

Original Article

A retrospective analysis of patients with head and neck cancer treated with radiation, hyperthermia, and cetuximab: A brief report of outcome

ABSTRACT

Purpose: Advanced head and neck cancer continues to have a dismal outcome. Chemoradiation remains the current standard of care. Chemoradiation has not achieved the desired increase in survival in locally advanced head and neck cancer. This is a retrospective analysis of six patients treated with hyperthermia, radiation therapy, and cetuximab. We wished to determine if this combination treatment would further improve the outcome.

Materials and Methods: Six patients with squamous cell cancer of the head and neck region were treated with hyperthermia, cetuximab, and radiation therapy. The end points assessed were acute toxicity and immediate response.

Results: All the six patients received the planned doses of cetuximab and radiation therapy. Two patients did not complete the planned hyperthermia sessions. All patients developed mucositis and acneiform rashes. None had thermal burns. One hundred percent complete response was observed in all the patients.

Conclusion: Addition of hyperthermia to cetuximab and radiation therapy is feasible and shows impressive response rates with manageable toxicity profile. Further studies evaluating the same are needed to confirm these findings.

KEY WORDS: Cetuximab, head and neck cancer, hyperthermia, radiation therapy

INTRODUCTION

Advanced head and neck cancer continues to have a dismal outcome. Radical radiation therapy with chemotherapy has marginally improved survival with a concomitant increase in acute toxicity. Cetuximab is a recombinant human/chimeric monoclonal antibody which binds to the extracellular domain of the human epidermal growth factor receptor which has shown to induce apoptosis, cellular growth retardation, decrease in matrix metalloproteinase as well as vascular endothelial growth factor production. Bonner *et al.* reported a survival benefit when radiation was combined with cetuximab to treat locoregionally advanced head and neck cancer.^[1] Hyperthermia combined with radiation and chemoradiation has shown survival benefit in small randomized and nonrandomized trials.^[2-4] It is hypothesized that hyperthermia in conjunction with cetuximab and radiation in the treatment of head and neck cancer

may improve survival. The underlying mechanism of this synergy maybe due to a combination of increased cellular uptake, longer intratumoral transit time, or inhibition of DNA repair.^[5] This is a brief retrospective analysis to study the outcomes of patients treated with cetuximab, radiation, and hyperthermia at our institution.

MATERIALS AND METHODS

Patients with a diagnosis of squamous cell cancer of the head and neck region were staged according to the International Union Against Cancer staging manual, 6th edition. All patients had appropriate imaging investigations done for staging such as X-ray, positron emission tomography-computed

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Cite this article as: Huilgol NG. A retrospective analysis of patients with head and neck cancer treated with radiation, hyperthermia, and cetuximab: A brief report of outcome. *J Can Res Ther* 2016;12:1164-6.

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Access this article online

Website: www.cancerjournal.net

DOI: 10.4103/0973-1482.194600

Quick Response Code:



tomography, and magnetic resonance imaging. Endoscopic evaluation and biopsy for histological confirmation was done in all patients. Patients who refused chemotherapy were offered treatment with cetuximab. One patient was offered cetuximab upfront in view of advanced age and poor performance status. The loading dose of cetuximab was administered 1 week prior to the start of radiation therapy. The loading dose of cetuximab was 400 mg/m², administered as intravenous infusion over 120 min. Subsequently, patients received cetuximab at a dose of 250 mg/m² as an intravenous infusion over 60 min on a weekly basis, concurrently with radiation therapy. Patients received radiation with conventional fractionation, that is, 200 cGy daily, 5 days a week, over 6–7 weeks. Radiation therapy was delivered using the Elekta Precise dual energy linear accelerator housed at our institution. 6 MV beams were used in the treatment of all patients. Appropriate radiation delivery techniques were used based on the target volume of interest. Standard curative radiation doses were prescribed; for nonoperated patients, 70 Gy in 35 fractions was delivered whereas in postoperative cases, 60 Gy in 30 fractions was prescribed. Two among the six patients needed an additional fraction of radiation so as to compensate for the treatment break that had occurred during the course of radiation therapy. Hyperthermia was delivered every week on modified Thermatron operating at 8.2 MHz. All patients were precooled to 5°C for at least 10 min before starting hyperthermia. Good impedance matching was achieved in all patients. The energy input varied from 400K watts to 600K watts. Radiofrequency (RF) input was stopped once patients complained of pain or discomfort. Each session of hyperthermia was for a duration of 30 min. A total of six sessions of hyperthermia were planned which was delivered once weekly. A total of six patients were treated with cetuximab, hyperthermia, and radiation therapy. Cetuximab followed by hyperthermia was delivered on the same day, but at variable intervals, till the treatment was complete.

All patients were evaluated every week. Hemogram and serum creatinine were assessed on a weekly basis. Patients were assessed for nutritional status and appearance of acneiform rashes and mucositis. Patients received analgesics, antihistamines, oral nutritional supplements, and oral

rinses. Parental nutritional or percutaneous endoscopic gastrostomy (PEG) was planned, if necessary. Prophylactic insertion of PEG is not practiced routinely at our institution. All patients have given written informed consent.

RESULTS

All the six patients completed the prescribed course of radiation and cetuximab. Hyperthermia was terminated in one patient due to unbearable systemic stress. Another patient, an elderly gentleman, found it uncomfortable to lie down for 30 min for hyperthermia session. He refused hyperthermia after three sessions. All patients developed brisk mucositis and acneiform rashes which were anticipated. None developed thermal burns. Complete response was seen in all the six patients. Table 1 shows the demographic details, treatments received, and outcome of all the six patients. There were no treatment-related interruption but for one in whom only hyperthermia was abrogated.

DISCUSSION

Head and neck cancer in its advanced stages poses an insurmountable challenge. A plateau has been reached; further improvement in survival begs innovations. Combination of proven modalities is one way of improving outcomes, pending for newer avenues.

Chemoradiation has emerged as a more frequently recommended treatment strategy for the treatment of locally advanced head and neck cancer. Pignon *et al.* have demonstrated an increase in the outcome by 4%–8% in survival with chemoradiation.^[6] This, however, was achieved with an increased acute toxicity. A plethora of cytotoxic drugs such as paclitaxel, 5-fluorouracil, cisplatin, hydroxyurea, and carboplatin have been used as radiation sensitizers. Cetuximab has emerged as one of the targeted drugs with a potential to improve survival.^[1] There is very sparse data available to test the effect of chemoradiation with hyperthermia in the prevailing literature. Our previous report has demonstrated a significant response and an improved survival in a small cohort of forty patients with advanced head and neck cancer.^[2,3] Datta *et al.* and Huilgol

Table 1 : Patient characteristics, treatment details, toxicities and outcome

Age (years)	Gender	Primary	TNM	Stage	RT Dose (Gy)	RT technique	HT (sessions/frequency)	Tolerance to HT (Yes/No)	Mucositis (oral/pharyngeal)	Acneiform eruptions (grade)	Response (initial)	Follow up (months)
63	Male	Supraglottis	T3N0M0	III	70	IMRT	6/weekly	Yes	2	2	CR	45
82	Male	Glottis	T2N0M0	II	72	3DCRT	3/weekly	No	3	2	CR	39(PD, DFS-12)
62	Male	Tongue	T3N1M0	III	72	IMRT	1	No	3	2	CR	Lost follow up
66	Male	Maxilla	T4N0M0	IVA	60	IMRT	5/weekly	No	1	2	CR	1
48	Male	Tonsillar fossa	T3N0M0	III	70	IMRT	6/weekly	Yes	3	2	CR	8
58	Male	Tongue (post operative)	T3N1M0	III	60	IMRT	12/twice weekly	Yes	2	2	NAD	12(PD, DFS-12)

IMRT=Intensity modulated radiotherapy, 3DCRT=Three dimensional conformal radiotherapy, HT=Hyperthermia, CR=Complete response, NAD=No abnormality detected, DFS=Disease free survival, PD=Progressive disease

et al. have demonstrated benefits of adding hyperthermia to radical radiation therapy.^[4,7] Issels has demonstrated thermal enhancement of cytotoxic drugs by inducing cellular death and necrosis.^[5] Issels has suggested that a combination of heat and cytotoxic drugs evoke genetically defined stress response which in turn stimulates host immune system.^[5] Addition of hyperthermia may increase the transit time of cetuximab or increase the concentration in tumor due to either stasis or increased perfusion. Miyamoto *et al.* have demonstrated improved penetration of cetuximab following mild hyperthermia in pancreatic tumor model of mice. An enhanced measurable effect was seen in pancreatic models following the administration of cetuximab along with mild hyperthermia.^[8] Zi has demonstrated enhanced apoptosis in Cellosaurus Cellline (CNE) cell lines (human nasopharyngeal carcinoma) when cetuximab was combined with hyperthermia. They concluded that cetuximab in conjunction with radiotherapy and hyperthermia synergistically increases the apoptosis in CNE cells, possibly through further upregulation of the Bax/Bcl-2.^[9]

Similarly, Curley *et al.* demonstrated enhanced cytotoxicity in mouse model, when cetuximab conjugated with nanogold was administered, and then it was subjected to RF-induced hyperthermia.^[10]

Neither patients developed thermal burns nor were the acneiform rashes unmanageable. Impressive initial response without any added toxicity seen in this study is a good reason for a larger randomized study to assess the effects of adding cetuximab to hyperthermia and radiation.

CONCLUSION

The effects of combining hyperthermia, cetuximab, and radiation may prove to be additive. This analysis has shown not only the feasibility but also an impressive initial response. This is to the best of our knowledge the first report of combining cetuximab with radiation and hyperthermia.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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