Clinical Status and Optimal Use of Amifostine

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An important, though as yet elusive, goal of cancer chemotherapy is the development of agents that are selectively toxic to tumor cells and, thus, permit effective cancer treatment to be administered without severe, often life-threatening toxicity to normal tissues. Until such agents are available, an alternative strategy to improve the therapeutic index of cancer chemotherapy is the administration of cytoprotective agents to selectively protect normal tissues from injury by cytotoxic drugs.

An ideal cytoprotective agent would be effective in protecting a broad range of normal tissues from the effects of both chemotherapy and radiation at doses that produce no side effects and do not interfere with the antitumor effects of treatment. Of the three cytoprotectants currently approved by the FDA for use in the United States (dexrazoxane [Zinecard], mesna [Mesnex], and amifostine [Ethyol]), only amifostine approaches this ideal. The protective effects of dexrazoxane are specific to the cardiotoxicity of anthracyclines, while the benefits of mesna appear to be limited to protecting the urothelium from the toxic effects of the oxazaphosphorines, cyclophosphamide (Cytoxan, Neosar), and ifosfamide (Ifex). Amifostine, however, protects a variety of normal tissues from both the acute and delayed toxicities of chemotherapy, as well as radiation, with an acceptable safety profile and without abrogating antitumor efficacy.

As reviewed by Capizzi, amifostine is the product of classified military research that aimed to identify compounds to protect US troops from radiation injury during nuclear warfare. Preclinical studies demonstrated its ability to protect a broad range of normal, but not tumor, tissues from the cytotoxic effects of radiation and chemotherapy. This normal tissue selectivity appears to be due, primarily, to greater alkaline phosphatase activity in normal tissues, resulting in greater formation of WR-1065, the active thiol that functions as a scavenger of oxygen free radicals in cells.

Broad Spectrum of Cytoprotective Effects
A number of clinical trials have established the safety and efficacy of amifostine and led to its approval by FDA in 1996 to ameliorate the cumulative nephrotoxicity associated with repeated doses of cisplatin chemotherapy. Since then, additional studies have suggested that amifostine may be useful in protecting bone-marrow progenitor cells during purging with 4-hydroperoxycyclophosphamide[1]; in attenuating thrombocytopenia induced by carboplatin (Paraplatin)[2]; in protecting against some of the late mucosal toxicities of radiation[3]; and in ameliorating platinum-induced peripheral neuropathy.[4] Among the more interesting effects of amifostine appears to be its ability to stimulate bone marrow progenitor cells, leading to evaluation of the drug as a primary therapy for myelodysplasia.[5]

Indeed, a recent search of ongoing clinical trials of amifostine listed in the Physician Data Query (PDQ) database revealed 42 ongoing trials of amifostine. These range from phase I trials of amifostine in combination with single chemotherapeutic agents to amifostine used alone or in combination with other drugs. Clearly, interest in this agent remains high, and the ongoing trials may reveal other uses for this broad-spectrum cytoprotectant.

An area of particular interest to pediatric oncologists is the potential for amifostine to protect against secondary malignancies that may be induced by chemotherapy or radiation therapy. Grdina and colleagues have clearly demonstrated the anticarcinogenic effects of amifostine in a number of animal models of radiation-induced tumors.[6] In both the laboratory and the clinic, these investigators have also demonstrated the utility of amifostine in reducing cyclophosphamide-induced mutagenesis at the HGPRT reporter gene locus.[7] These effects can be achieved at extremely low doses of amifostine, well below those required to
protect tissues from acute radiation- or cyclophosphamide-induced cytotoxicity. These findings thus raise the possibility that low-dose amifostine may be effective in preventing treatment-related secondary malignancies.

**Clinical Value Remains to Be Determined**

Although amifostine appears to have a role in preventing or ameliorating some toxicities of anticancer therapy, its real value in the practical, daily management of individual patients remains a bit unclear. After all, hematopoietic colony-stimulating factors appear to be at least as effective in ameliorating granulocytopenia; area-under-the-curve (AUC) dosing of carboplatin has mitigated much of the thrombocytopenia associated with this drug; and the clinical significance of preventing minor elevations of serum creatinine in patients with incurable solid tumors is uncertain at best. Whereas amifostine clearly could be valuable in preventing or ameliorating platinum- or taxane-induced neuropathy, its utility in doing so has yet to be clearly established.

Furthermore, despite its protective effects in normal tissues, administration of amifostine has not yet been shown to permit a clinically meaningful escalation in the dose of any cytotoxic agent. Indeed, the Cancer and Leukemia Group B (CALGB) conducted a prospective, randomized trial to determine whether amifostine was effective in further ameliorating the toxicities of high-dose cyclophosphamide (3 g/m² administered every 15 days) administered with granulocyte-macrophage colony-stimulating factor (GM-CSF [Leukine, Prokine]) and mesna uroprotection.[8] No significant differences were noted between the treatment arms with respect to granulocyte nadir, platelet nadir, duration of cytopenias, days of hospitalization, or incidence of febrile neutropenia.

**Cost-Effectiveness Analyses Needed**

Ultimately, deciphering the true role of agents, such as amifostine, in clinical oncology will require that cost-effectiveness analyses be done as part of randomized clinical trials. Administration of amifostine adds complexity, expense, and toxicity to any chemotherapy regimen. These factors could easily be balanced by a reduction in treatment-related costs associated with the amelioration of acute and chronic treatment-related toxicity.[9]

The true value of adding a cytoprotectant to any therapeutic regimen depends entirely on the specific clinical setting and requires that the protective agent not interfere with the antitumor efficacy of the treatment. In palliative therapy for stage IV non-small-cell lung cancer, it may be far more appropriate to mitigate chemotherapy toxicity with appropriate dosage reductions than to further complicate the treatment program with the addition of a cytoprotective agent. By contrast, agents such as amifostine may truly demonstrate their value in a curative treatment setting requiring cytotoxic drugs likely to produce long-term patient disability due to chronic or irreversible toxicity.

**Other Cytoprotectants Under Development**

Despite the uncertainty about the true value of cytoprotectants in clinical oncology, development of such agents continues to be an area of considerable interest. BNP7787, a dimesna compound that liberates a thiol-containing reactive species intracellularly, has recently entered phase I clinical trials. In several animal models, this agent has been shown to be highly effective in protecting against nephrotoxicity, emesis, and bone-marrow suppression induced by cisplatin (Platinol); BNP7787 has achieved these effects at doses that are otherwise nontoxic and do not abrogate antitumor activity.[10] Indeed, some studies suggest that BNP7787 may enhance the antitumor effects of cisplatin while completely preventing lethal toxicity from this drug.

As with amifostine, only carefully conducted, appropriately controlled clinical trials will ultimately determine the role of this agent in clinical oncology practice. At present, every oncologist should carefully review the comprehensive article by Capizzi to help make an informed clinical judgment about the value of adding amifostine to chemotherapy programs for common adult solid tumors.

**References:**


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