The Role of Amifostine as a Radioprotector

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Effective radiotherapy for patients with cancer should include maximal tumor cell killing with minimal injury to normal tissue. Radiation doses that can be delivered, without causing severe damage to surrounding normal

The article by Drs. Wasserman and Brizel concludes that protection of normal tissue from side effects due to radiotherapy will permit dose escalation and improve therapeutic efficacy and treatment outcomes. Although this concept is sound in principle, its generalized clinical application hinges critically on two controversial issues associated with the use of all putative radioprotective agents: (1) the extent of a reduction in normal tissue side effects afforded in a variety of dose-limiting normal tissues, and (2) the potential for tumor protection.

Modulation of Radiation Response
Although a great deal of effort has been expended on various approaches to sensitizing tumors to radiotherapy, attempts to protect normal tissue from ionizing radiation damage have focused primarily on sulfhydryl-containing compounds.[1] A lead agent initially developed at the Walter Reed Army Institute of Research (WR-2721) and subsequently known as amifostine (Ethyol) protects against sparsely ionizing radiation predominantly by scavenging free radicals.[1,2] The extent of this radioprotection is strongly dependent on oxygen concentration, because the active metabolite of amifostine and oxygen compete for free radicals.[2] Indeed, in a series of elegant preclinical studies, Denekamp et al[3] clearly demonstrated that amifostine protection in vivo is maximal at intermediate levels of oxygen. While the effective scavenging of free radicals offers an attractive model for the protective action of agents like amifostine, this explanation is likely to be an oversimplification, with other complex factors undoubtedly being involved.[1,4]

Protection of Normal Tissues
Preclinical investigations have shown that, in general, amifostine offers good protection to the hematopoietic system and salivary glands (protection factors near 3), intermediate protection to organs such as the kidneys and lungs (protection factors 1-2), and no protection to the central nervous system.[1,4] In addition to this intertissue variability, the extent of amifostine protection within normal tissues varies. The nature of the variability is uncertain, but factors such as differences in tissue oxygen tensions as well as amifostine distribution and pharmacodynamics may be involved.[2,5]

As discussed by Drs. Wasserman and Brizel, the use of amifostine may reduce the side effects of radiotherapy alone or in combination with chemotherapy in a number of clinical settings. In the largest study to date,[a phase III randomized trial in head and neck cancer][6] reported that patients who received amifostine had reductions in both acute xerostomia of grade 2 or greater (78% vs 51%, \( P < .0001 \)) and chronic xerostomia of grade 2 or greater (57% vs 34%, \( P < .002 \)). Median saliva production was also greater in patients treated with amifostine. However, no reduction in radiation-induced mucositis was seen. Long-term xerostomia is associated with difficulty in maintaining a normal diet and an increased risk of dental caries. Amifostine is clearly an option that may reduce the likelihood and severity of xerostomia and, thereby, improve quality of life. Another alternative is to reduce the treatment volume with conformal radiation therapy approaches. Intensity-modulated radiation therapy and three-dimensional radiation therapy techniques may not only reduce the incidence of acute and chronic xerostomia, but may also reduce the likelihood of other acute and late adverse events.

Therapeutic Index
The question of selectivity lies at the heart of the matter when discussing the use of radioprotectors in cancer treatment. In the early 1980s, this issue sparked a firestorm of scientific debate.[7,8] Almost 20 years later, concerns that amifostine may protect tumors from the effects of radiation have not been unequivocally alleviated. While some preclinical data, particularly those obtained from trials using large single-drug doses, may be brought to question, results reported in studies in which
such issues were not relevant cannot be so easily dismissed. Indeed, the observation that more protection may be conferred on well-oxygenated tumors, as well as tumors treated with fractionated radiotherapy,[2,9,10] remains worrisome.

Clinical studies examining the impact of amifostine on the therapeutic index are limited. In their article, Drs. Wasserman and Brizel conclude that there is no evidence in the literature that amifostine leads to tumor protection. However, most of these published studies are phase I/II or retrospective. The number of patients in the treatment arms is usually modest (typically 20 to 50), follow-up times are often relatively short, and the treatment administered may be quite variable in a given trial. All these factors increase the difficulty of evaluating these studies. Thus, while the available data suggest no apparent differences in tumor response rates, the statistical power of many of these studies is poor, and a 10% to 15% difference in locoregional control could escape detection.[11]

Conclusions
According to Hall,[1]

... One of the difficult and worrisome factors in the use of radioprotectors in the clinic is that their use is not fail-safe. To exploit a benefit, radiation doses must be increased with the confidence that normal tissues are protected and that the extra dose can improve tumor response. If radioprotection does not occur, unacceptable normal tissue injury results.

These statements are particularly relevant in light of the variable protection factors reported for amifostine in tissues treated with radiation. As noted by Lindegaard and Grau,[4] "A positive therapeutic index obtained with regard to some normal tissues, like the salivary glands, may be offset by a negative therapeutic index for the same treatment with regard to other normal tissues, like the spinal cord."

The findings of Brizel et al[6] clearly are encouraging and may ultimately lead to new therapeutic options in patients who will experience significant xerostomia after radiation therapy. Indeed, if subcutaneous injections prove to be equally efficacious, this route of administration will significantly enhance the ability to administer this agent expeditiously. Still, given that amifostine has shown variable protection factors in an assortment of tissues treated with radiation, and in the absence of clinical studies with patient numbers large enough to provide sufficient statistical power to detect modest changes in tumor control, it would be prudent to refrain from using a radioprotective agent to allow irradiation dose escalation outside a controlled clinical trial.

References:


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