, TSUKAGOSHI S, SAKURAI Y. Effect of quinidine and related compounds on cytotoxicity and cellular accumulation of vincristine and adriamycin in drug-resistant tumour cells. Cancer Res 44 : 4303-4307, 1984.
64. TSURUO T, LIDA H, TSUKAGOSHI S, SAKURAI Y. Overcoming of vincristine resistance in P388 leukaemia in vivo and in vitro through enhanced cytotoxicity of vincristine and vinblastine by verapamil. Cancer Res 41 : 1967-1972, 1981.
65. TSURUO T LIDA H, TSUKAGOSHI S, SAKURAI Y. Potentiation of vincristine and adriamycin effects in human hemopoetic tumour cell lines by calcium antagonists and calmodulin inhibitors. Cancer Res 43 : 2267-2272, 1983.
66. TSURUO T, LIDA H, TSUKAGOSHI S, SAKURAI Y. Increased accumulation of vincristine and adriamycin in drug-resistant tumour cells following incubation with calcium antagonists and calmodulin inhibitors. Cancer Res 42 : 4730-4733, 1982.
67. TWENTYMAN P R. RESISTANCE modification by non-immunosuppressive cyclosporins. Br J Cancer 57 : 254-258, 1988.
68. TWENTYMAN P R, FOX N E, BLEEHEN N M. Drug resistance in human lung cancer cell lines. Cross-resistance studies and effects of the calcium transport blocker verapamil. Int J Radiat Oncol Biol Phys 12 : 1355-1358, 1986.
69. TWENTYMAN P R, FOX N E, REES J K H. Chemosensitivity testing of fresh leukemia cells using the MTT colorimetric assay. Br J Haemat 71 : 19-24. 1989.
70. TWENTYMAN P R, FOX N E, WHITE D J G. Cyclosporin A and its analogues as modifiers of adriamycin and vincristine resistance in a multi-drug resistant human lung cancer cell line. Br J Cancer 56 : 55-57, 1987.

71. TWENTYMAN P R, FOX N E, WRIGHT K A, WORHMAN P, BROADHURST M J, MARTIN J A, BLEEHEN N M. The in vitro effects and cross-resistance patterns of some novel anthracyclines. Br J Cancer 53 : 585-594, 1986.

72. TWENTYMAN P R, FOX N E, WRIGHT K A, BLEEHEN N M. Derivation and preliminary characterisation of adriamycin resistant lines of human lung cancer cells. Br J Cancer 53 : 529-537, 1986.

73. VAN DER BLICK A M, VAN DER VELDE-KOERTS T, LING, V, BORST P. Over-expression and amplification of five genes in a multidrug-resistant Chinese hamster ovary cell line. Mol Cell Biol 6 : 1671-1678. 1986.

74. WANG A L, TEW K D. Increased glutathione-S-transferase activity in a cell line with a acquired resistance to nitrogen mustards. Cancer Treat Rep 69 : 677-628, 1985.

75. WORKMAN P, DOUBLE J A. Drug latentation in cancer chemotherapy. Biomedicine 28 : 255-262, 1978.

5

CHEMOENDOCRINAL THERAPY IN ADVANCED CANCER

Prof. A.M. Garin

The prevalance of breast cancer in USSR is on the increase. Nearly, 110 women per 100000 were detected in 1986 as compared to 69 in 1975. It has remained a major cause of mortality and morbidity for women in USSR, as in west. The incidence of breast cancer is higher in pre-menopausal women and, is rarely seen in women below the age of 30 years. Evaluation of 780 patients at cancer research centre of Moscow-showed that 25.5% were in stage III, 42.3 percent in Stage II and, 15.1% in stage IV. Only 9.4 percent were detected at an early stage of I. The reported survival rate for patients with breast cancer in USSR is 65 to 70% at the end of 5 years. However, it is well known that not more than 30 percent of the patients survive at the end of 20 years. Thus even in USSR, cancer of breast is a profound problem awaiting an optimal solution.

Progress in the treatment for breast cancer has been due to early diagnosis following mammography, improved understanding of loco-regional treatment like surgery and, radiation, effective adjuvant therapy, understanding of steroid receptors and, other growth factors, better drugs for improved endocrine manipulation and, advances in chemotherapeutic agents.

Adjuvant chemotherapy with CMF, CPE or AC for premenopausal patients with positive axillary node has been

demonstrated by Bonadonna and, others. Spratt and, Byrd calculated that cells disseminate from the main tumour bulk after 21 doublings which is much before it is clinically manifest. It takes 31 doublings for the tumour to become clinically obvious. It is hence not surprising that 35 percent of the patients recur even in node negative patients. Adjuvant chemotherapy with any of the above mentioned combination has proved useful. Cyclophosphamide may be excluded in node negative patients without risking additional recurrence. It may but reduce the chance of second malignancy.

The discovery of oestrogen receptors (ER), progestrone receptors (PR) have rationalised endocrine manipulation in clinical practice. They have been useful in pragnostication also. The distribution of the receptors is never uniform. Basalyx, (data from Moscow center) demonstrated higher level of ER and PR, in post menopausal women as compared to premenopausal women. And also, concentration of ER and PR, increased with increasing age after the menopause.

Receptor concentration decreases following a radical dose of radiation. ER & PR was positive in 29% and 21% of patients following 70 Gy of radiation which is significantly less as compared to pre-radiation levels of 86 and 93 percent. Pre-surgical chemotherapy with CAF in contrast showed an increase of 1.5 times in receptor positive tumours. The implication of this finding is not clear.

Tamoxifen and aminogluthethimide are two important discoveries for endocrine manupulations. Tamoxifen blocks estradiol binding to estrogen receptor on breast tumour. It also reduces circulating estradiol and also, inhibits estrogen stimulated prolactin. This prevents estradiol dependent proliferation of breast tumour. Tamoxifen alone can induce a remission in 30% for an average duration of 10 months. The finnish firm 'Farmos', is investigating a new anti-estrogen similar to tamoxifen, which is 'toremifen'. The drug is under trial. It appears that toremifen can induce remission much swifter than tamoxifen.

Aminoglutathimide which was initially tested for its anticonvulsant properties in 1960 exhibited a propensity to suppress adrenal function. It exhibits anit-oestrogenic properties by blocking the conversion of cholestrol to pregnenolone.

The biochemical mechanism involved is to inhibit the aromatisation of the A ring of the steroid. Several centres in USSR have evaluated the best dosage schedule for AG. Double blind controlled trials have evaluated the effectiveness of Aminoglutethemide at 500 and 1000 mgs strength. It has been demonstrated that AG given at 500 mgs is not only better tolerated but

induces a remission of disease for 186 days which is significantly more than 135 days. It is also observed that patients past the menopause do not respond as well as those who have undergone surgery or, radiation induced ablation or oopherectomy.

Table 1

REGIMEN OF TREATMENT

CTX1.3 G/M²										+	
MTX30 mg/m²										+	
Adr. 50 mg/m²										+	
5-FU 1.3 g/m²										+	
DES 1.3 g/m²										+	
TAM 20 mg											
	1	2	3	4	5	6	7	8	9	10	days

Table II

TWO-COMPONENT REGIMENS

	ER + PR in%	Duration of Remission in months
MTX + 5-FU	45.4	6.3
Mit.C+VLB	40.0	5
Adr.+Vib	30	4.2
Thio-TEPA+ Pharmarubicin	75	9
Adr.+Thio-TEPA	80	10

Cancer of breast has a propensity for an early systemic spread. Chemotherapeutic regimens with various combinations have been tried in the treatment of disseminated disease, one of our combination chemotherapy is described in Table 1. Eight of 17 patients responded. Another 5 patients had stationary disease. Patients had an average remission of 17 months. Many other chemotherapeutic strategies have been utilised in the treatment of disseminated cancer of breasts. The details are shown in table 2. Combination of Adriamycin

Farmambicin with thiotepa had maximum period of remission. The combination however is very toxic. There is a proposal to include colony stimulating factor in the last two reigmens to enhance tolerance. Patients with liver metastasis have a poor prognosis. But it is not a contraindication to attempt a treatment. We at our centre administer CAF, i.e. 5 FU, 400 mg/1m2 on day 1 and 8, Adriamycin 30 mg/m2 day 1 and 8 and, cytoxon 100 mg/m2 administered intravenously from day 1 to 14. The response was seen in 50% of 18 patients evaluated. Patients had a control of the disease for 12.6 ± 1.4 months.

Treatment of disseminated breast disease is both challanging and, frustrating. The best combination of cytotoxic drug needs a discovery. The outlook of patients of disseminated cancer of breast in USSR is no different from entire mankind.

6

RANDOMIZED STUDIES OF EPIRUBICIN-CONTAINING REGIMENS IN BREAST CANCER

P. Hurteloup

Doxorubicin, the first analouge of Daunorubicin, is considered as the most active chemotherapeutic agent against breast cancer. But, while producing a response rate of approximately 40% in patients as first-line chemotherapy and in nearly 20% as second-line therapy after failure or relapse to combination chemotherapy, the use of doxorubicin is limited by its acute side effects, mainly myelotoxicity, as well as its cumulative dose-induced cardiomyopathy (1.4)

Epirubicin, a new anthracycline compound was developed by Farmitalia Carlo Erba in order to improve the therapeutic index of Doxorubicin. This drug has been submitted to extensive clinical studies in breast cancer for more than ten years and now the drug's clinical credentials are well established both for significantly diminished acute and cardiac toxicity in humans.

A phase II study conducted by various authors listed in table I at a dose between 75 mgs to 100 mg/m , attested to the efficacy of epirubicin in lieu of doxorubicin in the treatment of breast cancer. Corososimo and Hong demonstrated equal potential of epirubicin as compared to adriamycin. They also reported reduced myelotoxicity, alopecia gastrointestinal, and cumulative cardiotoxicity (5). These initial good results with epirubicin as a single agent in breast cancer

Table 1

Investigator	Administration Schedule	Patients	Responses %)
Single-Agent Studies			
Bonadonna and Bonfante	escalating doses	20	3 (15)
Ferrazzi et al	75 mg/m²q² wk	14	6 (43)
Hurteloup et al	75 mg/m²q³wk	28	9 (32)
Kolaric et al	80 mg/m² for a period of 2d, q³ wk	13	5 (38)
Robustelli Della Cana et al	75-90 mg/m² q³wk	16	1 (6)
Beretta et al	12.5 mg/wk 8 then 20 qOW	9	3 (33)
Taguchi et al	50 mg/m² d1 + 8 q wk or 50-70 mg/m² q³-wk	32	8 (25)
Jones and Mattsson	20 mg/wk	39	20 (51)
Campara et al	75 mg/m² q³wk	25	4 (31)
Martoni et al	90 mg/m² q³wk	13	4 (31)
Comparative studies			
Bonadonna et al	E:75 mg/m² q³ wk	21	13 (62)
	D:75mg/m² q³wk	21	11 (52)
Van Oostero et al	E:75mg/m² q³wk	32	10 (30)
	D:90 mg/m²	32	10 (30)
Young et al	E:85 mg/m² q³wk	24	6 (25)
	D:60mg/m² q³wk	28	7 (25)
Aboud et al	E:90-100/m² 48/h	11	3 (27)
	E:90-100/m² bolus	7	0
	D:60-70/m²/48 h	8	1 (13)
Rozensweig et al	E:90/m² q³wk	34	9 (26)
	C:18/m² q³ wk	29	1 (3)
Total receiving epirubicin as a single agent		338	104 (31)

Abbreviations E: epirubicin; D, doxorubicin: C, carminomycin; FEC, 5-FU, epirubicin, cyclo-phosphamide; FAC, 5-FU, doxorubicin, cyclophosphamide; q³ wk, 3 weeks; qOW, every other week,

Epirubicin administered as a 48-hours infusion.

Epirubicin administered as an IV bolus.

Doxorubicin administered as a 48-hour infusion.

Adapted from Cersosimo (5)

has led to further studies to substantiate the initial claim and, also, to evaluate its place in poly chemotherapy.

INFLAMMATORY BREAST CANCER : PRIMARY CHEMOTHERAPY

A radomized study comparing FEC and CMF regimens (6).

After initial experience with CMF, undertaken in 1976 which showed an improvement in overall survival when compared with local/regional treatment, Mourali comparing CMF (CPM; 600/m iv - day 1; MTX 40mg/m iv - days 1.8;) and FEC (CPM ; 600mg/m iv - day 1; Epi : 60mg/m iv = day; 5 FU : 600mg/m iv- days 1-8)

Seventy patients suffering from a rapidly progressing breast cancer defined by clinical, mammographic and, thermographic criteria and without metastases, satellite nodules or supraclavicular lymphadenopathy were included in this study. The protocol consisted of three cycles of chemotherapy, followed by radical surgery, a further cycle of chemotherapy, radiotherapy and finally eight cycles of chemotherapy. Patient characterstics were well balanced between two groups and after three cycles of chemotherapy considering the 56 evaluable patients a superior response was clearly noted in favour of Epirubicin containing regimen (table 2). It must be emphasized that there was also a highly significant difference in favour of FEC considering the progression of disease (41% for CMF versus only 7% for FEC). (After surgery when analysing pathological response there was also a superiority in terms of complete histological response in favour of the FEC regimens. (9CR/26 pts-3CR/25 pts). The analysis of surgical specimen showed superior histological regression in favour of EFC regimen. Hence, only FEC regimen is being investigated.

To date only 4 deaths have been observed (FEC : 1, CMF : 3) and no specific conclusions can be drawn yet from this study regarding survival.

Twenty-three patients received more than 500 mg/m^2 of Epirubicin and in none cardiac dysfunction was observed. There was no significant difference in myelotoxicity, but, there was some incidence of nausea, vomiting and alopecia which was more frequent with FEC (table 3).

Advanced BREAST CANCER : Phase III trials compare EFC and FAC regimens. In advanced breast cancer two major multicenter phase II trials were carried out in France (France Epirubicin Study Group -

FESG) (7) and in Italy (IMBSE) (8) comparing EPI with DXR at equal doses (50mg/m^2) in the FEC and FAC combinations.

The first study began in France in 1982 at 11 different centres. Out of 263 patients 230 were evaluable for efficacy (FAC 113) FEC 117) and 244 for fairly well balanced, except for one important prognostic factor reflecting the fact that the extent of the disease was significantly greater in EPI patients than in those with DXR.

In the Italian study activated in February 1983, 497 patients were involved of whom 443 were evaluable for activity. The two experiemental groups were evenly balanced vis-a-vis patient characteristics.

In both studies FEC and FAC showed similar effficacy in terms of response rate, time to response, time to progression and survival time (table 4). The figure 1, pertaining to TMBSE trial, shows that the two survival curves virtually were superimposed (p=0.75)

Regarding cardiotoxicity expressed in terms of CHF a same trend favouring EPI was recorded in both studies (FESG; FAC 3 CHF - FEC, IMBSE : FAC, 4 CHF - FEC, 1 CHF). It bears mention that 59 of the 374 FEC treated patients (16%) received more than 550mg/m^2 of EPI.

Except for cardiotoxicity W.H.O. criteria were used in grading the toxicity observed. In both studies as regards mylotoxicity and gastro-intestinal toxicity, the EPI regimen demonstrated a significantly better tolerance than regimen DXR. Contrasting with the IMBSE study in which there was no difference concerning the frequency and the intensity of alopecia the French study recorded a significant difference favouring the FEC regimen (grade 3 : FEC, 40%; FAC, 64.5%)

Table 2 Inflamatory Breast Cancer : FEC VS CMF

Clinical Response Rate by Treatment Arm
(Evaluation 3 weeks after the 3rd cycle)

	FEC (n=27 pts)	CMF (n=29 pts)
COMPLETE RESPONSE	1	0
PARTIAL RESPONSE	15	6
NO CHANGE	9	11
PROGRESSION	2	12
RESPONSE RATE (CR+PR)	59% (± 19)	21% (± 15)
		P=0.004

In view of these results the FESG using FEC 50 as the standard regimen set about looking for different ways to improve over all treatment.

Table 3 : Inflammatory Breast Cancer : FEC VS CMF

	Toxicity					
	0	1	2	3	4	
GRANULOCYTES (D 28)						
FEC : 315 cycles (92)	305 (92)	8 (0)	2 (0)	-	-	
CMF : 290 cycles (105)	281 (105)	7 (1)	2 (0)	-	-	NS
NAUSEA-VOMITING						
FEC : 315 cycles (92)	97 (39)	49 (20)	166. (32)	3 (01)	-	
CMF : 290 cycles (105)	175 (57)	53 (26)	61 (22)	1 (10)	-	S
STOMATITIS						
FEC : 315 cycles (92)	284 (88)	26 (4)	5 (0)	-	-	
CMF : 290 cycles (105)	293 (105)	4 (0)	0 (0)	-	-	NS
ALOPECIA						
FEC : 32 pts	4 (6)	8 (15)	15 (11)	5 (0)		
CMF : 36 pts	24 (28)	8 (6)	4 (2)	0 (0)		S

THE FESG PROGRAMME IN ADVANCED BREAST CANCER.

1. FESG Trial 02

Taking into account the result of the FAC v/s FEC studies the group started a second randomised trial (FESG, 02) exploring dose dependence and mono versus poly chemotherapy concepts. A new randomised trial was started comparing 'FEC 50' with 'FEC 75', as well as with Epirubicin 75 mg/m^2 as a single agent. From 7/1984 to 7/1987 402 patients were included 364 of whom were evaluable at the time for the interim analysis. The randomisation was stratified by institution and according to bone lesion as unique target. As shown in table 5 the patient characteristics were well balanced among the three arms in the study. The results expressed in terms of efficacy parameters are presented in table 6.

FOLLOWING CONCLUSION WERE ARRIVED AT THE END OF INTERIM ANALYSIS OF FESG. TRIAL 02:

- a significant difference as regards complete responses in favour of FEC 75.

(FEC 75 : 15.5% CR Vs FEC 50 : 6.7% CRP
FEC 75 : 15.5% CR VS FEC 75)

–a significant difference in terms of objectives responses (CR + PR) favouring the polychemotherapy regimen FEC 75 versus the anthracycline alone (Epi 75)

–no significant difference in terms of overall objective response between FEC 50 and FEC 75.

–no significant difference in terms of overall objective responses between FEC 50, and Epirubicin alone.

For the whole population survival was not significant between the 3 arms eventhough survival rate in FEC 75 was higher at 8 months (95%), than FEC 50, and Epi 75, both showing a survival rate of 80% and 79% respectively (fig 2).

As far as toxicity is concerned there is no significant difference between FEC 75 and FEC 50, while Epirubicin alone (75mg/m^2) is better tolerated than the combination regimens (table7,8,9).

2: FESG Trial 03

Based on the favourable results, the September 1987, the FESG initiated a further 3 arm trial exploring does dependence and duration of treatment with FEC 75 as reference arm. The objectives of these trials are

FIGURE 1 : IBSE : PHASE II FAC VS FEC

SURVIVAL TIME ACCORDING TO KAPLAN AND MEIER

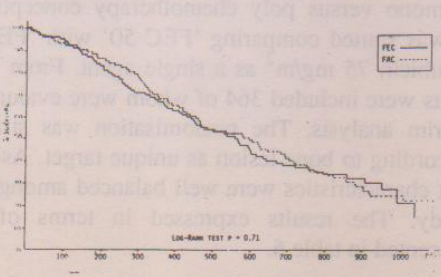


Table 4

FAC v/s FEC-FRENCH AND ITALIAN STUDIES

		FESG			IMBSE	
No response (CR + PR) No of patients response rate	59/113 (52%)	59/117 (50.4%)	NS	125/211 (56.3%)	119/222 (56.3%)	NS
Median time to response (days) Range	70 61-284	93 40-281	NS	not avaialable		
Median duration of responses (days) Range	355 87-1381	315 83-1278	NS	not available		
Median time to progression (days)	270	220	NS	314	273	NS
Median survival time	530	450	NS	613	591	NS

FIGURE 2

OVERALL SURVIVAL TIME SINCE THE BEGINNING OF TREATMENT

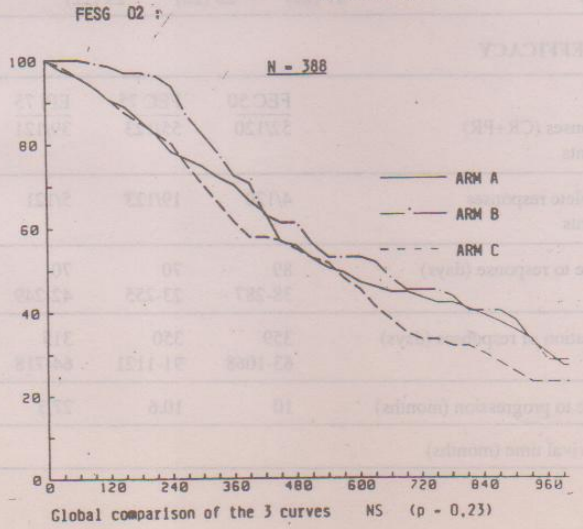


Table 5 :

FESG 02 : Patients Characteristics

		FEC (50)	FEC (75)	E (75)	
NO EVALUABLE PTS (EFFICACY)		120	123	121	
AGE MEDIAN (RANGE)		55 (33-70)	53 (29-70)	55 (26-70)	NS
PERFORMANCE STATUS, MEDIAN (RANGE)		1 (0-2)	1 (0-2)	1 (0-2)	NS
PRIOR ADJUVANT CMF. N(%)		19 (15)	29 (23)	30 (23)	NS
PRIOR RADIOTHERAPY a 6 ADMINISTERED ON LEFT PARASTERNAL FIELD, N (%)		64 (50)	70 (55)	75 (57)	NS
TIME ELAPSED FROM INITIAL DIAGNOSIS TO RANDOMISATION MEAN (MONTHS)		34.5±7.1	43.3±8.1	45.8±5.4	NS
SITE OF DISEASE					
SOFT TISSUE	N (%)	69 (52)	53 (41)	54 (47)	NS
NODE	N (%)	61 (48)	42 (36)	44 (33)	S
LUNG	N (%)	29 (33)	34 (26)	31 (23)	NS
LIVER	N (%)	38 (30)	37 (30)	39 (30)	NS
BONE	N (%)	62 (48)	62 (47)	73 (55)	NS
NO ORGANS SYSTEMS INVOLVED					
1 SITE		43 (34)	61 (48)	52 (39)	
2 SITES		48 (37)	41 (32)	51 (39)	NS
3 SITES		37 (29)	26 (20)	29 (22)	

TABLE 6 FESG 02 EFFICACY

	FEC 50	FEC 75	EPI 75
No of responses (CR+PR) No of patients	52/120	55/123	39/121
No of complete responses No of patients	4/120	19/123	5/121
Median time to response (days) Range	89 38-287	70 23-255	70 42-249
Median duration of responses (days) Range	359 63-1068	350 91-1121	315 64-718
Median time to progression (months)	10	10.6	27.3
Median survival time (months)			

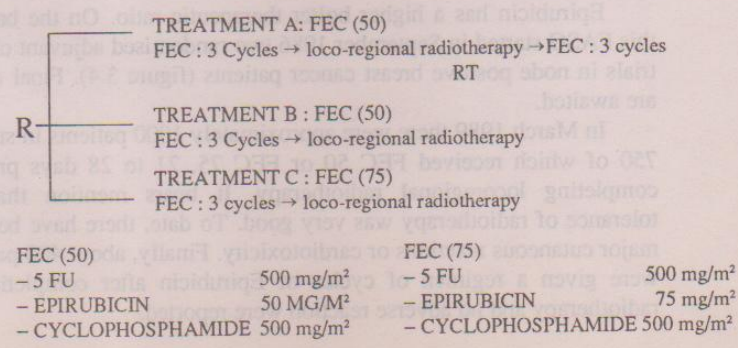
Table 7 FESG 02 : Hematological Toxicity

WHO GRADE	0	1	2	3	4	
GRANULOCYTES (2701 evaluable courses)						
FEC (50)	711	143	86	35	4	
			12.8%			X^2 glabal P=0.0002
FEC (75)	671	129	91	42	2	FEC (50)-FEC (75)=NS
			14.5%			FEC (50) E (75)=S
FEC (75)>E (75)=S	635	88	51	12	1	
			8.2%			
PLATELETS (2788 evaluable courses)						
FEC (50)	1011	2	4	0		NS
FEC (75)	956	2	1	1		
E (75)	806	1	0	0		

FIGURE 3

RADOMIZED TRIAL OF ADJUVANT THERAPY FOLLOWING SURGERY IN PRE-MENOPAUSAL PATIENTS

FASG 01



FEC (50)
- 5 FU 500 mg/m²
- EPIRUBICIN 50 MG/M²
- CYCLOPHOSPHAMIDE 500 mg/m²

FEC (75)
- 5 FU 500 mg/m²
- EPIRUBICIN 75 mg/m²
- CYCLOPHOSPHAMIDE 500 mg/m²

Figure 4

RANDOMIZED TRIAL OF ADJUVANT THERAPY FOLLOWING SURGERY IN POST-MENOPAUSAL PATIENTS

FASG 02

R

- TREATMENT A
  TAMOXIFEN : 30 mg/d. for 3 years
  (+ loco-regional radiotherapy)
- TREATMENT B
  FEC (50) : 3 cycles → loco-regional radiotherapy → FEC (50) : 3 cycles
- TREATMENT C
  TAMOXIFEN : 30 mg/d. for 3 years
  FEC (50) : 3 cycles → loco-regional radotherapy → FEC (50) : 3 cycles
- TREATMENT D : Control
  Loco-regional radiotherapy

– to pursue the escalation of the Epirubicin does hoping to increase response rate and survival (FEC 100 for 4 cycles followed by FEC 50 for 8 cycles), and

– to study the influence on the quality of life and survival of an interimittent FEC 100 treatment (4 cycles, stop until progression of the disease-4 cycles more).

160 patient have been recruited in this till March 1989. Analysis of results is awaited.

THE FRENCH ADJUVANT STUDY GROUP (FASG) PROGRAMME.

Epirubicin has a higher bolter therapeutic ratio. On the basis of this FASG started in September 1986 two randomised adjuvant clinical trials in node positive breast cancer patients (figure 3.4). Final results are awaited.

In March 1989 there were approximately 1000 patients in studies, 750 of which received FEC 50 or FEC 75, 21 to 28 days prior to completing locoregional radiotherapy. It bears mention that the tolerance of radiotherapy was very good. To date, there have been no major cutaneous reactions or cardiotoxicity. Finally, about 400 patients were given a regimen of cycles of Epirubicin after completion of radiotherapy and no adverse reaction were reported.

In conclusion, Epirubicin exhibits similar efficacy as reference anthracycline, but has better therapeutic ratio. The present data not only confirms the role of Epirubicin in cancer chemotherapy but also has opened new exciting possibilities of effective use of Epirubicin in high doses in the treatment of breast cancer.

TABLE 8

FESG 02

WHO GRADE	0	1	2	3	4	
NAUSEA-VOMITING						
N=2780 pts evaluable courses						
FEC (50)	264	333	272	137	9	
				14.3%		X^2 global P=0.15
FEC (75)	228	255	323	141	9	FEC (50) - FEC (75) = NS
				15.7%		FEC (50) - E (75) = NS
E (75)	224	265	219	96	5	FEC (75)>E (75) = S
				12.5%		
ALOPECIA	**0**	**1**	**2**	**3**		
N=329						X^2 global P=0.04
FEC (50)	16	24	21	48	(44.1%)	FEC (50) - FEC (75) = NS
FEC (75)	5	16	25	63	(57.8%)	FEC 50 - E (75) = NS
E (75)	8	22	33	48	(43.2%)	FEC (75)>E (75) = S

Table 9

	PEC (50)	PEC (75)	E (75)
NO OF CGF (treatment discontinuation)	N=124 0	N=126 2	N=124 1
TOTAL DOSE AT CHF OCCURED ($mg.m^2$)	–	600-675	668
NO OF PTS IN WHOM TREATMENT HAD TO BE STOPPED DUE TO CD TOTAL DOSAGE (mg/m^2	2 300-284	2 750-300	2 225-300-450 525-600-690
NO OF PTS WHO PRSENTED A DELAYED CD TOTAL DOSE (mg/m^2	0	3** 750-750-802	6 825
MEDIAN DOSE (mg/m^2) OF PER (range)	306 (47-842)	541 (72-900)	454 (71-882)
NO OF PTS RECEIVING >500 mg/m^2	26 (28%)	67 (52%)	60 (45.5%)

*CHF-** ONE CHF (802 mg/m^2)

REFERENCES.

1. TORMEY D.C. : ADRIAMYCIN (NSC 123-127) in breast cancer. An overview of studies. Cancer Chemotherapy Rep. 6 (part3), 319-327, 1975.
2. HOOGSTRATEN B., GEORGE S.C., SAMAL B., et al : Combination Chemotherapy and Adriamycin in patients with advanced breast cancer. Cancer 38, 13-20, 1976.
3. LEFRAK E. A.,PITHA J., ROSENHEIM,s, et al : Adriamycin (NSC -123,127) Cardiomopathy. Cancer Chemotherapy Rep.6 (3 part),203 - 208, 1975.
4. VON HOFF D.D., LAYARD M. W., BASARA P., et al : Risk factors for Doxorunicin-induced congestive heart failure. Ann. Intern. Med. 91, 710, 1979.
5. CERSOSIMOR R.J. and HONG W. K. : Epirubicin : A review of the pharmocology, Clinical activity and adverse effects of an Adriamycin analogue. J. clin. Oncol 4. 425–439, 1986
6. MOURALI N.: Inflamatory breast cancer : Primary chemotherapy - a randomised study comparing FEC & CMF regimens. ECCO) 4. Satellite Symposia Proceedings - P. 99, Madurid 1-4 November 1987.
7. FRENCH EPIRUBICIN STUDY GROUP : A prospective randomised phase III trial comparing combination chemotherapy with cyclophosphamide flurouracil and either Doxorubicin or Epirubicin. J. Clin. Oncol. 6 : 679-688 , 1988.
8. ITALIAN MULTICENTER BREAST STUDY WITH EPIRUBICIN : Phase III randomised study of Flurouracil Epirubicin and cyclophosphamide v/s Fluorouracil, Doxorubicin and cyclophosphamide in advanced breast cancer. An Italian Multicenter trial, J. Clin Oncol 6 : 976 - 982, 1988.

7

BREAST PRESERVATION BY LUMPECTOMY AND RADIATION FOR LOCALIZED PRIMARY BREAST CANCER NORTHWEST COMMUNITY HOSPITAL EXPERIENCE

P.A. Lobo

From September 1982 through December 1987, 131 women with carcinoma in situ and Stage I and II breast cancer were treated at Northwest Community Hospital in the Department of Radiation Therapy. Two patients developed contralateral breast cancer and were treated conservatively; and, three patients were lost to follow-up without disease at 4,4 and 15 months respectively. One patient expired 5 months following treatment free of disease. These four patients have been excluded from further analyses. Thus, a total of 129 breasts were treated in 127 patients, including 13 breasts in 13 patients for carcinoma in situ. Staging in all except 10 of the patients was on the basis of the pathological findings from the specimen of excision and from the dissected axilla. In 10 patients, an axillary dissection was not performed and the axillae were staged clinically. A TNM staging was used for classification according to the American Joint Committe for staging on cancer. The 13 patients with carcinoma in situ are analyzed separately Follow-up was obtained as of October 1988, the median follow-up for the 116 invasive lesions was 40 months (range 11 -72 months).

In the years prior to 1982, the majority of patients at North-West Community Hospital with breast cancer were treated by some form of mastectomy. Occasionally very old, medically inoperable patients or

patients who refused mastectomy were treated individually by some form of limited surgery, with or without radiation therapy. The availability of data on the conservation management of breast cancer from several institutions, includindg the National Surgical Adjuvant Breast Project (NSABP) study, has had an influence on how early localized breast cancers are treated at this institution. 1,2,5. The increased use of mammography has certainly contributed to the earlier diagnosis of the primary breast lesion and permitted a greater number of women to opt for breast preservation.

CARCINOMA IN SITU

Table I describes in detail clinical profile, disease free survival (DFS) and current status. The median follow-up of the 13 patients is 20 months (range 12-70 months)

INVASIVE CARCINOMAS

A Total of 116 breasts were treated in 114 women with ages ranging from 23-84 years. Seventy patients were above the age of 50 at the time of treatment of the primary breast cancer. Tables II and III show the age and TNM distribution respectively of the 116 lesions treated, with a median follow-up of 40 months (range 11-72 months).

TREATMENT TECHNIQUE

All patients, excepting 2, underwent a complete excision of the primary lesion in the breast. In 2 patients, a re-excision was desired but was not possible because of medical contraindication. In those patients with an incomplete excision, a reexcision was always carried out. An axillary dissection was carried out for all invasive cancers unless the patients medical condition or age precluded it. Approximatley 10 days to 2 weeks follwing suregey, external radiation therapy was begun to the whole breast, usually on Cobalt by a pair of opposing tangential beams, with treatment verification performed at the time of first treatment. Wedge filters were inserted in one or both beams whenever necessary for better dose distributions. If only one wedge filter was required, it was placed preferentially in the lateral opposing field. The routine use of bolus was avoided, except in the patient in our series with a T4 b lesion by virtue of localized invasion of the dermis by the underlying tumour. Earlier on a few patients were

given prophylactic radiation therapy to the peripheral lymphatics. Since the middle of 1983, this policy was virtually abandoned. Its use has been restricted to those patients whose axillae are not surgically treated or in whom pathological examination reveals extensive lymph node involvement, with extracapsular perinodal involvement of the axillary contents. In these patients the apex of the axilla was treated along with the supraclavicular lymph nodes. The dissected portion of the axilla was excluded from the radiation field.

The whole breast was radiated to a mid-plane dose of 45 Gy, given over a period of 5 weeks in 1.8 Gy daily fractions (5 days a week) in patients scheduled to have a boost. In those patients who did not receive a boost, the whole breast was treated to dose of 50 Gy in 6 weeks in 1.8 Gy daily fractions. Patients with larger breasts were treated with a combination of radiation from Cobalt and 15 MeV photons from a Linear accelerator. An external boost was usually given by an electron beam of appropriate energy to an additional dose of 15 Gy. Patients receiving an interstitial boost by Iridium 192 single or double planar implants were usually rested for one to three weeks following the completion of the external whole breast irradiation. The dose given by interstitial therapy was 20 - 25 Gy, since 1985, this has been reduced to 15 Gy. The dosimetry for the interstitial implants was done by the Paris system.

SYSTEMIC CHEMO HORMONAL THERAPY

The use of systemic chemo therapy was mainly restricted to patients with positive lymph nodes. Cytoxan, Methotrexate and 5-Fluorouracil (CMF) was given in pre-menopausal patients for 6 cycles and Tamoxifen in post-menopausal patients. Only one patient in this series with negative lymph nodes ($T_1N_0M_0$) received a 6 cycles of CMF prophylactically. Until the guidelines for the duration of Tamoxifen therapy becomes clear, patients will receive it indenfinitely or until progression.

One patient with $T_1N_0M_0$ (axilla undissected), whose tumor margins were positive histologically, was prophylactically placed on Tamoxifen. In those patients who received systemic chemotherapy, the first cycle of chemotherapy was initiated within a week of surgery. This was followed within three weeks with external radiation therapy to the breast. The second cycle of chemotherapy was administered during the 5th week of external radiation therapy. During the second cycle, a 50% dose reduction of Methotrexate and 5 Fluorouracil was made to

Table I CARCINOMA IN SITU

Patient		Surgery		Nodal Status	Radiation Therapy				NED and Overall Survival	Current Status
					Histology		Boost			
#	AGE	Lumpectomy	Axillary Dissection			External Beam Dose	Interstitial Implant	External		
1	64	yes	none	–	intraductal	45 Gy	yes		70 months	Alive NED
2	46	yes	none	–	intraductal	45 Gy	yes		50 months	Alive NED
3	35	yes	none	–	intraductal	45 Gy	yes		41 months	Alive NED
4	57	yes	yes	–	intraductal	45 Gy	yes		24 months	Alive NED
5	68	yes	yes	–	intraductal	50 Gy	no boost		24 months	Alive NED
6	50	yes	yes	–	intraductal	50 Gy	yes		18 months	Alive NED
7	39	yes	yes	–	intraductal	45 Gy	yes		14 months	Alive NED
8	51	yes	yes	–	intraductal	45 Gy	yes		14 months	Alive NED
9	44	yes	yes	–	intraductal	45 Gy	No boots		13 months	Alive NED
10	47	yes	yes	–	intraductal	45 Gy	yes		12 months	Alive NED
11	50	yes	none	–	intraductal	50 Gy	No boost		12 months	Alive NED
12	46	yes	none	–	lobular	45 Gy	yes		20 months	Alive NED
13	57	yes	none	–	lobular	45 Gy	yes		43 months	Alive NED

Median follow-up for the group is 20 months

avoid serious skin side effects. The remaining cycles of chemotherapy were administered without any further dose modification for a total of six cycles. Three patients were given an Adriamycin containing regimen. These patients had histologically extensive lymph nodal involvement.

TABLE II AGE DISTRIBUTION . PATIENTS WITH INVASIVE CANCER

(23-84 years)

Age range	Number of patients
20-30	2
31 - 40	17
41 - 50	27
51 - 60	23
61 - 70	26
71 - 80	18
81 - 84	3
Total	116 patients

2 patients had a contralateral breast cancer
Treated conservatively

Table III T N M stage distributions - invasive cancers

Axilla pathologically stage	number
$T_1 N_0 M_0$	63
$T_1 N_1 M_0$	21
$T_2 N_0 M_0$	16
$T_2 N_1 M_0$	5
$T_4 b N_1 M_0$	1
Subtotal	106
Axilla clinically staged	
$T_1 N_0 M_0$	5
$T_2 N_0 M_0$	5
Subtotal	10
Total	116

PATIENT FOLLOW-UP

Following the completion of radiation therapy, patients were seen every six months for a clinical examination which included an examination of the breasts and lymph node bearing areas. A complete blood count and blood chemistry were also obtained at each visit. Baseline mammography of the treated breasts was established at six months. This was repeated at six month intervals for the first three years. Mammography of the untreated breast was obtained once a year. Patients were instructed to perform monthly breast self-examination.

RESULTS

PATIENTS WITH IN-SITU LESIONS

As seen in Table I, a total of 13 patients were treated (11 intraductal, 2 lobular) with a median follow-up time of 20 months (range 12-70 months). Seven out of 11 patients with intraductal cancer were subjected to an axillary dissection. In none of the seven patients were the nodes found to be involved histologically by metastatic cancer. All the patients are alive and free from local breast relapse or distant metastases. None of the patients in this group have developed a cancer in the contralateral breast.

PATIENTS WITH INVASIVE CARCINOMA HISTOLOGY

The majority of patients with invasive cancer had an infiltrating ductual adenocarcinoma. Less than 10% of the patients had an infiltrating lobular cancer.

NODAL METASTASES IN PATIENTS WITH SURGICALLY STAGED AXILLAES

There were 84 patients with T_1 lesions ($\leq$ 2 cm), 21 of whom were found to have metastatic nodal disease (Table III). Of the 21 patients with T_2 lesions (2- 5 cms), 5 Were found to have histological involvement of the lymph nodes (Table III). One patient had a T_4b lesion by virtue of dermal infiltration demonstrated histologically. Axillary dissection in this individual revealed metastatic disease in the lymph nodes. None of the 10 patients whose axillae were staged clinically presented with palpable axillary lymph nodes.

RE-EXCISION OF THE PRIMARY SITE

CARCINOMA IN SITU

Of the 11 patients with intraductal carcinoma, 2 underwent

re-excision of the primary site. One of the patients was found to have residual intraductal carcinoma with histologically negative margins.

INVASIVE CANCERS

Histologically, nineteen patients with invasive cancer were found to have disease extension to the margins of resection. Eighteen out of 19 patients underwent a re-excision. One patient with histologically positive margins was not subjected to a re-excision because of poor medical condition. This patient received an external boost given by an electron beam. Five out of 18 patients who underwent a re-excision were found to have residual cancer, usually, microscopic. All these patients had histologically clear margins on re-excision.

LOCAL CONTROL

Out of 89 T_1lesions ($\leq$2 cm on path exam) with a median follow-up time of 40 months, two patients (2/88) have developed local skin recurrences in the treated breast at 24 months and 28 months, respectively. The axilla in patients #3 (table IV) was clinically staged. She underwent a modified redical mastectomy for her recurrence. Histological examination revealed metastasis to the lymph nodes. Patient #2 (table IV) had a simple mastectomy for her breast relapse. Three out of 4 surgical margins were histologically involved with disease.

Twenty-six T_2 lesions were treated with a median follow-up time of 42 months. One local recurrence (1/26) was noted at 35 months (Table IV).

The three recurrences were noted at 24, 28 and 35 months with follow-up times of 31, 46, and 43 respectively (Table IV). Accordingly, a total of 67 patients with T1 and T2 lesions have been followed for 36 months or more, giving a breast relapse rate at 3.0% (2/67) (Table VI.) The one patient with T_4 b (skin) N_2 M_o is now 65 months post-treatment, and is free from breast recurrence and distant disease, and is still on Tamoxifen.

DISTANT METASTASES

Table V lists individually the patients who developed distant metastasis. A total of 10 patients developed distant metastatic disease

TABLE IV BREAST RELAPSE

Stage		Site	Mode of presentation	Time interval from treatment	Treatment for recurrence	Current status
Axilla surgically staged						
1.	$T_2 N_0 M_2$	of original primary	Increasing mass clinically and on Serial mammography	35 months	Simple mastectomy plus systemic chemotherapy prophylactically	Alive NED 43 months
2.	$T_1 N_1 M_0$	skin of treated breast	Extensive oedema and erythema involving skin and subcutaneous tissues, without any underlying mass	24 months	Toilet mastectomy (3 out of 4 margins positive) Patient on systemic chemotherapy	Alive with disease 31 months
3.	$T_1 N_0 M_0$	skin of treated breast	Multiple 2-3 mm erythematous nodules distributed around the nipple-areola Complex in an Oedematous breast without an obvious underlying mass	28 months	Modified radical mastectomy. Lymph node involved histo-logically. Patient was placed on systemic chemotherapy	Dead at 46 months from cancer Patient developed bone mets at 34 months

All patients received external radiation therapy to 45 Gy rad plus a two planar interstitial breast implant for and additional 25 Gy in #1 and 2 a dose of 37 Gy in pt#3.
Patient #2 received systemic chemotherapy at the time of original treatment.

TABLE V DISTANT METASTASIS

	TNM	Site of first mets	Systemic therapy given initially	Disease free interval (NED)	Overall survival	Current status
Axilla surgically staged						
1.	$T_1 N_0 M_0$	Bones		21 months	50 months	Dead from disease
2.	$T_1 N_0 M_0$	Scalp		20 months	50 months	Alive in remission on chemotherapy
3.	$T_1 N_1 M_0$	Bones	Tamoxifen	28 months	58 months	Dead from disease
4.	$T_1 N_1 M_0$	Brain	No therapy	26 months	3 months	Dead from disease
5.	$T_1 N_1 M_0$	Bones	Chemotherapy	28 months	50 months	Dead from disease
6.	$T_2 N_0 M_0$	Subcutaneous tissues of arm supraclav lymph nodes		26 months	70 months	Alive in remission on chemotherapy
7.	$T_2 N_0 M_0$	?		?	46 months	Dead from disease
8.	$T_2 N_1 M_0$	Bones	Chemotherapy	15 months	29 months	Dead from disease
Axilla clinically staged						
9.	$T_1 N_0 M_0$	Bones		34 months	46 months	Dead from disease
10.	$T_2 N_0 M_0$	Brain		36 months	4 months	Dead from disease

Median time to recurrence - 6 months (15-36 months)

mainly to bones, brain, and subcutaneous tissue at a median time of 26 months (15-36 months). Eight out of 10 patients are dead from disease. Two patients are alive and in complete remission on systematic chemotherapy. Sixty-eight patients with T_1 and T_2 lesions have been followed for more than 36 months. The 3 year distant metastatic rate is 15.0% (10/67). The overall survival rate is 88.0% (59/67), and disease free survival rate is 85.0% (57/67)

TREATMENT SIDE-EFFECTS

The side-effects usually encountered during external radiation therapy included erythema, hyperpigmentation with moist desquamation in the inframammary fold and lateral chest wall in a few patients (less than 10%). The patients with large pendulous breasts and those receiving systematic chemotherapy were more prone to develop skin reaction. One patient developed an intense inflammation of the entire breast with oedema of the organ at 16 GY. External radiation therapy was stopped for a period of 10 days, during which time the patient received antibiotic therapy prophylactically. She was subsequently able to complete the treatment without any further events. This patient had not received prior chemotherapy.

Only one patient developed a complication subsequent to interstitial implant. Three weeks after receiving an interstitial implant, the patient developed an abscess confined to the implanted area. Following incision, drainage, and a course of antiboitic therapy, the infection was controlled. Healing was very slow to occur and took nearly 10 months. The patient is currently completely healed and asymptomatic. The healed area contains 1.5 x 1 x 1.5 cm retraction of the breast and the cosmetic appearance has been altered. This patient received systemic chemotherapy containing Adriamycin prior to the interstitial implant as extensive nodal involvement was present. The patient is currently alive and disease free at 56 months. The complication rate for patients receiving an implant was approximately 1% (1/92).

COSMETIC RESULTS

At a median follow up time of 40 months, the cosmetic results of the treated breasts appear to be good. This is as judged by patient satisfaction and comparison with the opposite breast. During the 18

months following treatment, approximately 25% of the patients developed a firming of the breast parenchyma. A noticeable softening was observed to occur in the beginning of the second year. By the end of the third year, the breast parenchyma of the treated breast was found to be similar to that of the untreated breast. The patient who developed a complication following the interstitial implant had a poor cosmetic outcome. It is our observation that patients who undergo biopsy and axillary dissection through two separate incisions, regardless of location of the primary tumour, have the best cosmetic appearance following treatment.

CONTRALATERAL BREAST CANCER

Three patients have developed a second primary in the opposite breast at 8, 10 and 64 months respectively. The first two patients opted for breast preservation; and, the third chose to have a bilateral mastectomy. The mastectomized breast which was previously irradiated was histologically free of disease at 64 months following treatment. None of these patients have developed distant metastases; all are alive and free of disease.

CONCLUSION

Our early experience treating carcioma in situ, Stage I and II breast cancers by lumpectomy and radiation plus systemic chemotherapy (when given) is tolerated well by patients. All the local recurrences and distant metastases that have occured in our patients have been observed within a period of 36 months from the date of diagnosis. The 3 year local recurrence rate of 3.0% (2.67), distant metastatic rate of 15.0% (10/67), disease free survival of 85.0% (59/67) (Table VI) compare favourably with the experience of others. 1,2,5 The outcome of the patient who developed the abscess with subsequent protracted healing could perhaps have been avoided by placing the incision for drainage away from the high dose area in the implanted breast.

The data from Fisher's study has had a major impact on our treatment policies.1. Presently, we do not treat patients with lobular carcinoma in situ whose disease is excised with clear margins. We continue to treat patients with intraductal carcinoma, although the use of routine axillary dissection is hard to justify. Upon the completion of

TABLE VI 3 YEAR ACTUAL BREAST RELAPSE, DISTANT METASTASIS, DISEASE FREE AND OVERALL SURVIVAL FOR 67 EVALUABLE PATIENTS (T1 & T2)

T N M category	Number evaluated at 3 years	Number experience breast	Distant metastases	Number dead from disease relapse	Number alive
Axilla surgically staged					
$T_1 N_0 M_0$	37	0	2	1	36
$T_1 N_1 M_0$	14	0	3	3	11
$T_2 N_0 M_0$	7	1 ER 3 PR 3	2	1	6
$T_2 N_1 M_0$	2	1	1	1	1
Axilla clinically staged					
$T_1 N_0 M_0$	2+	1 ER 3 PR 3	1	1	1
$T_2 N_0 M_0$	5	0	1	1	4
	67	2	10	8	59

BRR=2/67=3% DMR=10/67 = 15% DFS = 57/67 = 85% OS = 59/67 = 88%

ER = estrogen receptors PR = progesterone receptors BRR = breast relapse rate DMR = distant metastatic rate DFS = disease free survival OS = overal survival

+ one of the patients T N M (axilla clinically staged) developed an axillary recurrence. The axilla was initially treated with radiotherapy. The patient underwent an axillary dissection and is on Tamoxifen, free of disease. This patient also had a prophylactic re-excision of the tumour bed at the time of axillary dissection, no tumour was evident.

an excision with histologically clear margins, patients with invasive lesions are accepted for breast preservation. If any doubts exist, patients are subjected to a re-excision of the tumour bed. Only those patients who have a medical contraindiction or refuse further surgical intervention are treated without reexcision

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REFERENCES:

1. FISHER, B., BAUER M., MARGOLESE R. et. al: Five-year results of a randomised clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. New Eng Journal of Med, 1985; 312, 665-773.
2. HARRIS, J.R. HELLMAN, S.,: The results of primary radiation therapy for early breast cancer at the joint centre for radiation therapy, in HARRIS, J.R., HELLMAN. S., SILEN, W (ED): Conservative management of breast cancer: New surgical and radiotherapeutic technique. Philadelphia, J.B. Lipicott, 1983, 47-52
3. LOBO, P.A., KHAN, F.R., Conservative management of breast cancer by lumpectomy and radiating, Comprehensive Therapy. September 1985, 11:9, 16-25
4. LOBO, P.A. SHETTY, M.R. Treatment of breast cancer, July 11, 1985, New Eng Journal of Med, 313:2, 117
5. PIERQUIN, B., OTMEZGUINE, Y. LOBO, P.A. : Conservative management of breast cancer: The Creteil experience. Acta

8

PRESENT STATUS OF TOTAL BODY IRRADIATION FOR BONE MARROW TRANSPLANTATION IN JAPAN

Toshihiko Inoue

INTRODUCTION

The brilliant success of Thomas in the 1970s (1), led to the belief that bone marrow transplantation (BMT) is a sole curative treatment modality for high-risk leukemia. In addition a supralethal dose of total body irradiation (TBI) was widely accepted as form of preparation for BMT. Increase in number of BMT among various hospitals resulted in the large variety of TBI methods.

In 1981, TBI subcommittee in Japan for exchange of information, was organised by Inoue. It set out to collect the basic as well as clinical data concerning TBI for BMT. The Subcommittee proposed the standardized prescription of TBI dose and summarized TBI technique among 7 hospitals. In 1982, the Sub-committee reported the actual conditions of TBI time-schedules and dose schemes in order to promote the co-operative study in Japan. In 1983, the actual conditions of TBI for BMT were surveyed, and prognostic factors were analyzed for acute leukemia patients who underwent allogeneic BMT in 14 hospitals (2).

METHODS AND MATERIALS

Clinical data of BMT were obtained from Japanese BMT

Registry.' Records of 667 patients who underwent BMT from January 1975 through December 1987 were collected from 38 of participating hospitals. Before December 1980, only 43 patients received BMT. Annual number of patient registry was 20 or less, and total number of hospitals was 9 as of 1980. Since 1981, BMT cases increased rapidly year by year, and annual number of patients reached more than 100 in 1985. In 1987, records of 167 patients were collected from 38 of participating hospitals (Fig. 1).

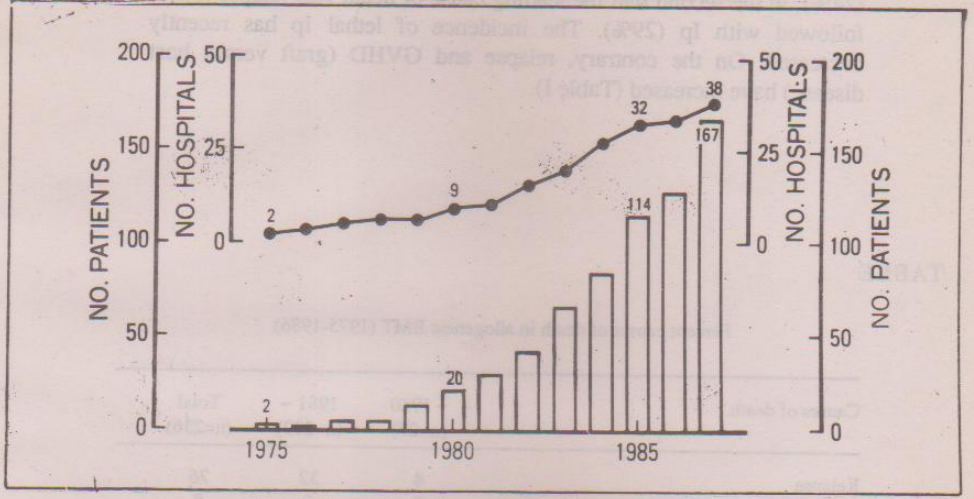

Fig. 1 Annual number of patients and cumulative number of hospitals in Japanese Bone Marrow Transplantation Registry (1975-1986).

One hundred and eightysix patients were diagnosed as having acute lymphocytic leukemia, 183 acute non-lymphocytic leukemia, 96 chronic myelocytic leukemia, 9 myelodysplastic syndromes, 63 malignant lymphoma, 34 solid tumours, 89 aplastic anemia, and 7 severe combined immunodeficiency. Ninety patients received autologous BMT, 551 allogenic, and 26 syngeneic. Follow-up data were up-dated in September 1988.

The fourth and fifth national surveys of TBI were performed by TBI subcommittee in July 1987 and August 1988, respectively. Technical reports of TBI were obtained from 42 of participating hospitals in Japan.

Survivals and the probability of interstitial pneumonitis (Ip) were calculated according to the method of Kaplan-Meier (3). The statistical significance of the result was tested by logrank test (4).

Results

Of 415 patients who received allogeneic BMT before December 1986, 236 patients (57%) have died as of September 1988. The major causes of death were Ip (30%), relapse (26%) and infections (11%). When the dead cases were divided into two groups before and after 1981, there was differences in the eause of death between two groups. While in the first half major causes were Ip (54%) and infections (24%), in the second half the leading cause of death was relapse (32%) followed with Ip (29%). The incidence of lethal Ip has recently decreased. On the contrary, relapse and GVHD (graft versus host disease) have increased (Table I).

TABLE

Percent causes of death in allogeneic BMT (1975-1986)

Causes of death	– 1980 (n=27)	1981 – (n=209)	Total (n=236)
Relapse	4	32	26
Graft versus host disease	0	8	8
Interstitial Pnemonitis	54	29	30
Septicemia	24	9	11
Others	18	22	25

(Sep. 1888)

Three hundred and twenty leukemia patients who underwent allogenic BMT were historically divided into three groups. Group A included 27 patients who underwent BMT before December 1980. Group B consisted of 64 patients who received BMT between 1981 and June 1983. Group C contained 229 patients who were treated from July 1983 through 1986. Three-year survivals were 4%, 34%, and 44% in groups A, B and C, respectively. These differences were highly significant (p=0.0001) (Fig. 2)

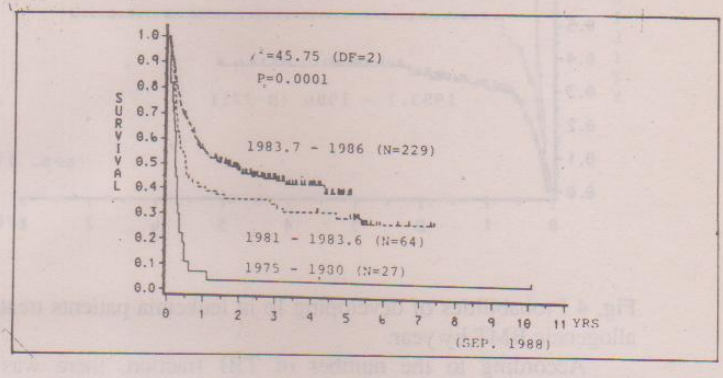

Fig. 2 Survivals of leukemia patients treated with allogeneic BMT by year.

According to the patient condition, 3-year survival was 52% for 163 acute leukemia patients in remission without infection at the time of BMT, and 19% for the remaining 91 patients. There was statistically significant difference between two groups (p=0.0001) (Fig. 3).

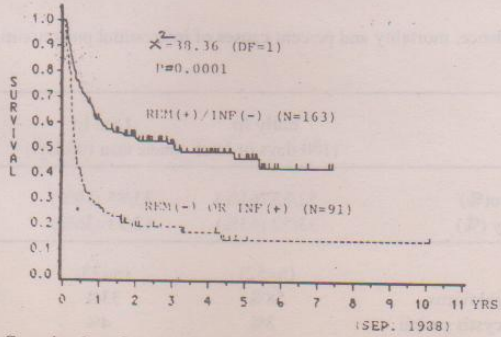

Fig. 3 Survivals of acute leukemia patients treated with allogenic BMT by clinical conditons. REM + remission; INF + infection.

Probabilities of developing Ip at one year were 92%, 52%, and 32% in groups A, B and C, respectively (Fig. 4). There were highly significant differences among these groups (p=0.0001).

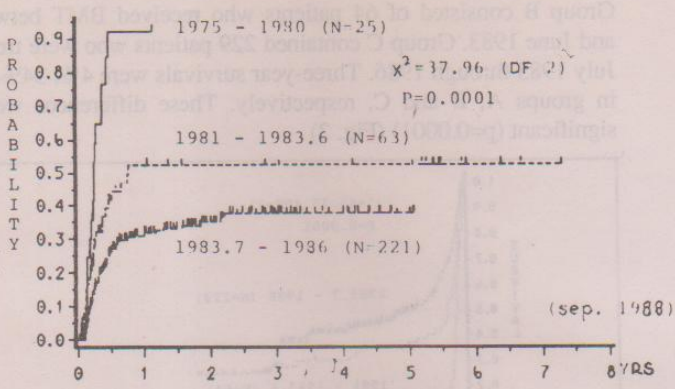

Fig. 4 Probabilities of developing Ip in leukemia patients treated with allogeneic BMT by year.

According to the number of TBI fraction, there was highly significant differences in the developing Ip between single dose TBI and fractionated TBI (p=00.0001). Probabilities of developing Ip at 3 years were 64% in the former group and 39% in the latter group. (Fig. 5)

TABLE II

Incidence, mortality and percent causes of interestitial pneumonitis (1981-1986)

	Early Ip (100 days or less)	Late Ip (more than 100 days)	Total
Incidence(%)	52/85 (61%)	33/85 (39%)	85/269 (32%)
Mortality (%)	33/52 (63%)	12/33 (36%)	45/269 (17%)
Causes	(n=52)	(n=33)	(n=85)
Cytomegalovirus	58%	33%	48%
Pneumocystis carinii	3%	4%	4%
Idiopathic	24%	44%	32%
Others	15%	19%	16%

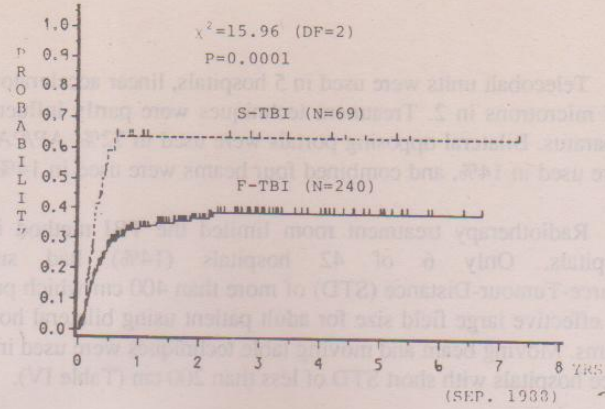

Fig. 5 Probabilities of developing Ip in leukemia patients treated with allogeneic BMT by fraction of TBI. S-TBI = single dose TBI; F-TBI = fractioned TBI.

Of 269 leukemia patients who received allogeneic BMT from 1981 through 1986, 85 patients (32%) developed Ip. Mortality rate was 17% (45/269). According to the time of occurance, Ip was divided into two groups, i.e., early and late Ip groups. Of 85 patients with Ip, 52 patients (61%) developed Ip within 100 days after BMT. The remaining 33 patients (39%) developed Ip more than 100 days after BMT. Mortality rate was higher in the early Ip group than in the late Ip group. In the early Ip group, cytomegalovirus was the most frequently causative organism. On the contrary, radiation associated idiopathic Ip was the leading cause in the late Ip group (Table II).

TABLE III

Treatment techniques and apparatus of TBI

Technique	Co-60	X-ray (MV)				Total
		4	6	8	10	
Bilateral	3	5	5	1	16	30
AP/PA	1	2	0	0	3	6
Combined	1	1	1	0	3	6
Total	5	8	6	1	22	42

TBI

Telecobalt units were used in 5 hospitals, linear accelerators in 35 and microtrons in 2. Treatment techniques were partly influenced by apparatus. Bilateral opposing portals were used in 72%. AP/PA beams were used in 14%, and combined four beams were used in 14% (Table III).

Radiotherapy treatment room limited the TBI method in most hospitals. Only 6 of 42 hospitals (14%) had sufficient Source-Tumour-Distance (STD) of more than 400 cm which produced the effective large field size for adult patient using bilateral horizontal beams. Moving beam and moving table techniques were used in two of three hospitals with short STD of less than 200 cm (Table IV).

TABLE IV

Source-Tumour-Distance (STD) and field size of TBI

STD	Long axis (cm)				
(cm)	35-50	51-100	101-125	125-150	151-250
100-200	2#*	0	0	0	1 $
201-300	0	1	6	2	1
301-400	0	3	10	9	1
401-500	0	0	0	4	2

short STD (110 cm).
* Moving couch (100 cm)
$ Moving beam (180 cm)

Supine position was most comfortable for TBI patients and used in 69% of the hospitals However, in most hospitals limitations of the STD forced the adult patient in supine position to bend his or her knees. On the other hand, lateral decubital position provided the patient with more homogeneous dose of TBI and lung shield for dose reduction with ease. However, this position was used in only 17% of the hospitals (Table V).

There were various dose specification systems. A point dose on midline of the patient was used to report the TBI dose in many hospitals (79%). Specification of the average dose at several reference points, such as shoulder, thorax, abdomen and pelvis, was used in 8 hospitals (19%), but could not be applied to calculate the thickness of compensator or bolus (Table VI). Doses at various points were monitored during TBI in 29 hospitals (69%).

Thermoluminescent dosimeter was used in 19 hospitals, ionization chamber in 19 and semi-conductor dosimeter in 3.

Various time-dose-fractionation patterns were reported and were divided into 5 groups according to the total dose and fraction size. One of the most widespread TBI schedules was 12 Gy in 6 fractions over 3 days. Concerning the dose rate of TBI, high-dose rate treatment was used in 5 hospitals, mid-dose rate in 28, and low-dose rate in 9 (Table VII and Fig. 6). Mean dose rate was 6 CGy/min.

TABLE V

Patient positioning during TBI

1)	Supine	29
2)	Lateral decubital	4
3)	Reclining	2
4)	Seated	1
5)	1) + 2)	2
6)	2) + 3)	1
7)	1) + prone	2
8)	5) + prone	1

The lung doses were reported from 36 hospitals. In 11 hospitals lung was partially shielded. In 20 hospitals lung compensator was used for dose homogeneity. However, in 5 hospitals no lung shield was employed and so lung dose was estimated about 1.2 times higher than the nominal TBI dose (Fig. 7).

In 81% of the hospitals compensator or bolus was used to correct the dose inhomogeneity due to contour variations, e.g., head and neck region. In 55% of the hospitals eye shield was used for dose reduction.

Concerning the preparation regimen, many groups (26/30) adopted the traditional regimens with chemotherapy followed by TBI. However, the remaining 4 groups used the preceding TBI preparation regimen. Median times to white blood cell count nadir were different between two groups, i.e., 7 days in chemotherapy/TBI group and 3 days in TBI/chemotherapy group. However, there was no difference between two groups, when the time was calculated from the last day of TBI. It was indicated that the time to white blood cell count nadir was more influenced by TBI compared to chemotherapy (Table VIII).

There were two different opinions concerning the patient conditions during TBI. Some prefered the patient in bioclean box during TBI to reduce infections, Ip and GVHD, but others prefered the

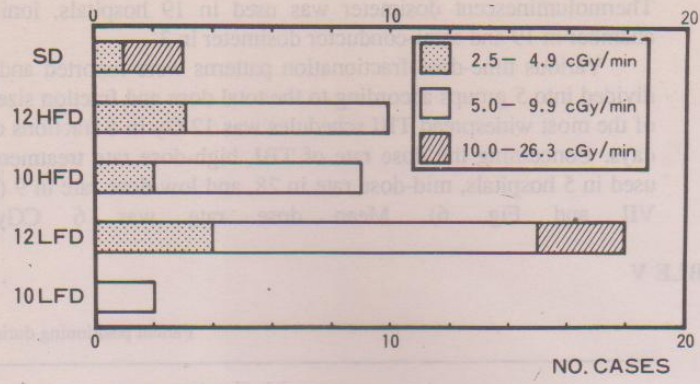

Fig.6 Fraction and does rate of TBI.

TABLE VI

TBI does specification

One Point	33
Shoulder	3
Thorax	2
Abdomen	4
Pelvis	22
Trunk	2
Average	8
Unknown	1

TABLE VII

TBI franctionation.

Nominal	Dose (Gy)/frx/day
Single dose (SD)	9,10,
12 Gy high fraction dose (12 HFD)	12/4/4, 12/5/5, 12/4/2, 12.5/5/3
10 Gy high fraction dose (10 HFD)	10/3/3, 10/4/4. 10/4/2, 10.8/4/3
12 Gy low fraction dose (12 LFD)	12/6/6, 12/6/3, 12/6/4
10 Gy low fraction dose (10 LFD)	10/5/5 10/6/3

patient in ordinary manner to deliver more precise TBI dose by correcting the inhomogeneity of contour variations or compensating the tissue heterogeneity. When the preceding TBI preparation regimen was adopted, there was no need to keep patient in bioclean box during TBI (Table IX).

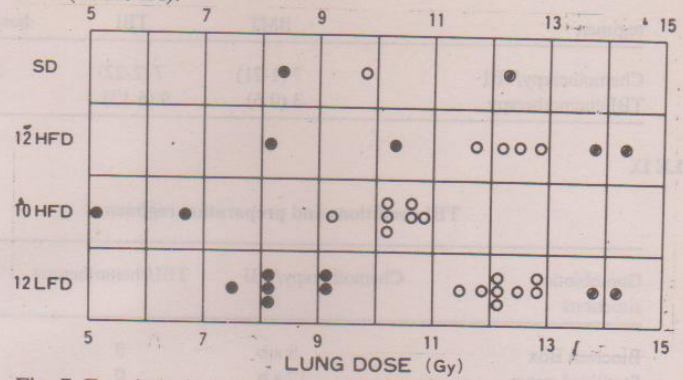

Fig 7 Fractionation and lung dose of TBI. Six cases were excluded because of no available data in lung dose Closed circle [], lung shield for [0] lung shield for dose reduction, Open circle [0], lung compensator for dose homogeneity, Dotted circle [] no lung shield.

DISCUSSION

During the last 10 years a rapid progress was shown in BMT for leukemia, other hematologic disease, some types of disseminated solid tumours, and severe combined immunodeficiency in Europe and America, and also in Japan. In 1970, a bioclean system was installed in a hospital room in the aim of preventing infections in leukemia patients in Japan. The number of lamina air flow room has steadily increased. As of 1981, medical isolators have been used in 79 institutions in Japan [5]. This figure reflected the increasing number of patients treated with BMT after 1981.

The various prognostic factors in BMT for leukemia patients were proposed and tested by many investigators. In the previous paper [2], multivariate analysis indicated that change in the selection of patients, e.g., in remission without infection at the time of BMT, resulted in the significant improvement in the survival. On the other hand, use of fractionated low-dose rate TBI, selection of cytomegalovirus seronegative platelet donor, and the prophylactic administration of

TABLE VIII

Preparation regimen and median time (range) to white blood cell count nadir

Preparation regimen	Days to WBC count nadir from BMT	Days to WBC count nadir from TBI	No. of hospitals
Chemotherapy/TBI	7 (1-21)	7 (2-22)	26
TBI/chemotherapy	3 (0-6)	9 (6-13)	4

TABLE IX

TBI conditions and preparation regimen

Gnotobiotic situations	Chemotherapy/TBI	TBI/chemotherapy	Total
Bioclean Box	8 a,b	0	8
Sterilized gown	12 a,b	0	12
Room cleaning + UV	2 a	0	2
No manipulation	7	4	11

a,b overlap

anticytomegalovirus high titer globulin resulted in the significant decrease in developing Ip [6, 7].

There were excellent reports based on the survey of TBI for BMT in Europe and America [8, 9, 10]. The physical aspects of TBI have been published by Van Dyk et al. [11]. In Japan, increase in the number of BMT among various hospitals resulted in the large variety of TBI methods, such as biological, physical and technical aspects. Treatment technique was partly influenced by treatment machine as well as treatment room. Since the variety of methods in practice makes it difficult to identify the optimal TBI, the standardization of TBI should be necessary for multi-institutional clinical trials in Japan. Concerning the beam direction, AP/PA beams are desirable to deliver the homogeneous dose and convenient for shielding the lung. Long SSD method is preferable, and moving couch or beam is the alternative in the case of limitation of treatment room. It is also recommended to compensate the dose inhomogencity due to contour variations and tissue heterogeneity. Concerning TBI dose-fraction-time and dose rate schedule, the following 5 schemes, the following 5 schems are proposed to find

the optimal schedule in near future : (1) 7.5 Gy in single fraction with 25 cGy/min. (2) 10 Gy in single fraction with 2 cGy/min. (3) 12 Gy in 4 fractions over 2-4 days with 3-5 cGy/min. (4) 12 Gy in 6 fractions over 3-6 days with 5-12 cGy/min. (5) 13.2 Gy in 11 fractions over 4 days with 20 cGy/min. Now co-operative study is in progress to find the optimal TBI schedules and techniques in Japan.

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REFERENCES

1. THOMAS, E.D., STORB, R., CLIFT, R.A., FEFER, A., JOHNSON, F.L., GLUCKSBERG, H.,C.D. and BUCKNER, Bone-marrow transplantation. N.

Engl. J. Med. 292: 832-843, 895-902, 1975.

2. INOUE, T. MASAOKA, T. and SHIBATA, H. Total Body irradiation for allogeneic bone marrow transplantation in acute leukemia : A co-operative Study from the TBI Subcommittee in Japan, Strahlenther. Onkol 162: 100-104. 1986.
3. KAPALN, E.L. and MELER. PNER P. Nonparametric estimation from incomplete observations. J. Amer. Stat. Assoc. 53: 457-481, 1958.
4. PETO, R., PIKE, M.C., ARMITAGE, P., BRESLOW, N.E., COX, D.R., HOWARD, S.V., MANTEL, N., Mc PI'ERSON, K., PETO, J. and SMITH, P.G. Design and analysis of Randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br. J. Cancer 35: 1-39, 1977.
5. YAMADA, K., YAMADA, H. and KODERA, Y. Clinical use of bioclean rooms in Japan with special reference to medical isolators. Jap. J. Clin. Oncol. 13 (Suppl. 1) : 91-94, 1983.
6. INOUE, T., MASAOKA, T. and SIIIBATA H. Risk factors associated with interstitial pneumonia following allogeneic bone marrow ransplantation for acute leukemia in Japanese experience. Strahlenther. Onkol. 162: 368-373, 1986.
7. TESHIMA, H., MASAOKA, T., INOUE, T., K., KATO, S. MORI, T., KANAMARU, A., SAITO, Y., OHIRA, M., MORIYAMA, Y., KODERA, Y., HARADA, M., BABA, M., NAKADE, Y., TASAKA, H., and YOSHIKAWA, S. Interstitial pneumonitis in allogeneic bone marrow transplantation: A report from the Japanese BMT study groups. Bone Marrow transplantation 1: 179-183, 1986.
8. KIM, T.H., KHAN, F.M. and GALVIN, J.M. A report of the work party: Comparison of total body irradiation techniques for bone marrow transplantation. Int. J. Radiat. Oncol. Biol. Phys. 6: 779-784, 1980.
9. SHANK, B. Techniques of magna-field irradiation. Int. J. Radiat. Oncol. Biol. Phys. 9: 1925-1931, 1983.
10. QUAST, U. Total body irradiation - review of treatment techniques in Europe. Radiother. Oncol. 9: 91-106, 1987.
11. VAN DYK, J., GALVIN, J.M., GLASGOW, G.P. and PODGORSAK, E.B. AAPM Report No. 17. The physical aspects of total body and half body photon irradiation. American Association of Physicists in Medicine, New York, 1986.

9

BASIS FOR THE USE OF HYPERTHERMIA IN THE TREATMENT OF CANCER

S.B. Field

INTRODUCTION

The first known report of the use of high temperature in an attempt to eradicate malignant tumours is described in the Edwin Smith Surgical Papyrus, an Egyptian papyrus from approximately 3000 BC. For many centuries the application of high temperature was a standard method of treating cancer - and most other diseases. Also more moderate increase in temperature have been known for a long time to be beneficial. In the 4th Century, Rufus of phesus observed that fever can be beneficial in many diseases, including cancer. More recently, a German physician, W. Busch, described in 1866 the disappearance of a sarcoma on the face of a patient who developed a high fever associated with erysipelis. There is a similar report from P. Blum, some 20 years later. Such reports led the New York surgeon, W.B. Coley, to administer bacterial pyrogens to cancer patients and the Swedish gynaecologist, F. Westermark, to the use of circulating hot water for treatment of uterine tumours.

The 20th Century saw many reports of tumour responses to hyperthermia, both total body and localized using a variety of techniques. Heating was also combined with treatment with ionising radiation, discovered by Roentgen in 1895. However, heat delivery and

temperature measurement were found to be difficult. The clinical reports were mainly anecdotal and despite this publication of many experimental studies interest declined, principally because of the technical difficulties together with the rapid development of surgery, radiotherapy and chemotherapy as the three main methods of treating malignant disease.

The field was revived, however, by the work of a group in Rome (1) who performed a series of biochemical studies on normal and malignant cells from rodents. They observed that heat resulted in a greater inhibition of respiration in the tumour cells than the normal cells. Aerobic glycolysis was unaffected. The group also reported responses of 22 cancer patients to treatment by hyperthermic perfusion. The results were very encouraging, especially for melanomas. This report stimulated a systematic investigation of the anti cancer effects of hyperthermia, including a variety of experimental studies and analysis of a vast literature of anecdotal clinical reports. The results confirm that temperature rises of only a few degrees have profound effects on cells and tissues and that hyperthermia in this range undoubtedly has an anti tumour effect.

Biological studies have now demonstrated a clear rationale for expecting hyperthermia to have a greater effect on tumours than on normal tissues. Techniques for heating tumours and raising and measuring temperatures have also improved an overall interest in the field of hyperthermic oncology has increased dramatically. Careful recent clinical studies indicate that temperatures of 41 C or greater do have an anti-tumour effect. However, hyperthermia appears to be far more useful if combined with either radiotherapy or chemotherapy.

RATIONALE FOR THE CLINICAL USE OF HYPERTHERMIA.

The reason for using heat in the treatment of malignant disease rest principally on differences in the vasculature and blood supply between tumour and normal tissues. In tumours the blood supply is frequently disorganised and heterogeneous, leaving some areas poorly perfused [27]), although the average blood flow in tumours is not necessarily less than in normal tissues. This difference results in a number of consequences.

i. Some tumours or regions within tumours will have a poor cooling capacity and may thus become hotter than normal tissues in a localised treatment field. There is clinical evidence to support this, but the extent to which a temperature differential may occur will be highly

variable.

ii. Deficiencies in tumour vasculature results in the development of cells which are

a) hypoxic, which has little effect on their response to hyperthermia (in contrast to other modalities).

b) at low pH and/or nutrient deficient, both of which cause cells to become more sensitive to heat. In addition it is widely believed that tumours have a natural tendency towards anaerobic metabolism and hence acidity [12].

iii. Combined treatment with hyperthermia and radiotherapy may also have therapeutic advantages, since cells in the DNA synthetic phase of the cell cycle are particularly sensitive to heat but relatively resistant to X-rays, to that a combined treatment with hyperthermia and radiotherapy may, in some circumstances, be advantageous. Also, for physiological reasons given above, those tumour cells which are most resistant to X-rays are likely to be the most sensitive to hyperthermia.

iv. Combining heat with chemotherapeutic drugs may enhance the therapeutic effect by increasing drug uptake or by enhancing sensitivity to the drugs.

For further discussion of these factors, see Hahn, [13] & Wike Hooley et al, [31].

BIOLOGICAL EFFECTS OF HEAT ALONE

Hyperthermia may cause direct cell killing or at lower "heat doses" may enhance the damage caused by radiation or chemotherapy. In general, temperatures greater than approximately 40 C cause important changes in mammalian cells.

However, it is not clear which, amongst these changes are primarily responsible for cell death and sentization to other agents. When cells in DNA synthesis are heated, they appear to die, principally as the results of chromosal injury. However, at other times during the cell cycle membrane damage, either plasma or cytoskeletal, is strongly implicated as the primary target. It is likely that hyperthermia results in denaturation of a membrane or chromosal protein or repair enzyme [21]. Membrane injury causes cells to die and lyse rapidly and many tissues, even those that are post mitotic or slowly dividing, rapidly respond to hyperthermia. In general, the pathology is similar to that following a mild thermal burn. Depending on its severity, hyperthermia may be followed by oedema, focal haemorrhage, granulocytic infiltration and even necrosis within the

first day or two. Later changes (but still fairly rapid) include monocycle infiltration, fibrosis and necrosis. Damage to supporting tissue, particularly the vasculature, plays an extremely important role in heat injury to both tumours and normal tissues. Once the "acute" response to heat has healed there appears to be no "late" effects. The pathological effects of hyperthermia in various normal tissues have been reviewed by Fajardo [7].

Although, it is possible to obtain survival curves after heating in situ the majority of in vivo studies rely on an assessment of gross tissue response.

TABLE

Influence of Hyperthermia on radiation effect

1.	Increase sensitivity to X-rays, i.e. causes a decrease in Do.
2.	Causes a raduction in the capacity for: i. repair of sublethal damage; and ii. repair of potentially lethal damage
3.	Selectively enhances effects on the cells in radioresistant phase of the cell cycle (e.g. late S)

TABLE II

Anticancer drugs which show a more than additive interaction with hyperthermia

Adriamycin
Actinomycin D
Bleomycin
Flourouracil
Nitrosoureas
Cisplatinum
Cyclophosphamide
Melphalan
Mitoxantrone
Mitomycin C
THio-TEPA

An example is shown in figure 1 where the probability of causing necrosis in the rat tail is plotted against time of heating at various temperatures. It is seen that at any given temperatures once the time of heating is sufficiently long to achieve a threshold of injury, a further

TABLE III

Phase II Studies comparing radiotherapy alone with radiotherapy combined with hyperthermia

STUDY	NUMBER OF CR TUMOURS	IMPROVED RT alone %	RT & HP %	PROBABILITY OF CR %
U et al	14	14	86	72
Hiraoka et al	33	25	71	46
Corry et al	34	0	62	62
Scott et al	62	39	87	48
Gonzalez et al	46	33	50	17
Valdagni et al	78	36	73	37
Bey et al	45	9	42	33
Bide et al	76	0	7	7
Van der Zee et al	71	5	27	22
Steeves et al	75	23	61	38
Lindholm et al	85	25	46	21
Dunlop et al	86	50	60	10
Kim et al	238	39	72	33
Arcangeli et al	163	38	74	36
Perez et al	154	41	69	28
Overgaard	101	39	62	23
Kochegarov et al	161	16	63	47
Li et al	124	29	54	25

from Overgaard [26]
By accepted standards, none of these studies were randomized.

increase in heating time of approximately 20% or an increase in temperature of only 0.5°C will increase the probability of necrosis to 100%. Variations in tissue temperature are impossible to avoid in clinical treatments, and thus may lead to marked variations in biological response. It is important therefore to monitor temperatures at as many points as possible and to take great care during treatments. On the other hand, if tumours are only slightly more sensitive, or at slightly higher temperatures than the surrounding normal tissues, then hyperthermia should result in a therapeutic advantage.

It is necessary to understand the relationship between temperature and time of heating to produce a given level of response. Such iso-effect curves may be derived from dose response curves such as those shown in Figure 1.

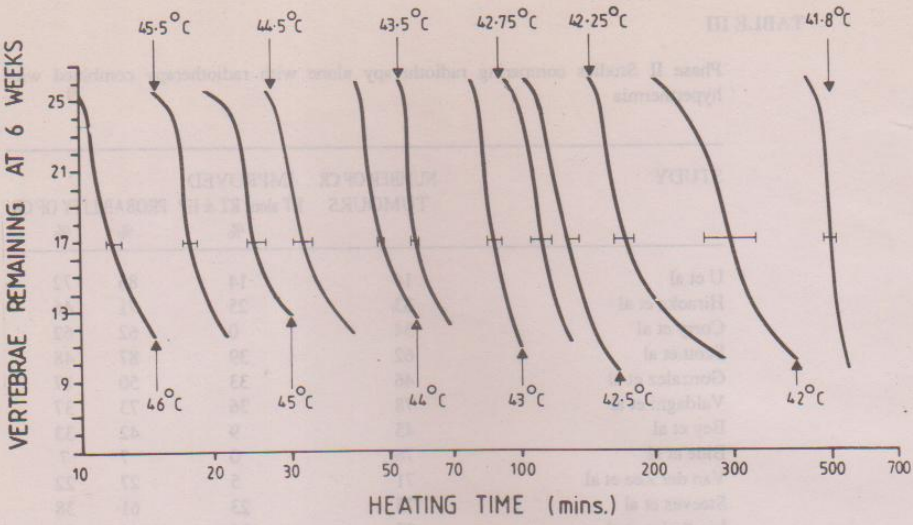


Fig.1. Dose response curves for loss of vertebrae in the tails of young rats (From Morris and Field [23]

A summary of in vivo iso-effect data is shown in figure 2. it is seen that in general there is a transition occuring between 42° and 43° C above which a change in temperature of 1 C is equivalent to a change in heating time by a factor of 2 and by a factor of 6 below. However, absolute sensitivity seems to be extremely tissue dependent [9]).

THEMOTOLERANCE

Clinical hyperthermia is normally given in several fractions. An important consideration then becomes the inductance of thermotolerance, i.e. induced reistance to subsequent heating. Two types of thermotolerance have been identified, i.e. that which develops during prolonged heating below a critical temperature (about 42 degree C) and that which develops between individual heperthermia fractions given at higher temperatures. Thermotolerance is an extremely large effect, but it is transient, its time course depending on the particular cell type or tissue and also on the magnitude of the heat treatment which induces it [8].

In experimental studies on cells and normal tissues, the peak tolerance often is reached after a few hours up to 1-2 days. Decay is

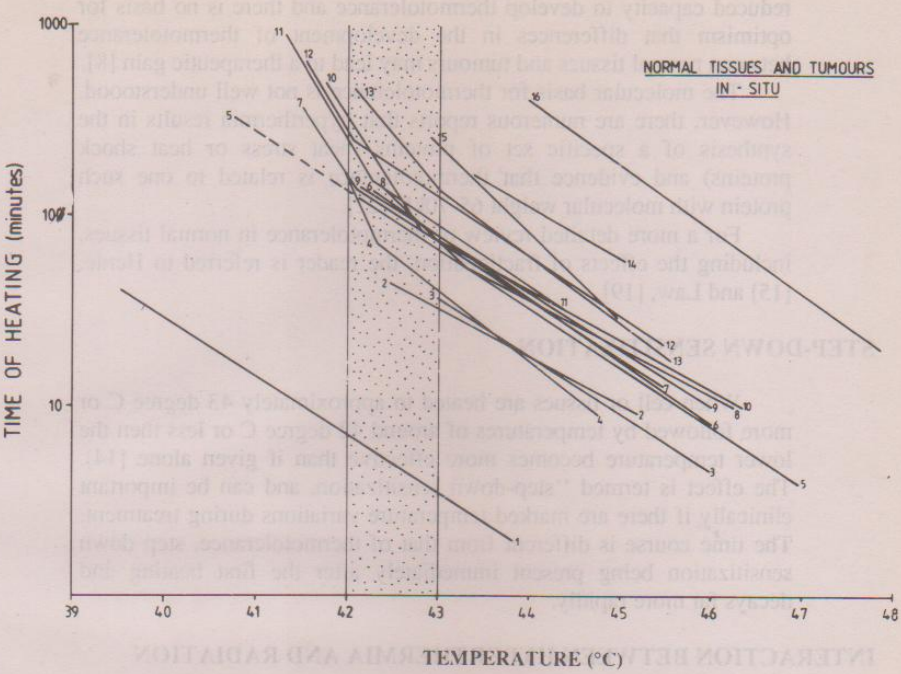


Fig.2. Relationship between time of heating and temperature for a given level of damage in a range of normal tissues and tumours in situ. (1) mouse testis weight loss (Hand et al) (2) rat tumour 9L, heated in vivo, assayed in vitro (Wallen et al; (3) mouse jejunum LD (Henle); (4) mouse jejunum, 50% loss of crypts (Humeet al); (5) mouse sarcoma 180, majority cure (Suit from Crile); (6) baby rat tail, 50% necrosis (Morris et al); (7) mouse ear skin, 50% necrosis (Law); (8) rat skin epilation (Okumura and Reinhold); (9) baby rat tail, 5% stunting (Morris et al); (10) baby rat tail (whole tail necrosis) (Morris and Field); (11) mouse tumour C3H/Tif regrowth (Nielsen and Overgaard); (12) mouse tumour F (Sal) (TCD) (Overgaard) and Suit); (13) mouse foot skin epilation (Overgaard and Suit); (14) mouse skin, feet and legs (Robinson et al); (15) mouse tumour C3H, 50% cures (Robinson et al); (16) pig and human skin necrosis and cutaneous burns (Moritz and Henriques). (From Field and Morris, [9].)

highly variable but can take 10 days or more for the effect to fully disappear [3, 10, 24]. An example is given in figure 3.

Reduced pH causes a reduction in thermotolerance, on which basis it has been suggested that it may be less in some tumours (or regions or tumours) than in normal tissues. However experimental studies to date have given no clear indication that tumours have a

reduced capacity to develop thermotolerance and there is no basis for optimism that differences in the development of thermotolerance between normal tissues and tumours may lead to a therapeutic gain [8].

The molecular basis for thermotolerance is not well understoood. However, there are numerous reports that hyperthermia results in the synthesis of a specific set of proteins (heat stress or heat shock proteins) and evidence that thermotolerance is related to one such protein with molecular weight 65-70kD [22].

For a more detailed review of thermotolerance in normal tissues, including the effects of fractionation, the reader is referred to Henle, [15] and Law, [19].

STEP-DOWN SENSITIZATION

When cell or tissues are heated to approximately 43 degree C or more followed by temperatures of around 42 degree C or less then the lower temperature becomes more effective than if given alone [14]. The effect is termed "step-down sensitization, and can be important clinically if there are marked temperature variations during treatment. The time course is different from that of thermotolerance, step down sensitization being present immediately after the first heating and decays far more rapidly.

INTERACTION BETWEEN HYPERTHERMIA AND RADIATION

When radiation is combined with a mild heat treatment which alone does not cause any visible damage the response to radiation may be enhanced. (See figure 4). Table 1 summarized the ways in which radiation responses are influenced by heating. After "mild hyperthermia the tissue response after such combined treatment is normally qualitatively identical with the radiation response. From such studies the thermal enhancement ratio (TER), i.e. the ratio of doses of radiation alone to that with hyperthermia to produce a given level of damage may be derived. However, when TER values for normal tissues are compared with those for experimental tumours there does not appear to be a consistently higher TER for tumours as was orginally predicted.

THE REASONS ARE :

1. Studies in vitro indicate that when heat is used to enhance radiation response, pH is less important than it is for direct heat cytotoxicity.

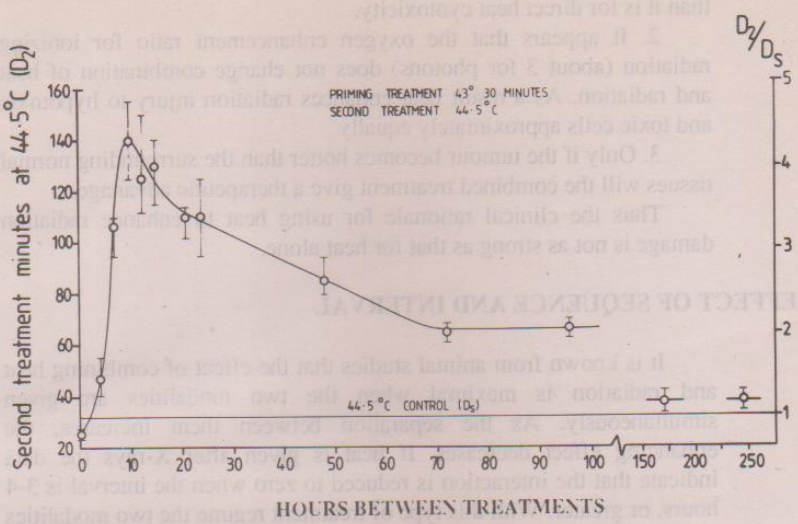


Fig.3. Thermotolerance in the rat tail follwing 43 degree C for 30 minutes, tested by measuring at 44.5 degree C at various intervals after the initial treatment. The dotted lines shows the effect of the test treatment alone. (From Field and Morries [10])

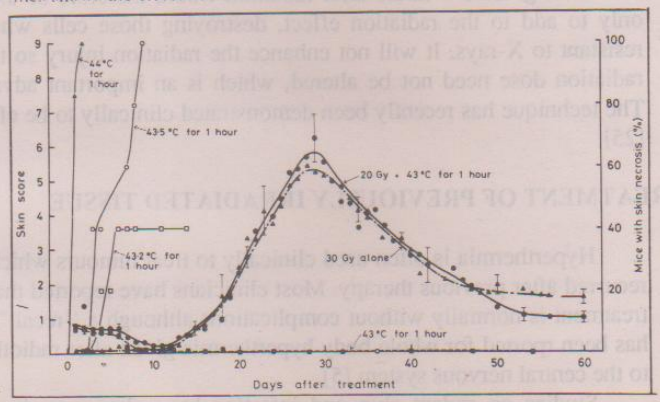


Fig.4. The response of the mouse ear to hyperthermia or ionizing radiation. Open symbols give the percentage of ears showing necrosis after heat alone (right-hand axis) : ()44 degree C for 1 h; (o) 43.5 degree C for 1 h; (0 43.2 degree C for 1 h. Closed symbols give skin reaction using an arbitrary numerical score (left-hand axis). Scores of 1 and 2 indicate degrees of erythema. Scores of 3-9 indicate increase areas of moist desquamation: () hyperthermia alone 43 degree C for 1 h; () X-rays alone; () X-rays followed by hyperthermia at 43 degree C for 1 h. (from Law et al. [20]).

When heat is used to enhance radiation response, pH is less important than it is for direct heat cyotoxicity.

2. It appears that the oxygen enhancement ratio for ionizing radiation (about 3 for photons) does not change combination of heat and radiation. As a result heat enhances radiation injury to hypotoxic and toxic cells approximately equally.

3. Only if the tumour becomes hotter than the surrounding normal tissues will the combined treatment give a therapeutic advanage.

Thus the clinical rationale for using heat to enhance radiation damage is not as strong as that for heat alone.

EFFECT OF SEQUENCE AND INTERVAL

It is known from animal studies that the effect of combining heat and radiation is maximal when the two modalities are given simultaneously. As the separation between them increases, the enhancing effect decreases. If heat is given after X-rays the data indicate that the interaction is reduced to zero when the interval is 3-4 hours, or greater. With this type of treatment regime the two modalities act independently and the heat damage to tumour would be expected to be greater than that to normal tissues for reasons given above.

Heat given 3-4 hours after radiation would therefore be expected only to add to the radiation effect, destroying those cells which are resistant to X-rays. It will not enhance the radiation injury so that the radiation dose need not be altered, which is an important advantage. The technique has recently been demonstrated clinically to be effective [25].

RE-TREATMENT OF PREVIOUSLY IRRADIATED TISSUE

Hyperthermia is often used clinically to treat tumours which have recurred after previous therapy. Most clinicians have reported that such treatment is normally without complications although a "recall" effect has been rported for whole body hyperthermia given after radiotherapy to the central nervous system [5].

Studies on rodent skin and intestine have shown an increased sensitivity to hyperthermia when heat is given at various times after radiation treatment. The time course of this increase in heat sensitivity is both variable and dependent on the prior radiation dose [19]. Clearly, care must be taken in re-treatment althogh currently available clinical, evidence has so far not shown a significant effect.

HYPERTHERMIA AND ANTI-CANCER DRUGS

The majority, but not all, of chemotherapeutic drugs become more effective in combination with hyperthermia. Examples are given in table II. Much of our knowledge of this field derives from the work of G.M. Hahn and his colleagues [13], with more recent reviews from Herman et al. [16], Engelhardt, [6] and Dahl, [4].

There are various ways of characterizing the interactions but they may be summarized briefly as follows:

(a) Some drugs are actually inhibited by heat, e.g. A.M. S.A. and Ara-C. (b)The cytotoxicity of some is inhibited by temperatures below 37 degree C, e.g. adriamycin, bleomycin, cisplatinum and BCNU. Above 37 degree C adriyamycin and bleomycin are unaffected by heat until a threshold temperature is reached, above which there may be a dramatic increase in drug toxicity. (c) Some are simply additive, e.g. the vinca alkaloids and most antimetabolites. (d) There are compounds which are not toxic to cancer cells at physiological temperatures. e.g. amphotericin B and alcohols, but become toxic at increased temperatures. (e) A continuous increase in toxicity with increasing temperature occurs with cisplatinum, alkylating agents and nitrosoureas.

It must be stressed, however, that these categories of interaction are very general. Reading the literature in this field one is struck by the enormous variability in results which can often be in direct contradiction with each other.

The sequencing and timing of heat and chemotherapy are also important. In general it nas been found that the maximum effect is achieved if the two modalities are simultaneous and that hyperthermia given before chemotherapy is usually more effective than the reverse. Prior heating may affect the subsequent effectiveness of heat and chemotherapy leading to protection (i.e. thermotolerance) or enhanced cytoxcity in some cases. The literature on the effects of sequencing and timing is, however, full of contradictions depending on the drugs, the cell lines studies, the temperature and times of heating employed and the timing of the two modalities, making it difficult to draw firm conclusions.

The mechanisms responsible for these effects of hyperthermia or anti-cancer drugs are far from fully understood. Factors include alterations in drug uptake, reduced capacity for repair, increased drug

reaction rates, changes in drug metabolism and intracellular distribution. More than a single mechanism is probably responsible for most of the drug and hyperthermia interactions.

Other factors which are strongly linked to hyperthermia may also affect the response to anti cancer drugs, for example, hypoxia and pH. Low pH potentiates the effects of BCNU and cyclophosphamide but protects against adriyamycin. Hypoxia dramatically enhances the effects of bioreductive agents, e.g. misonidasole and mitomycin C. In addition, hyperthermia itself might modify drug delivery by altering the circulation. Altering tumour blood flow may also be achieved by chemical means. It has been shown that administration of hydralazine selectively increases tumour hypoxia (in experimental animals). If such a treatment is given following the administration of melphalan, it also markedly increases the effectiveness of the melphalan, possibly by "locking the drug in the tumour [29]. From this discussion it is clear that the potential exists for enhancing the effects of chemotherapy and hyperthermia by appropriate manipulation of blood flow.

ROLE OF TUMOUR MICROCIRCULATION AND MICROENVIRONMENT

As tumours grow, they incorporate host vasculature and also develop new vessels, the proportion of each depending on tumour type, size and site. As a result, there are major differences between the vessels in normal tissues and those in most tumours (see review by Reinhold & Endrich, [27]). Tumour vessels tend to be longer, more tortuous and lack smooth muscle. In experimental tumours it has frequently been observed that blood flow is extremely heterogeneous so that regions exist where perfusion is virtually zero. Anaerobic glycolysis is more prevalent in tumours giving rise to lactic acid, which will be removed slowly. High interstitial pressure resulting from lack of lymph drainage will increase the probability of vessel occlusion. These factors will lead to reduced blood flow, slow removal of lactate and result in a decrease in pH. [30, 31].

Tumour vasculature appears to respond to hyperthermia differently from that of normal tissues. Normal vessels respond by a major increase in blood flow until very high temperatures (46-47degree C) are reached after which vascular stasis is induced. In contrast, it has been shown in transplanted tumours in animals that tumour flow is only marginally increased by hyperthermia with vascular stasis and damage following fairly mild treatments. This important finding,

however, has yet to be confirmed in man.

The application of hyperthermia may itself lead to a further reduction in nutrient flow and stasis via several pathways. It is known that the inflammatory response will increase the sticking of white cells to vessel walls, thus decreasing nutrient flow. High temperatures and low pH cause an increase in erythrocyte rigidity and aggregation and the formation of fibrinogen gel; all of which will decrease effective vascular diameter and cause occlusions. Further details of such effects can be found in a number of recent reviews [11, 18, 27, 30]. There is clearly considerable potential for manipulation of tumour blood flow and recently it has been shown in transplated tumours that administrations of hydralazine results in a decrease in tumour blood flow and an increase in sensitivity to hyperthermia [17].

THERMAL DOSE

The definition of thermal dose is rather difficult. The term "dose" is itself not very rigidly defined. Radiation workers use energy deposited as the dose unit since this relates clearly and meaningfully to the resulting effect. Pharmacologists use drug concentration or weight which also relates to effect. With hyperthermia the biological response is primarily dependent on the time at an elevated temperature, not on the deposition of energy [13].

Dewey et. al. [2] proposed a simple empirical formula, based on in vitro observations, i.e.

$$\frac{t2}{t1} <= R^{T1-T2}$$

as a means of relating treatments with different temperatures (T) and times of heating (t). A review of available data (9) suggested that R=2 for T<42.5°C.and R = 6 for T≥42.5°C. Saparcto and Dewey [28] proposed that 43°C should be used as a reference temperature and that all treatment be described in equivalent minutes of heating at 43°C.should be used as a reference temperature and that all treatment be described in equivalent minutes of heating at 43°C.This has become known as the thermal isoeffect dose TID and by using this formula account can be taken of variations in temperaure and time of heating.

The formula would not apply if there were very large changes in temperature sufficient to result in a significant effect of step-down sensitization or if the time to reach the target temperature was longer than about half an hour, resulting in thermotolerance. Also, the formula does not address the problem of varying sensitivity throughout a course

of fractionated heat treatments a difficulty common to chemotherapy and also to radiotherapy. The use of this iso-effect relationship must be seen as an interim solution to this problem, especially since R may be different for heats in combination with other modalities.

CLINICAL STUDIES

During the past decade various superficial tumours have been treated in phase I/II non randomized studies. Most of the studies are suspect on account of inadequate quality control. It is impossible in the majority of cases to know whether the tumour was heated adequately (if at all). Nevertheless complete response rates for heat alone of 10-15% have been reported and the combination of radiotherapy with hyperthermia appears to have a substantial advantage over radiotherapy alone, (TableIII), with few reports of complications [26]. Clinical studies with combination of heat and chemotherapy are much harder to interpret.

On this basis, phase III studies of the role of hyperthermia in combination with radiotherapy are indicated. Three such trilas are now starting, i.e. in the UK, a combined European study and in the USA.

REFERENCES

1. CAVALIERE, R., CICATTO E.C., GIOVANELLA, B.C., HEIDELBERGER, C., JOHNSON, R.O., MARGOTTINI, M., MONDOVI, B., MORRICA, G., ROSSI-FANELLI, A. (1967). Selective heat sensitivity of cancer cells. Cancer, 20. 1351-1381.
2. DEWEY, W.C. HOPWOOD, L.E. SAPARETO, S.A. and GERWECK, L.E. (1977) Cellular responses to combinations of hyperthermia and radiation. Radiology. 123, 463-474.
3. DIKOMEY, E. EICKHOFF. T. & JUNG, H. (1988) Effect of pH on development and decay of thermotolerance in CHO cells using fractionated heating at 43°C. Int. Journal of Hyperthermia 4. 555-565.
4. DAHL, O. Hyperthermia & drugs in hyperthermia. ED. D.J. WATMOUGH & W.M. ROSS. BLACKIE, 1986. pp 121-153.
5. DOUGLAS. M.A. PARKS. L.C. and BEBIN, J. (1981). Sudden Myleopathy secondary to therapeutic total body hyperthermia after spinal-cord irradiation. New Eng.J. Med. 210, 583-585.
6. ENGLHARDT, R. Hyperthermia & drugs in recent results in cancer Research. Vol.104. EE.C. STREFFER. SPRINGER-VERLAG, 1987. pp 136-203.
7. FAJARDO, L. (1984). Pathological effects of hyperthermia in normal tissues. Cancer Res. (suppl) 44,4826s - 4835s.
8. FIELD, S.B. (1985). Clinical implications of thermotolerance, in "Hyperthermia Oncology, 1984, Vol 2, ed. J. Overgaard, pub. TALYOR & FRANCIS, LONDON, pp. 235-244.
9. FIELD, S.B. and MORRIS C.C (1983). The relationship between heating time and temperature : its relevance to clinical hyperthermia. Radiotherapy and

Oncology, 1,179-186.

10. FIELD, S.B. and MORRIS, C.C. (1985). Experimental studies of thermotolerance in vivo. 1. The baby rat tail model. Int. J. Hyperthermia 1, 235-246.
11. FIELD, S.B. and MORRIS, C.C. (1989). Hyperthermia in the treatment of cancer in "Treatment of Cancer second Edition, ed. K. Halnan & K. Sikora, pub. Chapman & Hall, London.
12. GULLINO. P.M., CLARKE, S.H., GRANTHAM, F.H. (1964). The interstitial fluid of solid tumours. Cancer Res. 24, 780-794.
13. HAHN, G.M., (1982). "Hyperthermia & Cancer, pub. Plenum Press, New York.
14. HENLE, K.J. (1980). Sensitization to hyperthermia below 43°included in Chinese hamster ovary cells by step down heating. J. Nat. Cancer Inst. 68, 1033-1036. Henle, K.J. (1987). Thermotolerance Vols. I & II, C.R.C. Press.
15. HENLE, K.J. (1987). Thermotolerance. Vols. I & II, C.R.C. Press.
16. HERMAN, T./S. TEICHER, B.A., JOCHELSEN, M., CIARK, J., SVENSSON, G. COLEMAN. C.N., (1988). Rationale for use of local hyperthermia with radiation therapy and selected anti-cancer drugs in locally advanced human malignancies. Int. J. Hyperthermia, 4,143-158.
17. HORSMANN, M.R. CHRISTENSEN, K.L. and OVERGAARD, J. (1989), Hydralazine induced enhancement of hyperthermic damage in a C3H mammary carcinoma in vivo. Int.J.Hyp. 5, 123-136.
18. JAIN, R.K. and WARD-HARTLEY, K. (1984). Tumour blood flow characterization, modification and role in hyperthermia. IEEE Transaction of Sonics and Ultrasonics, Vol SU-31, 5, 504-526.
19. LAW, M.P. (1988). The response of normal tissues to hyperthermia. In Hyperthermia Oncology Ed. M. Urano, 1,121-159.
20. LAW, M.P., AHIER, R.G. and FIELD, S.B. (1978). The response of the mouse ear to heat applied alone or combined with X-rays. Brit. J. Radiol. 51-132-138.
21. LEEPER. D.B. (1985). Molecular and cellular mechanisms of hyperthermia alone or combined with other modalities in "Hyperthermic Oncology, 1984. Vol 2, Overgaard, J. (ed) pub. Taylor and Francis, London. pp, 9-40.
22. LI, G.C. and MIVECHI, N.F. (1986). Thermotolerance in Mammalian Systems, A review, in "Hyperthermia in Cancer Treatment" eds. L.J. Anghileri & Robert, C.R.C. Press, pp. 59-78.
23. MORRIS. C.C. and FIELD, S.B. (1985). The relationship between heating time and temperature for rat tail necrosis with or without occlusion of the blood supply. Int. J. Radiat. Biol., 47,41-48.
24. NIELSEN, O.S. and OVERGAARD, J. (1982). Influence of time and temperature on the kinetics of thermotolerance in L1A2 cells in vitro.Caner Res. 42, 4190-4196.
25. OVERGAARD J and OVERGAARD, M. (1987) Hyperthermia as an adjuvant to radiotherapy in the treatment of malignant melanoma Int. J. Hyperthermia 3,483-502.
26. OVERGAARD J. (1987). In Physics and Technology of Hyperthermia.
27. REINHOLD, H.S. ENDRICH, B. (1986). Tumour microcirculation as a target for hyperthermia. Int. J. Hyperthermia, 2, 111-137.
28. SAPARETO, S.A. and DEWEY, W.C. (1984). Thermal dose determination in cancer therapy. Int. J. Radiat. Oncol. Biol. phys. 10, 787-800.
29. STRATFORD I.J., GODDEN, J., HOWELLS, N., EMBLING, P. and ADAMS, G.E. Manipulation of tumour oxygenation by hydralazine increases the potency of bioreductive radiosensitizers and enhances the effect of melphalan in experimental tumours. Proceedings of the 8th International Congress of Radiation Research, Edinburgh, Vol. 2, pp 737-742, 1987.
30. VAUPEL, P., KALLINOWSKI, F. (1987). Physiological effects of

Hyperthermia in "Recent results in Cancer Research, Vol. 104, Springer Verlag, Berlin, Heidelberg, pp. 71-109.

31. WIKE-HOOLEY, J.L., HAVEMAN, J., REINHOLD, H.S. (1984). The relevance of tumour pH to the treatment of malignment disease. Radiother. Oncol. 2, 343-366.

10

REVIEW OF CLINICAL EXPERIENCE IN THE TREATMENT OF MALIGNANT TUMOUR WITH CHEMOTHERAPY AND HYPERTHERMIA

B. EMAMI

Recent experimental and clinical data strongly suggest that hyperthermia, when properly executed, in combination with radiotherapy and/or chemotherapeutic agents, have a significant potential role in multidisciplinary management of human malignancies. Biological and physiological rationale for hyperthermia has been reviewed by Dr. Field in another part of this book. I will briefly discuss the methodology of hyperthermia as related to the clinical practice, followed by a review of the clinical experience of hyperthermia with chemotherapeutic agents.

METHODS OF HYPERTHERMIA DELIVERY

Currently hyperthermia is delivered by one of the following methods:

1-local external
2-interstitial
3-local deep
4-regional
5-perfusion
6-whole body

Most of the clinical experience in the treatment of human

malignancies are in treating superficial tumours with local external hyperthermia. Macrowave waveguide applicators (915 MHz) used with this method are relatively simple to use, but have major deficiencies: a-lack of adequate penetrability (maximum therapeutic depth of 2 cm to 3 cm); b - nonuniform intratumoral temperatures; and c - heating of overlying normal tissue (skin in most cases). Ultrasound transducers although have a higher penetration capability (up to 5 cm to 6 cm), they have serious limitations in clinical use at the tissue interfaces such as bone and air. Ultrasound beam causes excessive heating of bone surface (periosteum) due to reflection and this in turn will result in severe pain which may make treatment unbearable for the patient. Ultrasound beam does not pass through the air. Therefore, ultrasound hyperthermia cannot be used in sections of the body containing air cavities or bone. Moreover, the thermometry with ultrasound hyperthermia is still a major challenge.

INTERSTITIAL HYPERTHERMIA

Interstitial hyperthermia, albiet being an invasive method, has several advantages; a,- by virtue of being invasive, the clinician does not hesitate to insert a few more catheters for thermometry and therefore allows better three dimensional temperature assessment within the tumour and normal tissue; b,- implant is usually confined to the tumour and therefore there is better normal tissue sparing; c- more uniform intratumoral temperature; and d- the technique is applicable both superficially and for deep-seated tumours. Currently three different methods of interstitial hyperthermia are in use in clinics; 1 - Localized Current Field (LCF) method; 2 - microwave coaxial antennas; 3 - ferromagnetic seeds. The detailed description of methodology and basic physics of these three methods are beyond the scope of current work.

LOCAL DEEP HYPERTHERMIA

This technique involves heating of superficial tumours of more than 3 cm depth. Although this group of tumours comprises a majority of recurrent tumours encountered in our clinics, there is no ideal applicator to deliver adequate hyperthermia to these tumours. Inadequacy of the most currently used applicators namely microwave waveguide applicators operating at 915 MHz and ultrasound

transducers have already been discussed. Systems utilizing radiofrequency such as Thermatron-8 have the physical capabilities to perform this task, but they also have serious problems with excessive subsurface heating resulting in the necrosis of subcutaneous fatty tissues. Newly designed microwave applicators operating at lower frequencies are very promising and may be able to help clinicians in this regard.

REGIONAL HYPERTHERMIA

Lack of suitable local deep heating devices, have led some centres utilize regional hyperthermia for the treatment of deep-seated tumours. These systems are usually composed of several external heating elements constructed as such that they deposit energy at the region of the body which also contains the tumour volume. The differential physiological properties of the tumour as compared to normal tissue (i.e. blood flow) may eventually heat tumours to higher temperatures than normal tissue. The newly designed systems with the capabilty of preplanning and manipulation of phase and amplitude may show more versatility for clinic use.[7]

PERFUSION HYPERTHERMIA

Two different versions of this technique have been used: 1 - perfusion of heated blood, usually containing a chemotherapeutic agent, through the arteriovenous shunt, for heating of the extremities[8] ; 2 perfusion of heated saline, containing chemotherapeutic agents, through body cavities such as peritoneal or bladder[9].

WHOLE BODY HYPERTHERMIA

As the name implies with this technique the whole body is heated to a tolerable temperature. A variety of different methods have been used to achieve this goal such as radiant heat device[10], blanket technique[11], etc. This method has often been used to treat metastatic disease with heat and chemotherapy.

REVIEW OF CLINICAL DATA

By far, the majority of published clinical data is in the treatment

of recurrent, superficial tumours with radiation and external local hyperthermia. A summary of selected published data is shown in Table 1[12]. Table 1 also depicts a summary of published series in the treatment of similar tumours with reirradiation (retreatment) alone. This data is from phase I/II studies and are not based on prospective randomized trials. Nevertheless, the results show a complete response rate of 25% to 30% for radiation alone as compared to 60% to 80% for radiation in combination with hyperthermia. Treatment of these lesions by hyperthermia alone has resulted in only 10% to 15% complete response rate (table 2)[13]. Complication rate for these trials has been within the acceptable range and mostly were the results of reirradiation of normal tissues with the exception of thermal burns (Table 3)[12]

Interstitial thermoradiotherapy has been used in some centres who have specific expertise with this technique. A selected summary of published series are shown in Table 4[14]. As noted, 60% complete response rate has been achieved in the treatment of lesions who failed to respond to other conventional therapeutic modalities. Table 5 shows the overall and severe complication rate of these series.[14]

It is worth mentioning that lesions treated with interstitial thermoradiotherapy were in general larger and more advanced than earlier series shown in Table 1.

Clinical experience with thermoradiotherapy using deep heated regional hyperthermia devices are very limited[7, 15].

IMPACT OF PROGNOSTIC FACTORS

Recent clinical trials have shown the significant impact of several factors on the outcome of treatment of tumours with hyperthermia.

A recently completed prospective randomized trial by the Radiation Therapy Oncology Group (RTOG) failed to show any difference in the overall complete response rate and tumour control between radiation alone and radiation plus hyperthermia (Table 6)[16]. When the lesions less than 3 cm in diameter (lesions most likely have received adequate hyperthermia treatments) were compared between the two groups, there was a significant difference in tumour control between the two arms of the protocol at twelve months. There was no difference in tumours over 3 cm in the largest dimension (the tumours which most likely did not receive adequate hyperthermia treatment). Statistical analysis of this and other trials have shown the following

Table 1 Complete Responses of Superficial Lesions to Irradiation or Irradiation plus Hyperthermia

Author	Evaluable Patients (Treatment Trials)	Same Patient Comparisons	Irradiation Alone	Irradiation + Hyperthermia	Response Criterion
U et al.	7	7	14%	86%	CR within 1 mo. of therapy
Kim et al.	86	59	33%	80%	CR during follow-up
Corry et al.	18 (21)	13	0%	62%	CR for 2 mo
Arcangeli et al.	I 26	26	42%	73%	CR at therapy completion or soon after
	II 17	17	35%	64.78%	
	III 16	16	37.5%	67.77%	
	IV 15	15	33%	87%	
Arcangeli	81	--	42%	79%	CR
Marmoretal	15	15	7%	47%	
Lindholmetal	17	17	29%	56%	CR
Lietal	31	29%	68%	CR	
Perezetal					
Breast 1-3 cm	99		48%	83%	Tumour control
Breast 3-5 cm			22%	68%	Tumour control
Valdagnietal	27		38.5%	78.6%	CR at 3 mo after treatment
Emamietal					
Melanoma less 3 cm	73	27.5%	54.5%		CR
Melanoma 3-5 cm	43	18.5%	68.7%		CR

1. Hyperthermia once per week (64%) or twice per week (78%)
2. Hyperthermia immediately after radiotherapy (77%), or delayed 4 hours (67%)

Table 2

INSTITUTION	HYPERTHERMIA METHOD (MHz)	PRESCRIBED TEMP. X TIME	NO. OF TREATMENTS	NO. OF EVALUABL PATIENTS	CR (%)	PARTIAL PARTIAL (%)
University of Arizona	MW* (915, 2450) RF capacitive (0.5-3.3)	42.5-44° x 40 min	2-22	11	2	3
University of California	MW (915, 2450)	42.5° x 60 min	5-12	11	2	2
Duke University	MW (915, 2450)	42-44° x 40-50 min	2-9	6	0	3
Kyoto University	RF capacitive 13.56	41-46° x 30.60 min	4-9	6	0	1
M.D. Anderson	US (1-3)	43-50° x 60 min	6-12	28	5 (18)	11 (39)
Memorial Hospital	RF inductive	41-43.5° x 30-40 min	2-9	19	4 (21)	6 (32)
Stanford University	US (1-3)	43-45° x 30 min	6	44	5 (11)	14 (32)
Washington University	MW (915)	41-43° x	NS	6	1	2
TOTAL			131	19 (15)	42 (32)	

* MW. microwave; RF, radio frequency; US, ultrasound; NS, not specified

factors to play a significant prognostic role in the outcome of local external hyperthermia (Table 7)[16].

We have analyzed results of three Phase II trials of interstitial thermoradiotherapy from three institutions (Washington University in St. Louis, Institute Gustav-Roussy, Paris and Memorial Hospital, Long Beach, California) in which information on the quality of heating sessions were available[17-19]. The results of this analysis are shown in Table 8[18]. As can be seen, in cases with at least one satisfactory hyperthermia session, 80% complete tumour regression was achieved; while none of the 17 patients with unsatisfactory Hyperthermia sessions achieved complete response.

Review of clinical Data in Thermo-chemotherapy of malignant Tumours

The biological rationale for using thermochemotherapy in treating patients has been reviewed by Dr. Fields in other sections of this book. The physical methods for delivering heat in thermochemotherapy trials are shown in Table 9. It should be noted that the experience with this combination is very limited. Moreover, some of the earlier trials lack enough scientific quality due to either incorrect selection of the chemotherapeutic agents or the inappropriate physical device delivering heat.

Local Hyperthermia Plus Systemic Chemotherapy

Dahl et al.[20] has reported on the treatment of five patients (9 lesions) with chemotherapy ± hyperthermia. The results are shown in Table 10. Although the results are preliminary, review of patients #4 is of interest. In these patients all four lesions were treated with chemotherapy. Two lesions received hyperthermia whereas two other lesions did not. The lesions who were treated with hyperthermia and Cisplatinum, both achieved complete response, whereas the two lesions treated with chemotherapy in the same patient showed progression of disease. Arcangeli et al.[21] has reported the treatment of 43 neck nodes with Chemotherapy ± hyperthermia. The results are shown in Table 11. As shown the complete and partial response for thermochemotherapy verus chemotherapy alone is 43% and 52% versus 14% and 32%. Overall response rate for thermochemotherapy is 95% versus 45% for chemotherapy alone. This difference is statistically significant with a p value of less than 0.01. Steindorfer et

al.[22] reported on the treatment of 10 patients with heat and radiotherapy and 12 patients with heat and chemotherapy. The chemotherapy consisted of Bleomycin and Cisplatinum. Although they achieved 8/11 overall response rate with radiation and hyperthermia, they only had 1/12 with partial response from heat and chemotherapy series. In contrast, Emami et al.[22] treated 24 recurrent superficial lesions (previously heavily irradiated) with hyperthermia and Bleomycin, 15 units/m^2. Of the 21 evaluable lesions with minimum follow-up of 3 months there were complete responses and 4 partial responses with an overall response rate of 67%. The difference in the discrepancy of these two small series might be in the method of treatment delivery. In Steindorfer's study, Bleomycin was given IM 4 to 6 hours before heating wherein in Emami's study, Bleomycin was given IV preceding hyperthermia within 60 minutes. Pharmokinetics of Bleomycin might explain the difference in the results. Ishiwata et al.14 have reported the treatment of 30 patients with abdominal tumours who were treated with combination of chemotherapy and RF capacity of hyperthermia. Their chemotherapy consisted of 5FU, Cisplatium and Mitomycin-C. Of 23 patients who were evaluable for response, they achieved 1 complete response and 11 partial responses with an overall response rate of 12/23 (52%).

Perfusion hyperthermia in combination with chemotherapy (Mitomycin-C plus Cisplatinum) has been reported for the treatment of bladder carcinomas by Zhung Zhen et al. In their series, 11/28 patients achieved complete response with an additional 12 patients achieving partial response. Yonemura et al. have reported on continuous hyperthermic peritoneal perfusion (CHPP) with Cisplatinum and Mitomycin-C for peritoneal dissemination of gastric carcinoma. They have treated 11 patients with this technique prior to peritoneal dissemination of disease as a prophylactic measure. The authors have compared them with 31 similar patients who did not have prophylactic hyperthermic perfusion treatment. Two year survival of 81% versus 50% was reported in favour of patients who received continuous hyperthermic peritoneal perfusion (HPP) with chemotherapy. The authors have tried similar method of treatment for 29 patient after gross peritoneal dissemination of the tumour and compared them with another 20 similar patients without HPP treatment. No significant difference in their survival or tumour control rate was observed.

Trimodality Trials

Favourable results with thermoradiotherapy as well as limited experience with thermochemotherapy have resulted in a recent increased interest in trimodality treatment using chemotherapy plus radiotherapy plus hyperthermia in recurrent malignant diseases. Herman et al.[27] have reported on the treatment of 22 patients with hyperthermia, radiation and Cisplatinum. The results are shown in Table 12. As can be seen in both groups, albeit a small number of patients, a very impressive complete response and overall response rate has been achieved. Zeung et al.[28] have reported the utilization of this trimodality treatment namely radiation therapy, Cisplatinum, and intracavitary hyperthermia for the treatment of 34 patients with esophageal carcinoma. They have reported an overall response rate of 94% with a two year survival of 44% in these 34 patients. In their report of 26 patients who had trimodality treatment as a primary management of these patients, one year survival of 85% and two year survival of 50% was achieved. In eight patients in whom treatment was delivered for recurrent disease, two year survival of 25% was achieved. Kubota[29] have utilized trimodality treatment in the management of bladder carcinoma. The authors report complete response rate of 1/6 for heat alone; 1/4 for heat + Bleomycin; 3/9 for heat + XRT and finally 8/15 for trimodality treatment (Hyperthermia + irradiation + Bleomycin). As can be seen, the results with hyperthermia plus radiation plus Belomycin is significantly higher than either hyperthermia alone or combination of the two modalities. Kait et al.[30] has utilized trimodality management namely radiation, chemotherapy (Bleomycin plus Cisplatinum), and hyperthermia in palliative treatment of unresectable advanced esophageal cancers. They have compared the results with 80 similar patients who have received radiation and chemotherapy without hyperthermia. Their results are shown in Tables 15 and 16 in terms of response rate and survival. Matsufuji et al.[30] from the same institution, have reported on preoperative hyperthermia combined with radiotherapy and chemotherapy for patients with incomplete resected carcinoma of the esophagus. In their report they have three groups: 16 patients treated with surgery alone, 38 patients treated with surgery, radiotherapy and chemotherapy and 10 patients treated with surgery in combination with trimodality treatment. Median survival for groups 1, 2 and 3 were 6 months, 7.5 months and 11 months respectively.

Whole body hyperthermia has been used in several centers who have suitable equipment and expertise in this method. Van der Zee et al.[32] have reported on 6 patients with hyperthermia alone, 5 patients with hyperthermia plus chemotherapy & 22 patients with hyperthermia plus radiotherapy. In their series, heat alone showed no complete or partial response; heat and chemotherapy has shown 1/5 partial response. Combination of radiotherapy and whole body hyperthermia in 22 patients resulted in 5 complete responses in 4 partial responses with overall response of 9/22 (41%). Bull et al.[33] have reported on whole body hyperthermia and Cisplatinum in the treatment of disseminated malignant melanoma. From 7 patients in their report they achieved one complete response and two partial responses. They utilized blanket techniques for hyperthermia which was 41.8°C for the duration of 2 hours and the dose of Cisplatinum was 100 to 135 mg/m^2 IV over 6 hours. Newman et al.[34] has reported on moderate whole body hyperthermia in combination with chemotherapy in the treatment of oat cell carcinoma of the lung. In their report of 18 patients they have achieved 9 complete and 7 partial responses with an overall response of 16/18 (90%).

CONCLUSION AND SUMARRY

The reported Phase II trials show impressive initial results in the treatment of recurrent tumours with combination of radiotherapy and hyperthermia. Analysis of these results points to the extreme importance of prognostic factors which includes the quality of hyperthermia. The results of limited trials with hyperthermia and chemotherapy are encouraging. Review of all these reports underlines the urgent need for a prospective randomized trial comparing standard treatment such as radiotherapy and/or chemotherapy with either modality alone or both in combination with well executed hyperthermia. Until such trials are completed, the true potential of this new modality in the management of human malignancies will not be recognized.

TABLE 3 ACUTE COMPLICATIONS (WITHIN 6 MONTHS OF START OF RX) PATIENT WITH SINGLE LESIONS

Most Severe Complication Reported Within 6 months of RX Start	All Patients Analyzed	
	RT Alone	RT + Heat
Not visible reaction	28%	23%
Erythema	34%	27%
Dry desquamation	16%	11%
Moist desquamation	8%	3%
Ulceration	7%	7%
Necrosis	7%	6%
Thermal Blister	--	23%

TABLE 4 INTERSTITIAL THERMORADIOTHERAPY CLINICAL RESULTS

	Number of Evaluable Patients	CR	PR	NR	Follow-up (months)
Vora et al. (1982)	15	11	1	3	1-13
Oleson et al. (1984)	52	20	22	10	3-18
Strohbehn et al. (1984)	6	3	2	1	short
Yabumoto et al. (1984)	7	1	2	4	2-13
Bicher et al. (1984)	8	5	2	1	--
Cosset et al. (1986)	5745752				
Linares et al. (1986)	10	5	5	--	short
Puthawala et al. (1985)	43	37	6	--	6
Emami et al. (1986)	44	26	12	6	----
	242	153 (63.5%)	59 (24%)	30 (12.5%)	

CR - Complete Response; PR - Partial Response (over 50%) regression
NR - No Response

TABLE 5 COMPLICATIONS OF INTERSTITIAL THERMORADIOTHERAPY

	Number of Cases	All complications	All Complications
Vora et al. (1982)	16	3 (19%)	1 (6%)
Oleson et al. (1984)	52	10 (19%)	6 (11%)
Cosset et al. (1985)	29	12 (41%)	4 (14%)
Puthawala et al. (1985)	43	9 (21%)	5 (11%)
Linares et al. (1986)	10	4 (40%)	1 (10%)
Emami et al. (1986)	48	12 (52%)	8 (17%)

TABLE 6 RTOG PROTOCOL 81-04 OVERALL COMPLETE RESPONSE BY TREATMENT AND LESION SIZE ALL SINGLE LESIONS

	Lesion Size		
Treatment	<3 cm	>3 cm	Total
RT	11/28 (39%)	24/89 (27%)	35/117 (30%)
RT + Heat	14/27 (52%)	23/92 (25%)	37/119 (32%)
P = .51			

TABLE 7 PROGNOSTIC FACTORS IN CLINICAL HYPERTHERMIA

1 - Tumour size (including depth)

2 - Tumour site

3 - Irradiation related factors :
Dose/fractionation

4 - Chemotherapy related factors :
Type of drug/dose/schedule/delivery type

5 - Quality of hyperthemia treatments

TABLE 8 INTERSTITIAL THERMORADIOTHERAPY COMPARISON OF COMPLETE RESPONSE RATE (EVALUABLE LESIONS)

	Total No. of Patients	CR (%)
Total number of lesions with satisfactory heating 3 institutions *	96	77 (80)
Total number of lesions with unsatisfactory heating 3 institutions	14	0 (0)
Total number of lesions reported from the 3 institutions	120 *	77 (64)
Total number of patients from Selected Published Series	201	112 (55.7)

* Results from series reported from Washington University, Memorial Medical Center, and Institute Gustav-Roussy in which information regarding quality of hyperthermia and tumour response was available.

TABLE 9

Local Hyperthermia + Systemic Chemotherapy
Regional Hyperthermia + Systemic Chemotherapy
Systemic (Whole Body) Hyperthermia + Systemic Chemotherapy
Perfusion Chemotherapy and Hyperthermia : Extermities Peritoneal
Trimodality Trials : XRT + Chemo + Hyperthermia

TABLE 10

PATIENT	TUMOUR SITE	SIZE (MM)	THERAPY	NO.	MAXIMUM	MINIMUM	EFFECT
1	Chest Wall	16 x 13	Iphosphamide + HT	1	43.1	42.9	SD
			Cisplatin + HT	3	44.8	41.1	
2	Neck	60 x 32	Cisplatin + HT	2	42.8	41.6	PD
	Neck	60 x 25	Cisplatin	0			PD
3	Neck	50 x 45	Cisplatin + HT	2	41.0	40.4	PD
4	Neck	20 x 18	Cisplatin + HT	6	39.9		CR
		31 x 24	Cisplatin + HT	6	44.8	38.4	CR
		50 x 35	Cipslatin	0			PD
		40 x 37	Cisplatin	0			PD
5	Neck	87 x 64	Cisplatin + HT	2	42.6	42.0	NE

Dahl et al., 1987

TABLE 11 N^2 ---- N^3 (HEAD AND NECK CANCER), END OF TREATMENT

DRUG	HEAT		NO HEAT	
	CR	PR	CR	PR
ADM...	4/10 (.40)	5/10 (.50)	1/11 (.09)	3/11 (.27)
BLM...	5/11 (.45)	6/11 (.54)	2/11 (.18)	4/11 (.36)
Total...	9/21 (.43)	11/21 (.52)	3/22 (.14)	7/22 (.32)
GRAND TOTAL (*)		20/21 (.95)		10/22 (.45)

(*) Statistical significance : $p<0.01$

TABLE 12

Drug Dose 30-40 mg/m^2
Heat Dose 43° C/60 min
XRT Dose 2400-3600 cGY (previously irradiated)[a]
6000-6600 cGY (previously not irradiated)[b]
Results : (a) 9/16-CR 7/16-PR
(b) 4/6-CR 2/6-PR
3 Patients (at 40 mg/m^2) had significant blood count

REFERENCES

1. FIELD SB, BLEEHEN NM: Hyperthermia in the treatment of cancer. Cancer Treatment Rev 6:63, 1979.
2. IMAMI B, PEREZ CA, LEYBOVICH L, STRAUBE W, VON GERICHTEN D: Interstitial thermoradiotherapy in treatment of malignant tumours. Int J of Hyperthermia 3: 107-118, 1987.
3. PEREZ CA, EMAMI B, NUSSBAUM GH, SAPARETO S: Hyperthermia. In: PRINCIPLES AND PRACTICE OF RADIATION ONCOLOGY, (ed) Brady LW and Perez CA, 1987, J.B. Lippincott, Philadelphia, pp. 317-352.
4. HAHN GM: Hyperthermia and Cancer. New York, Plenum Press, 1982.
5. OVERGAARD J: The effect of local hyperthermia alone, and in combination with radiation, on solid tumours. In: Streffer C (ed): CANCER THERAPY BY HYPERTHERMIA AND RADIATION. Proceeding of the 2nd International Syonposium, Essen, 1977. Munich, Urban and Schwarzenberg, 1978, p. 49.
6. VALDAGNI R, LIU F-F, KAPP DS: Important prognostic factors influencing outcome of combined radiation and hyperthermia. INT J RADIAT ONCOL BIAL PHYS 15:959, 1988.
7. EMAMI B, GRIGSBY PW, LEYBOVICH L, MYERSON RJ, PEREZ CA, SATHIASEELAN V, STRAUBE W AND VON GERICHTEN D: Combination of deep hyperthermia and radiotherapy/chemotherapy in the management of recurrent pelvic tumours. Abstracts of the 5th In International Symposium on Hyperthermic Oncology, Kyoto, 1988, p. 225.
8. DI FILIPPO F, CARLINI S, SANTORI FS, GIANNARELLI D, CALABRO AM, BUTTINI GL, CAVALIERE F AND CAVALIERE R: Hyperthermia and chemotherapy for the treatment of osteogenic and soft tissue sarcoma. Abstracts of the 5th International Symposium on Hyperthermic Oncology,Kyoto, 1988, p. 103
9. NEWSAM JE AND LAW HT: Hyperthermic perfusion of the distended urinary bladder in the management of recurrent transitional cell carcinoma. A review after 6 years. BR J OF UROL 54:64, 1982.
10. ROBINS HI, DENNIS WH, SHECTERIE LM, NEVILLE AJ, MARTIN PA, GROSSMAN J, NEVILLE SR, RUSY BF, BRYAN GT, DAVIS TE: Results of a phase I clinical trial of a whole body hyperthermia-radiant heat device (WBH-RHD). PROC AM SOC CANCER RES 21:481, 1980.
11. BULL JM, LEES DE, SMITH R, SCHUETTE WH, KATIN M, GLASTEIN E, AND DEVITA VT: Whole body hyperthermia combined with nitrosourea in malignant melanoma. PROC AM ASSOC CANCER RES 21:481, 1980.
12. PEREZ CA AND EMAMI B: Clinical trials with local (external and interstitial) irradiation and hyperthermia: Current and further perspectives. Refresher Course No. 402C. Presented at THE 30TH ANNUAL SCIENTIFIC MEETING OF THE AMERICAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY, October 9-24, 1988, New Orleans, Louisiana 1988.
13. MEYER JL: The clinical efficacy of localized hyperthermia, CA RES (Suppl) 44:4745S, 1984.
14. EMAMI B: Interstitial thermoradiotherapy. Refresher Course. Presented at THE 30TH ANNUAL SCIENTIFIC MEETING OF THE AMERICAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY, October 9-24, 1988, New Orleans, Louisiana 1988.
15. PETROVICH Z, LANGHOLZ B, GIBBS FS, SAPOZINK MD, KAPP DS,

STEWART RJ, EMAMI B, OLESON J, SNEZER N, SLATER J, STRAHAN M: Regional hyperthermia for advanced tumours: A clinical study of 353 patients. INT J RADIAT ONCOL BIOL PHYS 16:601-607, 1989.

16. PEREA CA, GILLESPIE B, PAJAK T, HORNBACK NB, EMAMI B, RUBIN P: Quality assurance problems in clinical hyperthermia and it's impact on therapeutic outcome. A report by the Radiation Therapy Oncology Group. INT J RADIAT ONCOLO BIOL PHYS (in Press).
17. COSSET JM, DUTREIX J, DUFOUR J, JANORAY P, DAMIA E, HAIE C, CLARKE D: Combined interstitial hyperthermia and brachytherapy: Institue Gustave-Roussy technique and preliminary results. INT J RADIAT ONCOL BIOL PHYS 10:307-312, 1984.
18. EMAMI B, PEREZ CA, LEYBOVICH L, STRAUBE W, VON GERICHTEN D: Ineterstitial thermoradiotherapy in treatment of malignment tumours. INT J HYPERTHERMIA 3:107-118, 1987.
19. PUTHAWALA AA, NISAR AM, SHEIKH KHALID MA, RAFIE S, MCNAMARA S: Interstitial hyperthermia for recurrent malignancies. Endocurietherapy/Hyperthermia Oncol 1:125-131, 1985.
20. DAHL O, MELLA O, MEHUS A, LIAVAAG PG: Clinical hyperthermia combined with drugs and radiation. A phase I/II study. Strahlentherapie und Onlkologie 163:446-448, 1987.
21. ARCANGELI G, CIVIDALLI A, NERVI C, CRETON G, LOVISOLO G, MAURO F: Tumour control and therapeutic gain with different schedules of combined radiotherapy and local external hyperthermia in human cancer. INT J RADIAT ONCOL BIOL PHYS 9:1125-1134, 1983.
22. STEINDORFER P, JAKSE R, GERMANN R, SCHNEIDER G, BERGER A, MISCHINGER HJ, REHAK P: Hyperthermia as an adjuvant to radiation-and/or chemotherapy in far advanced recurrences of the head and neck region. STRAHLENTHERAPIE UND ONKOLOGIE 163:449-452, 1987.
23. EMAMI B, MYERSON RJ, PILEPICH MV, PARIS KG, LEYBOVICH L, STRAUBE W AND VON GERICHTEN D: Treatment of recurrent superficial tumours with hyperthermia and bleomycin. Presented at the 9TH ANNUAL MEETING OF THE NORTH AMERICAN HYPERTHERMIA GROUP, March 19-21, Seattle, Washington, 1989.
24. ISHIWATA J, KAMISAWA T, EGAWA N, KATO K, SOEJIMA Y, ISWAL T, SAKAKI N, KIDE T, TABATA I, TAJIMA T, SASAKI T, MAEDA T, KOIKE M AND MATSUDA, T: RF Capacitive heating in combination with chemotherapy for obdominal tumours. Abstract of the 5th International Symposium on Hyperthermic Oncology, Kyto, 1988, p. 105.
25. ZHANG Z, ET AL: The effect of hyperthermia-chemotherapy on bladder carcinoma-experimental and clinical studies. Abstracts of the satellite meeting of the International Congress on Hyperthermic Oncology, Beijing, China, September, 1988.
26. YONEMURA Y, FUJIMURA T, URADE M, KATAYAMA K, MIWA K AND MIYAZAKI I: Continuous hyperthermic peritoneal perfusion with cisplatin and mitomycin C for peritoneal dissemination in gastric carcinoma. Abstracts of the 5th International Symposium on Hyperthermic Oncology, Kyoto, 1988, p.163.
27. HERMAN TS, JOCHELSON MS, CLARK JR, TEICHER BA, SVENSSON GS, JORGEN HH, COLEMAN CN: Systemic cisplatin (CDDP), local hyperthermia and radiation for treatment of locally advanced human mallignancies.

Proceeding of the 30th Annual American Society of Therapeutic Radiology and Oncology Meeting, October 9-14, 1988, New Orleans, Louisiana. INT J RADIAT ONCOL BIOL PHYS 15 (1): 123, 1988.

28. ZEUNG A (personal Communication).
29. KUBOTA Y: Hyperthermic therapy of the bladder cancer. III: Clinical studies. NIPPON HINYOKIKA GAKKAI ZASSHI 72:742-751, 1988.
30. KAI H, MATSUFUJI H, OKUDAIRA Y AND SUGIMACHI K: Heat, drugs and radiation given in combination is palliative for unresectable esophageal cancer. INT J RADIAT ONCOL BIOL PHYS 14:1147-1152, 1988.
31. MATSUFUJI H, KUWANO H, KAI H, MATSUDA H AND SUGIMACHI K: Preoperative hyperthermia combined with radiotherapy and chemotherapy for patients with incompletely resected carinoma of the esophageal. Cancer 62:889-894, 1988.
32. VAN DER ZEE J, VAN RHOON GC, WIKE-HOOLEY JL, FAITHFUL NS, REONHOLD HS: Whole-body hyperthermia in cancer therapy: A report of a phase I-II study. EUR J CANCER CLIN ONCOL 19:1189-1200, 1983.
33. BULL JM, MANSFILD B, CRONAU L: Whole body hyperthermia and cisplatin in the treatment of malignment melanoma. Abstracts of papers from the 36TH ANNUAL MEETING OF THE RADIATION RESEARCH SOCIETY, April 16-21, 1988, Philadelphia, Pennsylvania, p. 31.
34. NEUMANN H, FABRICIUS H-A AND ENGELHARDT R: Moderate whole-body hyperthermia in combination with chemotherapy in the treatment of small cell carcinoma of the lung: A pilot study. Natl Cancer Inst Monogr 61:427-429, 1982.

11

LEUCOVERIN AND FLUOROURACIL IN COLORECTAL CANCER

Leslie R. Laufman

INCIDENCE, PREVENTION AND SCREENING

In the United States, the incidence of colorectal cancer is approximately one in fifteen for both sexes, making it our most common malignancy. This high incidence is generally attributed to a diet low in bulk, and high in animal fats. The mortality rates for colorectal cancer have remained relatively stable over the last 50 years, at 50 per 100,000 per year, and are surpassed only by lung cancer in both sexes and breast cancer in women (Figs 1,2)

These statistics may change dramatically in the future if current trends in adopting better diet continue. Recent studies clearly identify the populations at highest risk for the development of colorectal cancer.

* people with ulcerative colitis
* people with family history of hereditary polyposis
* people with prior colorectal cancer or polyps, or family history of same.
* people with family history of breast or uterine cancer. The American Cancer Society currently recommends routine screening sigmoidoscopy for these people as well as for all Americans over the age of 50.

Screening is especially important in this disease, because of new evidence confirming that polyps are precancerous lesions. Polyps and early cancers can be removed endoscopically, and even established cancers have a 45% chance of cure with approriate surgical techniques (Fig 3) [1]. Unfortunately, these screening programs are new and have not yet been widely implemented. Therefore, we do not yet see an impact on the statistics compiled by Sugarbaker (Fig 3) - 30% of patients with colorectal cancer have metastases at the time of diagnosis and 25% develop metastases later. Thus, 55% of all patients with colorectal cancer will be candidates for systemtic (palliative) therapy, but will eventually die of metastatic cancer.

SYSTEMIC THERAPY FLUOROURACIL .

The activity of fluorouracil (FU) in patients with colorectal cancer was described in 1958, and since then, hundreds of trials have been performed to test newer drugs or drugs combinations, against single agent FU. All these trials yielded negative results. For example, Buroker [2] recently tested FU against four FU-containing regimens, one of which was the widely used MOF-strep regimen of Memorial Sloan Kettering. None of the regimens produced a significant improvement in response or survival compared to FU alone (Table I, Fig 4).

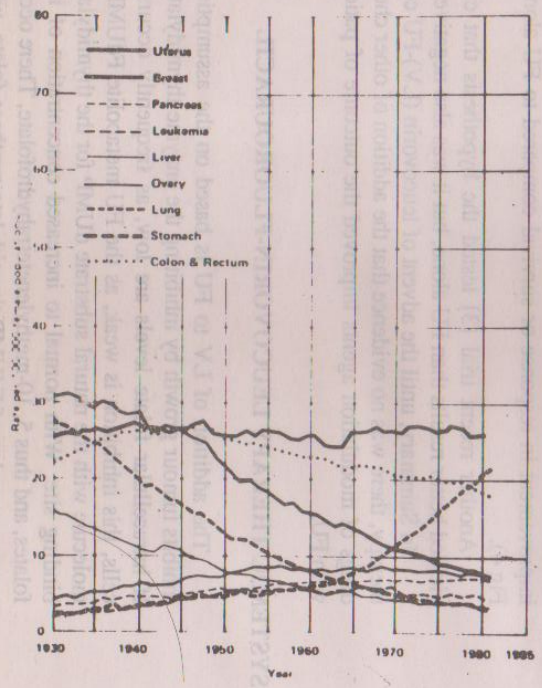
Another recent trial [3] tested the hypothesis that cisplatin-FU yielded better results than FU alone, but it was also negative (Table II).

In Summary, until the advent of leucovorin (LV)-FU combination therapy, there was no evidence that the addition of other chemotherapy drugs of modulation agents improved the outcome of patients treated with FU.

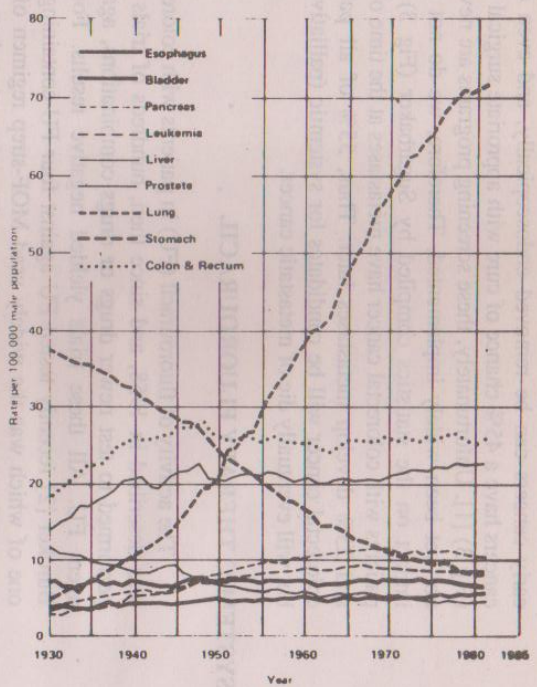
SYSTEMIC THERAPY LEUCOVORIN-FLUOROURACIL

The addition of LV to FU is based on the assumption that FU inhibits tumour growth by inhibiting the enzyme thymidylate synthase. If intracellular folate levels are low, as frequently occurs in cancer cells, this inhibition is weak, as the FU metabolite FdUMP competes molecule with the natural substrate dUMP for the thymidylate synthase binding site. With normal to increased concentration of intracellular folates, and thus 5, 10-methylenetetrahydrofolate, There occurs a stable ternary complex of FdUMP-thymidylate synthase-folate, which results in a much greater inhibition of DNA syntheses

AGE-ADJUSTED CANCER DEATH RATES* FOR SELECTED SITES
FEMALES, UNITED STATES, 1930-1981



AGE-ADJUSTED CANCER DEATH RATES* FOR SELECTED SITES
MALES, UNITED STATES, 1930-1981



The original trials of LV-FU were reported by Machover [4] and Bruckner [5] in 1982. Each investigator used different doses and schedules, but both demonstrated responses in patient whose metastatic colorectal cancers had been refractory to FU alone. Both also observed improved response rates and survivals, compared to historical controls at their individual institutions (Fig 5).

Many authors have subsequently reported similar results in uncontrolled trials. (Table III) [6]. Response rates range from 18-40%, but are always better than those previously observed for single agent FU in each institution. Some authors also observe that the cancer stabilization rate is high, which may be a reasonable goal for palliative therapy, if a good quality of life can be maintained.

Unfortunately, the toxicity of the LV-FU combination is greater than that of FU, and can be manifest as life-threatening, cholera-like diarrhoea, which is unpredictable in incidence and onset. Weakness, sometimes with cerebellar dysfunction, is also seen frequently. Both are toxicities which have a profoundly adverse impact on the patient's quality of life.

Randomized trials comparing FU versus LV-FU are now being reported (Table IV) [7]. Almost all controlled trials show a significantly better response rate for LV-FU versus 5 FU, and at least one shows a modest improvement in survival [8]. Most authors have attempted to use doses of FU which will induce toxicity equivalent to LV-FU, but this is difficult because of the different toxicity patterns.

Two important ongoing trials are NSABP adjuvant trials, one comparing LV-FU for Dukes' B-2 or C colon cancer and the other comparing LV-FU to methyle CCNU-vincristine-FU with or without irradiation, for Dukes' B-2 or C rectal cancer.

SYSTEMIC THERAPY - ORAL LEUCOVORIN-INTRAVENOUS FLUOROURACIL

The use of oral rather than intravenous LV has two advantages. The first advantage is practical, in that oral LV is well tolerated, and the active 1-isomer is completely absorbed, up to a threshold dose of 25 mg [9], so chronic maintenance of increased levels is easily achieved. The second advantage is theoretical, in that oral administration results in preferential absorption of the active 1-isomer, whereas intravenous administration of the recemic mixture yields high levels of the unmetabolized d-isomer. It is currently known whether the inactive d-isomer interfered with the cellular uptake and

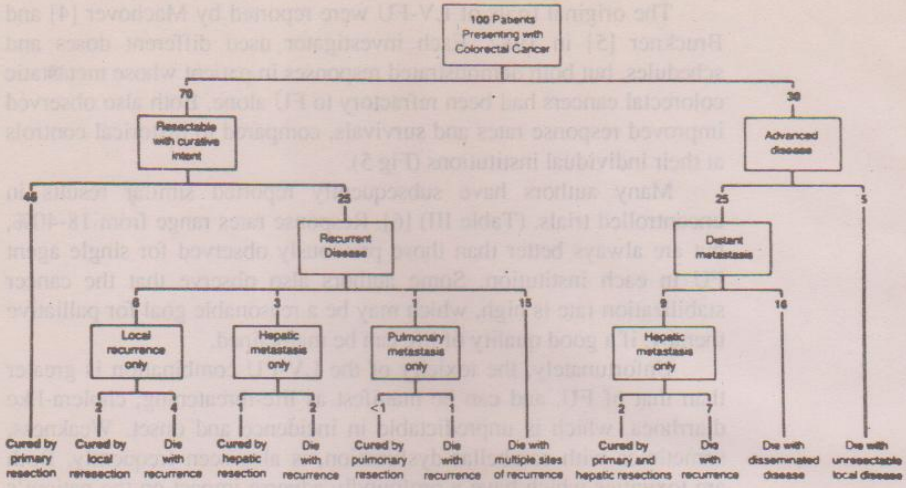


FIG. 25-6. Patterns of failure in 100 patients presenting with large bowel cancer. (August DA, Ottow RT, Sugarbaker PH: Clinical perspectives on human colorectal cancer metastases. Cancer Metastasis Reviews [in press])

DeVita, Cancer Principles & Practice of Oncology, 2nd Edition, 1985

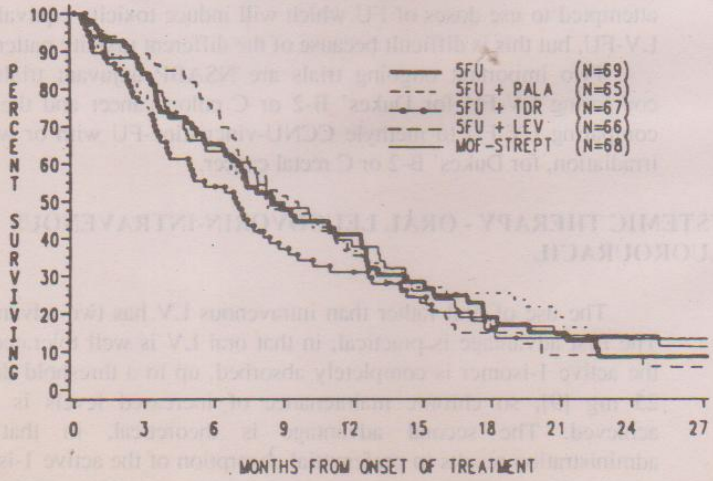


Fig 2. Survival according to treatment regimen.

Buroker et. al. Journal of Clinical Oncology, December, 1985

metabolism of the 1-isomer.

TABLE I

OBJECTIVE RESPONSE ACCORDING TO REGIMEN

Toxic Reaction	5-FU Alone (n=37)	5-FU Plus PALA (n=34)	5-FU Plus Thymidine* (n=34)	5-FU Plus Levamisole (n=40)	MOF-Strept (n=38)
Best response (%)					
Regression	29.7	11.8	17.6	22.5	34.2
Stable	56.8	55.9	53.0	62.5	23.7
Progression	14.5	32.7	30.4	15.0	42.1
Duration of regression#					
Median (wk)	40	55	18.5	25	26
Range (wk)	5-66	5-151+	12-30	5-123	5-139+

* One patient refused observations and could not be evaluated.
# Measured from first day of therapy to last day of documented measurements meeting criteria for response.

Buroker et.al.Journal of Clinical Oncology, December, 1985

TABLE II

CHEMOTHERAPY OF METASTATIC COLON CANCER

	# Patients	%CR+PR	Survival, Weeks
5 FU	57	18	41
5FU-DDP	53	19	30

Two uncontrolled trials of oral LV and intravenous FU have been done. Of 31 evaluable patients, Hines [10] reported a 46% response rate. Brenckman [11] reported a 35% response and 35% stable disease rate in 18 patients, with a median survival of 14 months. A 200+ patients, multi-institution, double-blind placebo-controlled trial has also been done, but results are pending.

QUESTIONS FOR THE FUTURE
WHICH PATIENTS SHOULD BE TREATED?

In many communities, surgeons are the primary caregivers for patients with colorectal cancer. Although resection of primary tumours cures 45% of all patients with colorectal cancer, it cures fewer than 10% of patients with metastatic disease [11]. The reason why surgery is ever effective is the slow growth rate of colorectal cancer. This slow growth rate is also one of the reasons cited for not treating metastases. Conventional therapy is often conservative, as described by Spiro: ".....it is wise not to treat the asymptomatic patient with known metastases until symptoms develop;...it is better then to postpone chemotherapy until metastases manifest themselves by obstruction or pain or bleeding"[12].

A careful examination of this hypothesis is necessary. Most trials of non-LV-FU chemotherapy in metastatic colon cancer show median survivals of no more than six months, whereas LV-FU trials show median survival of nine to fifteen months. In none of these trials do we find patients with longlasting, unmaintained remissions, but there are many patients with objective remissions or disease stabilizations lasting more than one year. If symbiosis between patient and cancer can be established and maintained at minimal cost and toxicity, one might wish to initiate therapy before the tumour burden becomes large and the patient becomes symptomatic.

The natural history of patients with asymptomatic, metastatic colorectal cancer has not been studied recently, even though sensitive biochemical and imaging tests now allow early identification of metastases. We recently observed 57 asymptomatic patients with measurable metastatic colon cancer for eight weeks without treatment, to obtain data on the growth rate of their tumours [13]. Of these 57 patients, 46 required treatment before the end of the eight week observation period, because of tumour progression or the development of symptoms. On this basis, we believe that patients should be treated as soon as metastases are diagnosed.

WHAT IS THE NEXT DOSE AND SCHEDULE OF LV-FU?

Widely varying doses of LV are recommended to modulate FU's effects. Some in vitro studies [14] suggest that a serum concentration of 10uM LV is necessary for optimal binding of FdUMP and maximal inhibition of thymidilate synthase; others demonstrate that 1 uM LV is

adequate to produce these effects [15, 16]. The situation in vivo is even less clear, with LV doses ranging from 25mg/month to 2,000mg/m2/month producing roughly equivalent results [6]. Two randomized, controlled trials were designed to examine the effect of LV dose. The first study [17] compared LV 200mg/m2 IV plus FU 370mg/m2 IV to LV 20mg/m2 IV plus FU 425mg/m2 IV, both given daily for five days every four weeks, and found a significantly better response rate and survival for patients treated with LV 20-FU 425. Whether these effects were due to a lower LV dose or to a higher FU dose is unknown. The second trial [18] compared LV 25 mg/m2/10 minute infusion to 500mg/m2/2 hour infusion, both followed by FU 600mg/m2 IV bolus, given weekly for six weeks, and yielded better results for the higher LV dose regimen.

There are as yet no trials designed to answer whether FU dose is an important factor in patient outcome, although one of the above trials [17] demonstrated that the regimen with lower LV and higher FU doses yielded a better response rate. Physicians who are experienced with this regimen observe occasional patients who relapse when treated at reduced FU doses (for toxicity) and in whom response can reinforced following FU dose escalation.

It is not clear whether the toxicity of this regimen is more strongly related to LV or to FU dose. If a patient experiences toxicity, it is best to withhold further therapy until toxicity has resolved, and, if necessary, to decrease the FU dose in subsequent courses of therapy. Two studies [6,11] examined the relationships between the FU dose and response, and between toxicity and response, but no correlations were found. One of these studies [11] used fixed dose oral LV, and FU dose escalated to toxicity, which occurred from 375mg/m2 to 850/m2. Thus, FU dose should be individualized for each patient.

The phase II trials of LV-FU show no clearcut advantages for either the once-weekly or the five day per month schedules, but no randomized comparison of these two popular schedules has been performed. The once weekly schedule may allow greater safety, because patients experience and recover from the side effects of each dose before receiving the next.

TOXICITY OF LV-FU

As described by Erlichman [8], the toxicity of LV-FU differs from that of FU alone in that diarrhoea, mucositis, skin changes, and watery eyes are more common, and myelosuppression is less common.

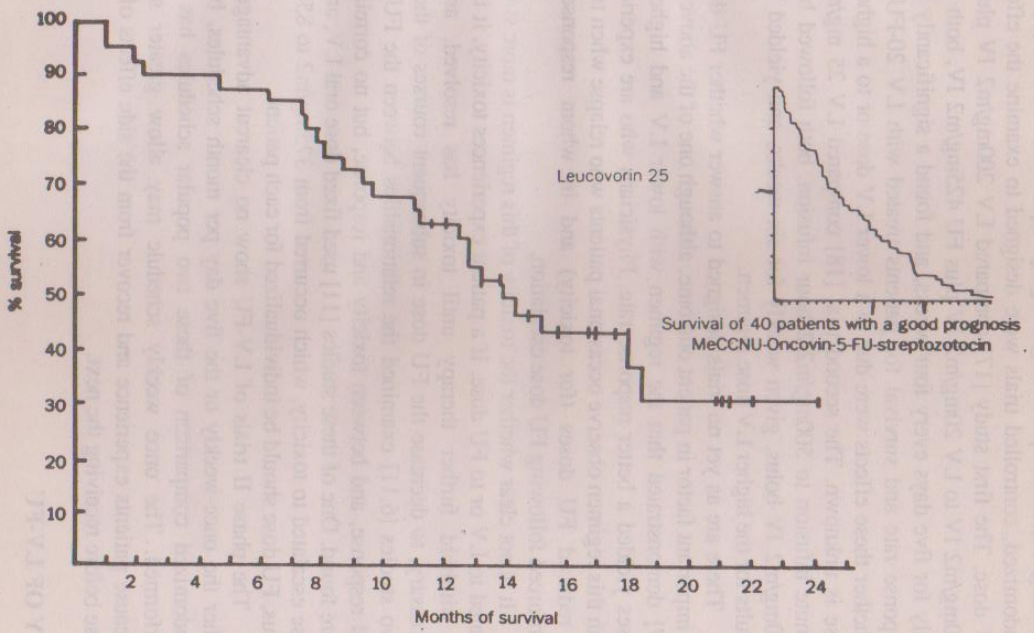


Figure 2. Survival times for patients with colorectal cancer treated with leucovorin-5-FU. Inset: Survival of 40 patients with a good prognosis from a GITSG trial of MOF-STZ in patients with advanced measurable colorectal cancer.[11]

Bruckner, RPMI Symposium, 1984

Almost every study of LV-FU treatment for metastatic colon cancer patients describes a significant incidence (approximately 5%) of catastrophic diarrhoea requiring hospitalization for hydration, usually occuring in the first six weeks of therapy. In the Gastrointestinal Tumour Study Group trial [18], 11 of 221 patients (5%) in the two LV-FU arms died of treatment related toxicity. Ten of these patients were more than 63 years old. In contrast, only 1 of 122 patients treated with FU alone died of treatment related toxicity (pancytopenic sepsis). Whether these deaths are preventable by closer monitoring and awareness on the part of physician and patient remains to be seen.

Risk factors for this 'unpredictable' toxicity have yet to be elucidated. Prior pelvic irradiation has been implicated in several patient deaths due to diarrhoea and neutropenic sepsis [6]. Concurrent LV-FU and irradiation can produce very brisk skin reactions, as well mucosal irritation. Medications that may be suspect, based on anecdotal reports [11], are phenytoin and trimethoprimsulfamethoxazole. The histories of patients who experience idiosyncratic toxicities must be examined carefully to identify additional risk factors and to improve the safety of this regimen.

DOES LV REALLY IMPROVE THE THERAPEUTIC INDEX OF FU?

Because of the different toxicities of LV-FU and FU alone, it is difficult to analyse studies with regard to this question. Although standardized toxicity grading systems are used, it may be difficult to equate the impact of toxicites in different organ systems. For example, a person may be totally asymptomatic with grade 4 myelosuppression but may take several months to recover from grade 4 diarrhoea. Quality of life assessments will help evaluate these problems.

Table III PUBLISHED RESULTS WITH LV- 5FU

(20 + Patients Without Prior Chemotherapy

Study	# Pt	Dose Frequency (Weeks)	% PR + CR	% Stable
Bruckner	32	3-4	22	59
Budd	107	4	22	?
Schmoll*	68	3	18	60
Erlichman	52	4	40	?
Machover	54	4	39	20
Laufman	33	1	39	24

*Tumour progression documented before entry.

Laufman, JCO, 1987.

Table IV Summary of Phase III Trials with the combination of 5 FU/LV in Advanced Colorectal cancer

Study	5-FU Treatment arm	Response %	LV and 5-FU Treatment arm (s)	Response %
Princess Margaret Hospital	370 mg/m2 daily for 5 days. Repeat every 4 wk	7	LV 200 mg/m2 followed by 5-FU 370 mg/m2 daily for 5 days. Repeat evey 4 wks.	33
Roswell Park	450 mg/m2 daily for 5 days then 200 mg/m2 every other day for 6 doses maximum. Repeat 4 wk after last 5-FU dose.	9	LV 500 mg/m2 by 2-hr infusion. 5-FU 600 mg/m2 mid-infusion. Repeat every week for 6 wks then 2-wks rest.	40
City of Hope	370 mg/m2 daily for 5 days Repeat every 4 wk	15	LV 500 mg/m2 by continuous infusion beginning 24 hr before 5-FU 370 mg/m2 daily for 5 days. Repeat every 4 wks.	45
Genoa (preliminary)	600 mg/m2 weekly. Repeat without scheduled treatment breaks.	5	LV 500 mg/m2 by 2-hr infusion. 5-FU 600 mg/m2 mid-infusion. Reapeat weekly without treatment breaks.	16
Gastro-intestinal Tumour study Group	500 mg/m2 daily for 5 days. Repeat every 4 wk	12	LV 500 mg/m2 by 2-hr infusion. 5-FU 600 mg/m2 mid-infusion. Repeat every wk for rest. LV 25 mg/m2 over 10 min followed 1 hr later by 5-FU 600 mg/m2. Repeat every wk for 6 wks then 2-wk rest.	28
Northern California Oncology Group	12 mg/kg daily for 5 days then 15 mg/kg weekly.	18	LV 200 mg/m2 followed by 5-FU 400 mg/m2 daily for 5 days. Repeat every 4 wks.	16
North Central Treatment Group	500 mg/m2 daily for 5 days every 5 wk.	8	LV 200 mg/m2 then 5-FU 370 mg/m2 daily for 5 days. Repeat every 4 wks for 2 courses then every 5 wks.	41*
(interim analysis)			LV 20 mg/m2 followed by 5-FU 425 mg/m2 daily for 5 days. Repeat every 4 wks for 2 courses then every 5 wks.	

*Low-dose LV arm; 5-FU : 5-Fluorouracil; LV ; leucovorin; Response includes complete and partial remissions.

Arbuck, Cancer Supplement, 1989.

Assuming that different organ system toxicities are comparable, and that no observer bias colors toxicity reports, it is still difficult to determine whether the improved antineoplastic effect of LV-FU is achieved only with higher toxicities. The three trials reporting antineoplastic benefit for LV-FU [17, 18, 19], also report more severe toxicity. A study from the Northern California Oncology Group [19], showed no difference in response rate or survival, but had higher hematologic and non-hematologic toxicity in the FU-alone arm.

The double blind randomized trial described earlier may answer these questions, in that all patients are treated with escalating doses to first toxicity, by physicians who are blinded with regard to treatment. Since toxicity, rather than arbitrary selection of dose, determines each patient's treatment plan, there can be no argument whether the patient is receiving an adequate dose level. Such a dosing scheme prevents the overdosing of sensitive patients and eliminates the artifical dosage ceiling of conventional treatment plans.

CONCLUSIONS

Whereas colon cancer is a major problem in the United States, there are new and exciting developments in the areas of prevention, screening and treatment. The use of leucovorin-fluorouracil to palliate patients with metastatic cancer is becoming widely accepted, and may lead to significant improvements in adjuvant treatments.

REFERENCES

1. SUGARBAKER PH, GUNDERSON LL, WITTES RE, Colorectal cancer. In : Cancer: Principles and Practice of Oncology, p 869, Editors : VT DEVITA, S HELLMAN, SA ROSENBERG. Lipponcott, Philadelphia, 1985.
2. BUROKER TR, MOERTEL CG, FLEMING TR, et al. A controlled evaluation of recent approaches to biochemical modulation or enhancement of 5-fluorouacil therapy in colorectal carcinoma. J CLIN Oncol 3:1624-1631, 1985.
3. LOEHRER PJ, TURNER S, KUBILIS P, et al. A prospective randomized study of 5-fluorouracil alone or with cisplatin in the treatment of metastatic colorectal cancer: A Hoosier Oncology Group trial. Proc ASCO 6:297, 1977.
4. MACHOVER D. GOLDSCHMIDT E, SCHWARZENBERG G, et al. Treatment of advanced colorectal and gastric adenocarcinomas with 5 FU combined with high dose folinic acid: Pilot Study. Cancer Treat Rep 66:1803-1807, 1982.
5. BRUCKNER HW, OHNUMA T, HART R, et al. Leucovorin potentiation of 5-fluorouracil efficiency and potency. Proc AACR 23:111, 1982.
6. LAUFMAN LR, KRZECZOWSKI KA,

ROACH R, et al. Leucovorin-5-Fluorouracil: An effective treatment for metastatic colon cancer. J Clin Oncol 5:1394-1400, 1987.

7. ARBUCK SG, An overview of clinical trials with LV/5-FU in advanced colorectal carcinoma. Cancer Suppl 63:1037, 1989.
8. ERLICHMAN C, FINE S, WONG A, et al. A randomized trial of fluorourancil and folinic acid in patients with metastatic colorectal carcinoma. J Clin Oncol:269-475, 1988.
9. MC GUIRE BW, SIA LL, HAYNES JD, et al. Absorption kinetics of orally administered leucovorin calcium. Development of Folates and Folic Acid Antagonists in Cancer Chemotherapy. pp. 47-56. NCI Monograph, 1987.
10. HINES JD, ADELSTEIN DJ, BAST J, et al. High-dose oral (PO) leucovorin (CF) and intravenous 5-fluorouracil (5FU) in advanced metastatic colorectal carinoma: Results of a pilot-phase I study. Am Soc Clin Oncol 7:110, 1988.
11. BRENCKMAN WD, LAUFMAN LR, MORGAN ED, et al. Pilot trial of 5FU with high doses of oral Wellcovorin (R) in advanced colorectal carinoma. Am Soc Clin Oncol 7:376, 1988.
12. SPIRO HM. Carcinoma of the colon and rectum. In: Clinical Gastroenterology, pp 691-706. Collier MacMillan Limited, Canada. Toronto, 1970.
13. LAUFMAN LR, BRENCKMAN JR. WD, COLLIER MA, et al. Interim analysis of a phase III randomized, double-blind, placebocontrolled trial of 5-fluorouracil (FU) with oral leucovorin (LV) vs. FU alone in metastatic colorectal cancer. Proc ASCO: 1989.
14. EVANS RM, LASKIN JD, HAKAKA MT. Effects of excess folates and deoxyinosine on the activity and site action of 5-fluorouracil. Cancer Res 41:3288-3295, 1981.
15. ULLMAN B, LEE M, MARTIN DW, et al. Cytotoxicity of 5-fluoro-2' -deoxyuridine: Requirement for reduced folate cofactor and antagonism by methotrexate. Proc Natl Acad Sci USA 75:980-983, 1978.
16. KEYOMARSI K, MORAN RG. Folinic acid augmentation of the effects of fluoropyrimidines on murine and human leukemic cells. Cancer Res:5229-5235, 1986.
17. O'CONNELL MJ, WIEAND HS. A controlled clinical trial including folinic acid at two distinct dose levels in combination with 5-fluorouracil for the treatment of advanced colorectal cancer: Experience of the Mayo Clinic and North Central Cancer Treatment Group. The expanding Role of Folates and Fluoropyrimidines in Cancer Therapy, 1988.
18. PETRELLI N, STABKEIN D, BRUCKNER H, et al. A prospective randomized phase III trial of 5-Fluorourcil versus 5FU-high dose Leucovorin in Patients with metastatic colorectal adenocarcinoma. A report of the Gastrointestinal Tumor Study Group. Am Soc Clin Oncol 7:357, 1988.
19. VALONE FH, DRAKES T, FLAM M, et al. Randomized trial of 5FU versus leucovorin plus 5FU versus sequential methotrexate, 5FU leucovorin in patients with advanced colorectal carcinoma: A Northern California Oncology Group trial. Proc ASCO 7.95, 1988.

12

NATURAL HISTORY AND TREATMENT OF UNDIFFERENTIATED CARCINOMA OF THE NASOPHARYNX

J.P. Armand

Schmineke and Regand simultaneously described the pathological uniqueness of nasopharyngeal carcinoma. Radiation therapy has been the mainstay of the treatment of nasopharyngeal tumours as they are very radiosensitive. There has been an impressive progress in staging, imaging and technology of radiation. The survival rate however varies from 15 to 50% in published literature.

An abundant literature on the role of EBV as a carcinogen has resulted in more confusion than crystalisation of concepts. There is a subset of poorly differentiated tumour with heavy lymphocytic infiltration. It is quite different from other tumours in that there is a lack of classic carcinogenic antecedent (tobacco and alchohol), bimodal age distribution particularly in European and African series, the less preponderance of male sex, EBV positive serology and different natural history. It is a disease different from squamous cell carcinoma of the same site.

STAGING AND PROGNOSTIC FACTORS

NPC is initially a locoregional disease with a great systemic dissemination potential. Till recently its curability was confined to the locoregional stages and the great majority of patients presented with

advanced disease. The staging systems developed and available through the years are: HO (1970) AJC (1977), UICC (1978), KYOTO (1978) and Chinese classification (1979). The main feature of the TNM system is its simplicity, but the lack of adaptation to clinical reality made the HO and KYOTO stagings more attractive to clinicians. The nodal volume and the anatomical extent were recognized as the main determinants of systemic failure, while osseous base of the skull and neurological involvement hold the key of the local evolution. the modern TNM classification (UICC-AJC 1986) is probably adequate since it gives the possibility of staging before treatment with imaging workup, and the role of the CAT scan is recognized in all its helpfulness.

CLINICAL HISTORY

The course of UCNT is marked by florid local growth and frequent distant metastasis. However, good performance status, younger age group and female sex have a better prognosis. The aggressiveness of UCNT is many times more as compared to NPC of WHO. I. variety. The autopsy series of TEOH highlighted the virulent behaviour of UCNT which till then was not adequately appreciated by both radiation and, medical oncologists. We at IGR have started an exhaustive staging procedure for UCNT since Sept. 85. The staging work up includes clinical, and ENT evaluation besides, SMA 12, CT scan of nasopharynx X-ray chest, sonography of liver, bone scan and bone marrow biopsy or aspiration. It is our experience so far that 87% who die of disease harbour distant metastasis mostly in bone, lung and liver. The nodal status in UCNT is a good indicator of spread. The meticulous staging procedure as described above yields 50% of metastastic deposits in disease with N3. (UICC-AJC 1986). A massive 'encuirasse, skin infiltration is occassionally seen in those patient who have failed in treatment. This form of spread has been acknowledged only in the HO staging of UNCT. Most of our findings (between 10/85 to 06/88) can be summarised as follows :-

Metastatic disease can present at all stages, but is closely related to N3 nodal status (45/78 patients).

*High proportion of patients presents with metastatic bone disease (79% - 62/78 patients). It can be indolent clinically as in prostate and breast cancer in about 20% of patients.

*Bone marrow invasion, never described before is common (30% - 24/78 patients) and is linked to bone metastasis; 3t A is a poor

prognosis.

*Liver metastasis (41% - 32/78 patients) are clinically and biochemically silent early and can be detected by echography. They are also late disease/poor prognostic factor.

*Patients with a few bone metastasis exclusively are a manageable good prognosis group (17%).

Lung metastasis (26% - 20/78 patients) are clinically silent during follow up, and may have a long evolution. They have been associated with the 'Pierre-Marie syndrome'.

*The overall natural history of progressive disease is short, with most metastasis (80%) appearing within 18 months from the first symptoms.

* T stage has no influence on metastatic potential, but determines local evolution, with important T4 bone erosion of the base of the skull being hard to control even with a high dose of radiation.

*Paraneoplastic syndromes are associated with this disease. Hypertropic osteoartheropathy has been described, and is usually associated to pulmonary or hilar metastasis. Leukemoid reaction and tumour specific fever have been recently described by our group and are present in 14% (11/78 patients) of high tumour volume cases.

*Extraregional lymph nodes are frequently involved, not always in continuity with neck nodes. 18% of patients (14/78 patients) will present this ''pseudo-lymphoma'' clinical picture (retroperitoneal, pelvic, inguinal, axillary nodes) detected by CAT scan, and sometimes through symptoms. There is also frequent bone metastatic disease associated. The general immunological status of NPC patients has been studied. Its prevalence in areas with high rates of chronic parasitic and bacterial infections is known, as well as a simultaneous pathology consistant with this association in a high proportion of patients (unpublished observations). Its relevance to the pathogenesis and evolution of the disease remains to be assessed. Incidence in siblings or in familial groups has been described but it is anecdotal. HLA typing has been done but no hard data confirm any positive links in this regard.

In conclusion, UCNT has a metastatic evolution in most patients dying with or of disease. Its presence is associated with large nodal volume at presentation. It is often asymptomatic and an intensive workup is essential in all prospective trials, as well as a good therapeutic guide before starting treatment. Liver disease and bone marrow involvement are very advanced disease indicators, and their presence can be detected only by workup. Bone disease is the most

prevalent metastatic site.

CHEMOTHERAPY IN U.G.N.T. WITH ADVANCED NODAL DISEASE:

Management of UCNT with cytotoxic drugs is not a novelty. But, the data available so far which is generally scattered do not measure upto the current standards of methotrexate in assessment. If one has to extrapolate, drugs like adriamycin, cisplatinum and bleomycin prove to be active agents. Vinca alkaloids, methotrexate and, 5 FU seem to be active but not as much as the preceding group. Alkyating agents are generally disappointing though a short term response is observed.

ADJUVANT CHEMOTHERAPY

The present review deals with a conglomerate of adult and paediatric data. NPC of squamous cell UCNT from different centers with varying level of staging work up also have been included. Patients have been pooled from diverse geographical area. We have herein reviewed major reported trials from various centers. The Milan trial and Princess Margaret trial have demonstrated no clear advantage with chemotherapy. Milan trial has inadequate drug scheduling and poor compliance while, Tannocks analysis of later series is a retrospective analysis with historical control which has an inherent problem in interpretation. The Isrieli series and Taiwan experience do not demonstrate a clear advantage of adding chemotherapy to radiation. While, Huang has demonstrated that neoadjuvent or, concomitant chemotherapy with radiation is useful against the historical control. M.D. Anderson with the same strategy as Huang has demonstrated the utility of neoadjuvent, or concomitant chemotherapy. Long term follow up is required to prove the benefits of above strategies.

There exists a close relation between nodal status and, local control. Huang has reported 64 percent-5 year survival in patients with N3-2C, status treated with cyclophosphamide, methotrexate, and or bleomycin and C.D.D.P., as against only 49 percent for those treated with radiation alone. American experience recently published also shares the same optimism. Our institution evaluated patients of U.C.N.T. treated with radiation and with combined modality. This prospective non randomised study conducted between Jan. 84 to Dec. 84 doesn't as yet show a survival benefit. However, significant proportion of patients treated with both modalities have demonstrated increased

disease free survival We have started a new neoadjuvant chemotherapy protocol since (10/85-12/87) consisted in alternating chemotherapy. Chemotherapy is as follows, CDDP 100 mg/m^{21} dl, Bleomycin 15 mgs. I.V. push day 1 then 16 mg/d x 5 days of 35 cGY. in 25 days, was delivered starting on D43 and, D95. Nearly 30 patients with N2C, and non-metastatic patients have been assessed so far. The median follow-up has been 26 months. 15/28 evaluable patients that is 60% are without evidence of disease.

The second generation protocol has replaced 5 FU with epirubicin. The anterior chemotherapy in this protocol is as follows: CDDP 100 mg 1 m^2 on day 1, Epirubicin 70 mgs/m^2/day 1 and Bleomycin 15 mgs. I.V. bolus followed by 12 mg 1 m^2/dx 5 continous day parentrally. The chemotherapy is delivered on day 1, day 2, following which radiation commences on day 5. A total of 70 cGY, in 7 weeks is delivered to primary and nodal area with suitable techniques. Evaluation of response to chemotherapy before radiation (WHO - criterian and C.T. Scan) has shown complete response in 24 of 29 patients i.e. 83% and, 5 of 29 have shown partial response. Thus there has been a total response following chemotherapy.

These two pilot neoadjuvant trials compared to other recent experience suggest curability with combined treatment in most cases of UCNT. This will be further tested by prospective randomised study.

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CURRENT STATUS AND PERSPECTIVE OF LOCOREGIONAL CHEMOTHERAPY

J. Schueller

New techiques have brought new impulses to an old method, namely intra-arterial chemotherapy described by kopp in 1950. The discussion ranges from uncritical praise for the rising remission rate, which is not reflected in an improved survival rate; to an equally unfounded damnation, whereby the side effects are often blamed on the method itself instead of possible improper administration.

Reasons for the increased interest in this therapy are found in the increasing incidence of colorectal carcinoma in practically all western industrial countries, with the exception of Japan. In 1987 in the USA, 145.000 new incidences of colorectal carcinoma were documented, with 60.000 deaths. In Austria an increase in this carcinoma was also registered in the last 10 years (roughly 4.000 new cases per year). Half of these patients relapse or metastasize and do not survive the 5-year limit. Only 10-20% are solitary liver metastases and, therefore surgically resectable, with better survival.

For the others there remains a median survival time of 6 - 8 months. Fluoropyrimidine therapy, mainly 5-Fluorouracil, induces remission rates of a mere 15 - 20%. This percentage could not be improved, despite numerous combination therapies (1) (2).

Reasons for this relative chemoresistance in gastrointestinal

carcinoma lie in the high Go-cell portion, a higher doubling time, (80 days for colon carcinoma, over 100 days for lung metastasis) and a lower Thymidin labeling index. This makes only a small portion of the cells in proliferation vulnerable to 5-FU, an antimetabolite whose effects are mainly seen in-proliferating cells.

Biomodulation of 5-FU through high dose folinic acid enhances the inhibitory effect of the major acting compound FdUMP on the key enzyme Thymidilat syntheses ase by formning a stable tertiary complex which causes cell death by thymidine starvation. Objective responses in FU-resistant patients form a strong argument in favour of the combianation. Thus far, results of Phase II clinical studies are promising. Preliminary results of onging Phase III studies also reflect the higher remission rate. Some authors even believe they can infer improved survival rates in their studies.

Another future concept may be the combination of 5-FU with delayed high dose uridine, a natural pyrimidine nucleoside, which can rescue G.I. toxicity induced by 5-FU.

Considering this recent concept, which David Santi transferred directly from the biochemistry lab to the clinic, the concept of locoregional chemotherapy almost seems to be a historical medical procedure. After the first description of an intra-arterial chemotherapy in head and neck tumours by Kopp in 1950, Biermann performed one on a liver just one year later. It would take another 14 years until Sullivan operatively implanted a hepatic catheter by laparatomy for the first time in 1964.

So the idea to increase the cytostatic concentration by direct perfusion of the target organ and to simultaneously reduce the systemic side effects is almost 40 years old. The reason why this seemingly simple procedure could not establish itself lies mainly in many complications caused by the externally placed catheter, haemorrhages, thrombose, infections, time limited usage of the catheter and repeated hospitalization of the patient.

The discovery of a fully implantable catheter system (a by-product of space research) brought improvement not only to the technical problems, but also to the patients' quality of life (Port-a-cath; PHARMACIA). A silicone catheter is connected to a subcutaneously implanted port with a metallic or plastic coating (recently also of titanium). The port also consists of a rubber membrane that can repeatedly be punctured percutaneously with a special needle. This system can be used intravenously, (also facilitating the removal of blood samples), intraarterially and intraperitoneally. The main

advantage is easy to see, namely that sterile handling practically eliminates the risk of infection, especially the much-feared peritonitis abexterni seen with external Tenkhoff catheters.

In addition to avoiding these types of complications, this catheter system serves another important goal in palliative cancer treatment: 'an improved quality of life'. A good ambulatory implementation is secured; the unavoidable isolation of the patient in the hospital despite all efforts of doctors and nursing staff is spared; and the patient can be with his family under the care of his family physician.

INTRAPERITONEAL CHEMOTHERAPY

The main indication lies in the treatment of carcinosis peritonel in gastrointestinal carcinoma and ovarian cancer. The main advantage of intraperitoneal chemotherapy is the essentially higher concentration of cytostatic drugs in the tumour, compared to systematic therapy (6). Depending on the size of the molecule and the water-solubility of the applied drug, the concentration increase 1000-fold with Cytosinarabinoside or Mitoxantrone, an even 5000 times higher increase in concentration was observed using 5-FU in peritoneal carcinosis. An added bonus is the decreased systemic toxicity, as FU reaches the liver via the portal circulation and is metabolized and eliminated from liver in its first passage itself. Compared to 5-FU, Cisplatin only has a 30-times higher concentration and is not likely to show diminished systemic side-effects, especially nephro toxicity, because it is not eliminated in the liver. But a peripheral inactivation is possible by adding sodium thiosulphate. Despite these theoretical pharmacokinetic disadvantages, Cisplatin remains one of the most attractive drug for clinician in IP-therapy, especially in the peritoneal carcinosis in ovarian cancer.

A considerable disadvantage of the IP-method lies in the fact that the increased concentration is only fully effective in the upper layers of the cells, as Ozol (7) was able to prove at a very early stage with Doxorubicin. The very uncertain degree of penetration indicates that IP-therapy is mainly suitable for micronodular forms of peritoneal carcinosis up to 5mm and not for larger tumour masses. However, Howell, reported responses to i.p. Cisplatin and Etoposide in patients with bulky intraabdominal disease, may be due to the ability of these drugs to reach the core of tumours masses by capillary flow in substantial concentrations. Therefore, besides surface diffusion which would not be expected to produce good drug exposure for deeper

portions of bulky tumours, there exists a second route. Levels equivalent to those resulting from intravenous drug administration reach the tumours by capillary blood flow.

Cisplatin seems to compensate its pharmacokinetic disadvantage with a deeper penetration, roughly 3mm, based on examination using proton-induced X-ray emission (8), (9). Its derivative, Carboplatin, appears to surpass Cisplatin from the pharmacokinetic point of view, because of its greater molecular weight (371 vs 299), increased water-solubility and a consequently slower peritoneal clearance. No nephrotoxicity is seen.

This was our motivation in administering Carboplatin intraperitoneally in increasing dosages to 8 female patients with peritoneal carcinosis (5 ovarianeal carcinomas, 2 mesotheliomas, 1 corpus uteri). The maximum tolerated doses is currently 450 mg/square meter (highest total dose 750 mg). The marrow toxicity rose in all 3 pretreated cases - eventually also due to the previous therapy - to WHO-degree II-III (thrombopenia up to 20.000, leukopenia around 1000), indicating that Carboplatin may cause systemic toxicity even when administered by IP route.

A pharamacokinetic study is being planned, using neutron absorption method performed in the nuclear reactor center at Seibersdorf. A similar study involving Mitoxantrone has been finished. In widely varying peritoneal clearance, possibly induced by a high tissue binding in slow release of the active substance, a relationship between the AUC of peritoneal fluid to serum was 1108. A 30 mg/sqm dosage of Mitoxantrone is recommended. Following the study of drug kinetics and also keeping the possibility of chemical pertionitis in mind serious chemical peritonitis is common with doxorubicin. Intraperitoneal application of doxorubicin must be forbidden. In 14 patients with colon carcinoma a 42% remission rate was recorded to date using 5-FU 1200 mg/sqm with Leucoverin 500 mg/sqm x 5/every four weeks. Speyer pointed out that a large amount of intraperitoneally administered Fluoropyrimidines is absorbed by portal system, thus delivering a high drug concentration to the liver (4-10 times the concentration in peripheral venous blood). However, in a subgroup of 5 patients who had intraabdominal and intrahepatic disease as well, no responses were observed in the liver. Further trials will be needed to define the efficiancy of the i.p. approach to the treatment of metastatic liver disease. The catheter problems seen in the 34 patients and the 186 cycles that we have followed, were minimal (2 port infections and 2 port revisions). This method is also feasible on an out-patient basis.

Nevertheless in time other difficulties can occur. Perfusion difficulties from fibrin deposits on the catheter tip (inflow or outflow obstruction) and distribution problems in the peritoneal cavity caused by adhesions and sometimes due to progressive disease, are important difficulties.

For these reasons we used two control methods - nuclear medicine check-ups with 99 Tc instillation and, computer tomography using intraperitoneal infusion of 2 1. dialysate with 70 ml Jopamiro. We also use intraperitoneal instillation of 32% 70 000 molecular weight Dextran (HYSCON, Pharmacia), which has proven to be effective in controlling adhesion formation following fertility surgery (6x5 ml HYSCON at each cycle).

In Sugarbaker's adjuvant study comparing colorectal carcinoma with IP-therapy and systemic doses of FU a noticeably reduced rate in intial relapses in the peritoneum was observed (12). In future, an IP therapy would also lend itself well to adjuvant application with small volume tumours, in gastrointestinal carcinoma. And also, in consolidation of complete remission in ovarian cancer.

INTRA-ARTERIAL THERAPY

The main indication is doubtlessly the non-resectable bilateral liver metastatic spread of colorectal carcinoma. Liver is frequent site of metastasis in colorectal carcinoma. This type of large liver tumour is almost solely fed arterially by neoangiogenesis. Small liver tumours derive their main blood supply by the portal vein, just as the normal liver. Therfore intraportal infusion is best for adjuvant application and intraarterial infusion in palliative treatment.

Compared to uncertain penetration in intracavitary use, the entire area surrounding the tumor fed by arteries benefits from the higher drug concentration. In 5-FU the concentration is 100 times higher, in FUDR 400 times higher, with this method compared to systemic application. The advantage of less systemic toxicity with this method will also be apparent when the target organ concomitantly is the main organ of metabolization and elimination of the used drug. This requirement will best be fulfilled by the fluoropyimidines. The first liver passage shows a 5-FU extraction rate of 50%, and for FUDR (Floxuridine) up to 90%. This is comparable to isolated liver perfusion. (16)

A prolonged perfusion time with Mitomycin is not rational because of the danger from DNA repair mechanism in alkylating substances. Based on shorter half life, a long tumour doubling time and

increased vulnerability to antiproliferative effects during the DNA synthesis phase, fluoropyrimidines as antimetabolites are applied in an optimal way by long-term continuous perfusion (over 1-2-weeks).

New techniques have made externally worn or fully implantable pumps a possibility for out-patient treatment. Examples for this are the fully implantable pumps from Infusaid with inexhaustible energy source independent of batteries. This consists of 2 separate chambers, a drug resevoir, and an outer chamber with an inert 2-Phase gas mixture that is compressed by percutaneous filling. The energy for the next pump cycle is supplied by the pressure from this step (17). The pump is implanted in the right lower abdominal area, filled volume is 50 ml and a side port allows additional bolus application. Essential disadvantages are the fixed flow rate per day of 2-3 ml, not being able to reuse the pump and the extremely high cost. After implantion just 3 of these pumps, we changed to using only externally worn, reusable, battery-powered peristaltic pumps. The newest models of such external pumps are of high technical standard, using microprocessor steering and allowing a precise flow rate programming, with the possibility of controlled bolus administration. (Deltec CADD I and II, Pharmacia.)

Based on the above mentioned consideration, FUDR in 0.3 mg/kg dosages per day with extended perfusion for two weeks with a two-week break was mainly used. Later this was reduced to 5-7 days due to increasingly apparent toxicity. In the estimated 1000 patient cases reviewed in the diverse studies made in the USA and in German-speaking countries, a surprisingly unified and impressive remission rate of 50% could be noted.

We were able to confirm this in our own 30 cases of FUDR treatment (13) (20). The median survival rate for our patients was 17 months, compared to 6-8 months historically. The patient to survive longest died after 31 months from brain metastasis, although the liver was in remission. This illustrates one of the basic critiques of this method: Even in pure liver metastatic spread, there is apparently the chance of peripheral micrometastatic spread. How far this could react to a combined systemic/intraarterial therapy or if this would only worsen the patient's quality of life remains to be investigated.

For Sugarbaker, Atlanta, a tumour involvement on hepatic lymph nodes represents a contraindication for intraarterial therapy based on the worsened prognosis (21). For Patt, Houston, the importance of palliation in the liver compared to slowly spreading lung metastasis with no symptoms is important. Because of extrahepatic disease, patt felt compelled to end the intraarterial liver tratment when this became

life-endangering (24) (14). Both do agree that this type of palliative measure should mainly serve to improve the patient's quality of life and not to prolong survival at any price.

This problem is closely related to the question raised in many studies regarding the disproportionally high rate of local toxicity (15) (18). Even if chemical hepatitis is relatively easy to control by exact observation of the transaminase peak - and even though chemical cholecystitis can be stopped by prophylactic cholecystectomy - and, correctly placed catheter using a pre-operative angiogram, can help to avoid unwanted perfusion in neighbour organs, the demand for not only better but particularly for less toxic therapic remains unchanged.

Following these particular goals, we made pilot study on 12 patients with a combination of Leucovorin 300 mg/sqm bolus-infusion followed by 5-FU 750-1000 mg/sqm infusions continually for 4 hours. This was done to combine the advantages of biomodulation of 5-FU with the advantages of regional application. A remission rate of 45% (even in 1 pretreated patient) at a considerably decreased toxicity makes it worth while to go on testing this new combination, may be as a simultaneously administered continuous 5-day-infusion, due to short half life of the major action part of Leucevorin, the L-Leucovorin with t/2 of 1,2 h. The search for better and less toxic intraarterial therapies lead to a third aspect, namely influence by reduced blood flow in the target organ, as hepatic blood streaming always remains an uncertain factor and is difficult to calculate.

CHEMOEMBOLISATION :

This can be achieved through regionally applied vasoconstrictors such as epinephrin or angiotensin. This leads to a redistribution of blood from the normal liver tissue to the tumour. Due to the lack of smooth muscle strands in tumour vessels, these do not react to the vasoconstrictor.

Artery ligation and permanent occlusions are no longer being used due to serious side effects and rapid development of collateral vessels which feed the tumour. Therefore the future should lie in short-term flow disruptions, caused by self-dissolving microspheres or chemobolisation mixed with a cytostatic agent (Spherex, Pharmacia) (22,23). This is a starch particle with a diameter of roughly 40 mm injected intra-arterially and entrapped in the tumours arterioles. This causes a circulation block which lasts roughly 20-30 minutes. Based on the fact that circulation is normalized after 30 minutes, the patients are

usually spared serious side effects, as microspheres are then degraded by serum alpha-amylase. Sometimes ischemia pain occurs, such as a sense of pressure in the abdominal-thoracic area, which in very few cases increases to an intolerable level. (This was the case in 2 of the 15 patients we treated with Spherex).

Most of the side effects were caused by arteriovenous shunting of the microspheres mostly to the lungs. In one case we observed shunting even via the main circulation up to the left eye ball, causing an amaurosis fugax. However, this rather dramatic incident represented no real danger for the patient either. Nuclear medicine controls using 99Tc Maa particles can follow the microsphere's trail and trace possible shunting routes. To avoid the possibility of retrograde flow with possible adverse effects on neighbour organs with an overdose of Spherex (unwanted accompanying cytostatic perfustion), an individualized Spherex-dosage is absolutely necessary. This is achieved with DSA-angiographic control. This tested dosage, is often between 300 and 900 ug (but which can also be higher) is mixed with the administered cytostatic agent in a suspension fluid. Mitomycin C has been proven especially efficient in hypoxaemic areas and could be administered in high dosages (20 mg/sqm every 3 weeks) without increased systemic toxicity because of Spherex's blockade effect. In hypoxaemic conditions, fluoropyrimidines were less effective because of the reduced anabolic metabolism in the tumour cells.

Because the side effects that appeared in most cases were only apparent for a short time, the method of chemoembolisation using an implanted Port-A-Cath catheter was easily applied on an out-patient basis. Still, unequivocal randomized study is just starting.

SUMMARY : A great deal of both technical and financial investment has been made, justifiably so as patients with liver metastase have previously been neglected.

After euphoria subsides and, after evaluation the soaring remission statistics, basic principles should never be forgotten. Therefore, a short reminder of the pharse inscribed on the main entry way of the Vienna General Hospital in 1784 as a memorial from the founders should stand at the very end of this article''

SALUTI ET SOLATIO AEGRORUM

''Not only is the cure important, but also the comforting''

And the 'solatium' of a terminal patient with liver metastases is one of our greatest medical challengs.

REFERENCES

1. WAGNER, H.S.; ADSON, M.A.; VAN HEERDEN, J.A.; ADSON, M.H.; ILSTRUP, D.M.: The natural history of hepatic metastases from colorectal cancer. A comparison with resective treatment. Ann. Surg. 199:502-508 (1984)
2. WOOD, C.B.: Natural history of liver metastases; in Van de Velde, Sugarbaker, Liver metastasis, pp. 47-54 (Ni jhoff, The Hague 1984)
3. COLLINS, J.M.: Pharmacologic rationale for regional drug delivery. J. clin. Oncol. 2:498-504 (1984)
4. MACHOVER, D. : GOLDSCHMIDT, E.; CHOLLET, P., et al. : Treatment of advanced colorectal and gastric adenocarcinomas with 5-fluorouracil and high-dose folinic acid. J.clin. Oncol. 4:685-696 (1986)
5. WATKINS, E. JR.; SULLIVAN, R.D.: Cancer chemotherapy by prolonged arterial infusion. Surgery Gynec. Obstet. 118: 3-19 (1964)
6. MYERS, C.E., et al. : Pharmacology of intraperitoneal chemotherapy. Cancer Invest. 1:395-407 (1983)
7. OZOLS, R.F., et al.: Phase I and pharmacological studies of adriamycin administered intraperitoneally to patients with overian cancer. Cancer Res. 42:4265-4269 (1982)
8. HOWELL, S.B., et al.: Intraperitoneal cisplatin with systemic thiosulfate protection. Ann. intern, Med. 97:845-851 (1982)
9. HOWELL, S.B., et al.: Intraperitoneal chemotherapy with melphalan. Ann. intern. Med. 101:14-18 (1984)
10. RAINER, H.; BLOCHI-DAUM, B.; SCHULLER, J.; DINSTL, K.; PROKSCH, B.; EHNINGER, G.; JAKESZ, R.J.; MOSER, K.: Phase-I-Studie: Mitoxantron intraperitoneal bei Carcinosis peritonei. FAC Fortschritte der antimikrobiellen u. antineoplastischen Chemotherapie, Band 6-9 1987, S. 1371-1379
11. DE GREGORIO, M.W.; LUM, B.L.; HOLLERAN, W.M.; WILBUR, B.J.; SIKIC, B.I.: Preliminary observations of intraperitoneal carboplatin pharmacokinetics during a phase I study of the Northern California Oncology Group. Cancer Chemother Pharmacol (1986) 18: 235-238
12. SUGARBAKER, P.H.; GIANOLA, F.J.; SPEYER, J.L.; WESLEY, R.; BAROFSKY, I.; MYERS, C.E.: Prospective randomized trial of intravenous vs. intraperitoneal 5-FU in patients with advanced primary colon or rectal cancer. Semin, Oncol. 12:suppl. 4, pp 101-111 (1985)
13. PATT, Y.Z.; BODDIE, A.W.; CHARNSANGAVEJ, C., et al.: Hepatic arterial infusion with floxoridine and cisplatin: overrding importance of antitumour effect versus degree of tumour burden and determinants of survival among patients with colorectal cancer. J.clin. Oncol. 4:1356-1364 (1986)
14. PATT, Y.Z.; MCBRIDE, C.M.; AMES, F.C., et al.: Adjuvant perioperative hepatic arterial mitomycin C and floxuridine combined with surgical resection of metastatic colorectal cancer in the liver. Cancer 59:867-873 (1987)
15. HOHN, D.; MELNICK, J.; STAGG, R., et al.: Biliary sclerosis in patients receiving hepatic arterial infusion of floxuridine. J.clin. Oncol. 3:98-102 (1985)
16. NIEDERHUBER, J.E.; ENSMINGER, W.; CYVES, J., et al.: Regional chemotherapy of colorectal cancer metastatie to the liver. Cancer 53:1336-1343 (1984)
17. BALCH, C.M.; URIST, M.M.; MCGREGOR, M.L.: Continuous regional chemotherapy of metastatic colorectal cancer using a totally implantable infusion pump. Am.J. Surg. 145:285-290 (1983)

18. KEMEY, M.; REICHMAN, B., et al.: Update of randomized study of intrahepatic versus systemic infusion of fluorodeoxyuridine in patients with liver metastases from colorectal carcinoma. Proc. Am. Soc. clin. Oncol. 5:89 (1986)
19. ENSMINGER, W.D.; ROSOWSKY, A.; RASO, V., et al.: A clinical pharmacological evaluation of hepatic arterial infusions of 5-fluoro-2'-deoxyuridine and 5-fluorouracil. Cancer Res. 38:3784-3792 (1978)
20. TUCHMANN, A.; SCHULLER, J.; STEINHOFER, M.; WIRTH, M., DINSTL, K.: Intraarterielle Chemotherapie der Leber - Indikation, Risiko und Ergebnisse. Akt. Chir. 22 (1987) 201-204
21. CHANGE, A.E.; SCHNEIDER, P.D.; SUGARBAKER, P.H.; SIMPSON, C.; CULNANE. M.; STEINBERG, S.M.: A Prospective Randomized Trial of Versus Continuous 5-Fluorodexyuridine Chemotherapy in the Treatment of Colorectal Liver Metastases. Ann. of Surgery, Dec. 1987, Vol. 206, Number 6
22. STARKHAMMAR, H.; HAKANSSON, L.; MORALES, O.; SVEDBERG, J.: Effect of microspheres in intra-arterial chemotherapy. A study of arterio-venous shunting and passage of a labelled marker. Med. Oncol. & Tumor Pharmacother. Vol. 4, No. 2, pp 87-96, 1987
23. THOMB, A.L.; SIGURDSON, E.R.; DALY, J.M.: Use of degradable starch microspheres (DSMs) in patients with hepatic metastases. Proc. Am. Soc. clin. Oncol. 6:8 (1987)
24. PATT, Y.Z.: Hepatic Arterial Infusion of Chemotherapy for Metastatic Colorectal Cancer in the Liver: Why, How and What? Antibiot. Chemother., Vol. 40, pp. 1-11 (Karger, Basel 1988)