INVITED EDITORIAL

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Has the Time Come for Routine Use of Amifostine in Clinical Radiotherapy Practice?

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In the study by Kruse et al. (1) published in this issue of *Acta Oncologica*, the heart is added to a growing and long list of preclinical normal tissues, in which damage induced by ionizing irradiation is ameliorated by amifostine. Such radiobiological observations nourish a long-standing dream concerning the possibility of improving outcome of clinical radiotherapy by use of radioprotectors (2). Ever since the Cold War this effort has waxed and waned, but has recently been boosted by the commercialization of amifostine, FDA approval and authoritative guidelines (3). But why has this research been so long underway and what are the prospects for an imminent introduction of amifostine into routine clinical radiotherapy.

The primary hindrance is the subject matter itself, since there is no fail-safe modification of traditional radiotherapy (4). Numerous normal tissues are dose limiting and an evaluation of the overall therapeutic benefit of using a radioprotector is therefore very complex. Essentially, two scenarios are at hand: If the radioprotector can assure absolute normal tissue selectivity, fewer complications with unchanged rate of tumor control can be obtained for a given level of radiation dose. However, if selectivity is uncertain then an increase in radiation dose may be needed to maintain the same rate of tumor control when using the protector. However, this strategy requires that the protective effect on tumor tissues is predictable and exceeded by the protection offered to all relevant normal tissues. But even the perfect preclinical radioprotector must have an acceptable toxicity profile and must be easy to handle if generalized clinical use is to be expected with routine fractionated radiotherapy (5).

Based on the available preclinical knowledge, including the present study by Kruse et al. (1), the variability of the protection observed in different normal tissue models is unfortunately heterogeneous. Some normal tissues such as the central nervous system, which is often the dose-limiting organ in radiotherapy, are not protected at all, since amifostine does not cross the blood–brain barrier. In other normal tissues such as the salivary glands and the hematopoietic system, amifostine affords significant radioprotection. To make things even more complicated, tumor protection has been impossible to rule out by preclinical experiments. Large single doses of irradiation have often been used and relevant comparisons between tumor effects have been absent or difficult to translate into a clinically meaningful context (5).

On the clinical side, decades have passed with publication of phase I–II studies with limited numbers of patients and a few underpowered randomized studies. The problems involved in the interpretation of the results from such trials are exemplified by a recent correspondence (6). Despite the long list of preclinical normal tissues with proven effect of amifostine, disappointingly few have been confirmed in the clinical setting. Amelioration of acute radiation toxicity has been observed in studies that have often employed various types of treatment intensification such as concomitant chemotherapy or accelerated radiotherapy. However, definite confirmation regarding late morbidity such as fibrosis has not been obtained.

Hope rose with the recent publication of the study by Brizel et al. (7) showing that amifostine significantly protected against radiation-induced xerostomia, with no apparent loss of tumor control in the head and neck. Unfortunately, the study was not powered as an equivalence trial and was therefore incapable of ruling out the possibility of amifostine-induced tumor protection. In addition, postoperative radiotherapy was used in two-thirds of the included patients, diluting potential protection in the one-third of patients treated with definitive radiotherapy. Finally, the study required that at least 75% of both

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parotids were irradiated. Modern three-dimensional target definition and dose delivery, for instance by intensity-modulated radiotherapy, often makes sparing of significant parts of the parotids possible, thereby rendering the attempts for pharmacological protection more or less redundant.

Following the study by Brizel et al., the FDA has approved the use of amifostine in patients undergoing postoperative fractionated radiotherapy in the head and neck region in order to decrease the incidence of acute and chronic xerostomia. The European regulatory agency has also approved amifostine but, astonishingly, does not discriminate between postoperative and definitive radiotherapy, despite the manufacturer's warnings against the use of amifostine in the latter situation. Likewise, the American Society of Clinical Oncology has twice awarded amifostine with the highest level of recommendation (IA) for both postoperative and definitive radiotherapy (3,8). The ASCO recommendation, IA, is awarded for meta-analysis of multiple, well-designed, controlled studies and/or high power randomized trials. In light of the paucity of clinical data, this recommendation seems premature. To sustain such strong and generalized approval, a replication of the trial by Brizel and colleagues employing definitive irradiation of head and neck cancer in an adequate number of patients to rule out significant tumor protection is the minimum evidence that should be required by independent scientific or governmental authorities. But even confirmation of the Brizel trial may not completely solve the issue. In the Brizel study, 34% of the patients developed chronic xerostomia despite the use of amifostine (7). For patients and their radiotherapists, it may well be difficult to choose between a 20–30% reduction in the risk of moderate to severe xerostomia at the price of an increased possibility of tumor recurrence no matter how small this risk is.

Nonetheless, the reduction of treatment toxicity is as important as ever. Traditionally, late-reacting tissues have been dose limiting in radiotherapy. However, treatment intensification using alternative fractionation schedules, concomitant chemotherapy and biological modifiers are increasingly being explored. It is therefore foreseeable that radiation dose will increasingly be limited by acute toxicity. Whether sufficient and tolerable doses of amifostine can be applied in this scenario even by the subcutaneous route is currently unknown. In addition, it is important to remember that even though amifostine may show evidence of protective activity in this setting, it does not imply therapeutic benefit. It is therefore important that future trials do not expose the control arm to a treatment intensification that places them at greater risk of the toxicity the protective agent is designed to prevent (9).

So despite research during half a century, the routine use of amifostine in clinical radiotherapy practice is not recommended and additional evidence for its assumed positive influence on the therapeutic ratio is needed. If not, the amifostine case may unfortunately begin to resemble a pattern described by Phillips & Tannock in their review of pitfalls in clinical trials that evaluate agents that may offer protection from toxic effects of cancer chemotherapy (9):

> There is an unfortunate historical precedent that flawed trials have been accepted by the FDA and other regulatory authorities for licensing of some chemoprotective agents. Some of these agents have been adopted subsequently by the oncology community in settings where there is inadequate evidence of clinical benefit to patients

We can only hope that yet another 50 years will not have to pass before well-designed preclinical experiments and clinical trials with traditional radioprotectors, and perhaps new biological modulators of radiation injury, find their way to our patients, ensuring them of a better therapeutic ratio than we can offer them to day.

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