

## Editorial

# Orphans of oncology

Science and medicine are replete with ideas which failed or never took off. The process of enquiry is not only complex but risky as well. The adage right man at the right time always succeeds, perhaps, is true about ideas as well. Looking back at the history of radiation oncology had its fair list of ideas which failed despite adequate proof of usefulness. Amifostine, a radiation protector; hypoxic cell sensitizers; hyperthermia; and low dose rate (LDR) brachytherapy are some of those outstanding ideas which failed to have lasting effect. LDR radiation was an innovative idea in brachytherapy which lasted over decades and contributed to a better survival of patients with cancer. LDR brachytherapy helped to overcome the limitations imposed by shallow depths of radiation during the era of orthovoltage X-rays. LDR radiation was initially inevitable due to lack of isotopes with higher specific activity and higher dose rate. The advent of high dose rate (HDR) radiation backed by the industry has almost replaced LDR brachytherapy. One does not see many discussions about pros and cons of HDR and LDR radiation any more. LDR one can say has run its course. A great idea and technology had its day in the sun. The obsolescence of LDR is a consequence of creative destruction and efficient marketing of HDR.

The quest for an ideal radioprotector started way back in 1948 following nuclear holocaust perpetration on Japan. Cold war with a constant threat of nuclear warfare made the prospect of a discovering a perfect radioprotector an exciting possibility. Laboratory in Walter Reid screened nearly 3,000 molecules before coming up with amifostine. Amifostine has a toxicity profile which is acceptable but the ease of administration is lacking. Besides it is not a universal radiation protector. Notwithstanding many positive trials, amifostine has slowly moved in to oblivion. The generic versions of the drug have been withdrawn from the Indian market. The earlier enthusiasm to pursue the idea of radioprotectors is significant by its absence. May be manned expedition to Mars will revive the interest in radioprotectors! As of now it is an orphan molecule for the lack of adequate market. In fact the need for radioprotectors is more than ever what with chemoradiation and escalated dose of radiation, all of which have the potential

to enhance toxicity. Amifostine has moved off the shelf despite being effective. Market forces work in mysterious ways. It is not enough for a drug to be effective, but has to have a potential to garner profits. May be public sector should take up orphan molecules for manufacturing and distribution. That is the only way to save great ideas from fiendish destructive forces of market place.

Practice of hyperthermia which peaked in the 1980s is now confined to a very few centers in the world. There is an ample evidence for the effectiveness of heat as therapeutic modality for cancer. Hyperthermia in conjunction with radiation has been shown to improve overall survival in head and neck cancer and cervical cancer. Many randomized trials have shown benefit in survival. Technology has improved since the 1980s, magnetic resonance (MR)-based noninvasive thermometry has added scientific rigor to the practice of hyperthermia. High-intensity focused ultrasound (HIFU) has gained in popularity, but not conventional hyperthermia. Perhaps the high initial cost is deterrent to a wider acceptance of the modality.

Thomlinson's elegant work paved the way for the concept of hypoxia in tumor. Further work demonstrated hypoxia of tumor to be the cause of failure of radiation therapy. Hypoxic core which is resistant to radiation therapy was an obvious target for manipulation. Imadazoles to nitrotriazole, fluorinated compounds, and hyperbaric oxygen were evaluated for effectiveness. Nimarazole, senzole, and hyperbaric oxygen were shown to be effective in randomized trial. Nimarazole was marketed in Europe. It failed to succeed in the market place. Senzole was never marketed even after a level I evidence of effectiveness. Radiation resistance due to hypoxia is an operational concept for which relatively effective drugs were discovered. Yet it never really took off. Hypoxic cell sensitization has remained an orphan concept long abandoned.

Practice in medicine generally has a robust empirical basis. Yet the best ideas get abandoned for a lack of support from opinion leaders or due to market forces. Hopefully when one looks back,

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the list of orphaned ideas will be small. We also need to have mechanism to negate the destruction unleashed by market forces. We have reached the limits of optimization. There is a need not only to come up with new ideas but also to pursue orphan ideas which have proved to be effective.

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