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 tissue.

The goal of radiation therapy is to eradicate tumors or to reduce their size to make them easier to remove surgically. Advances in radiation oncology have sought to increase therapeutic efficacy while preserving normal tissues. Equipment capable of generating high-energy photons and high-energy electron beams have increased the penetration of radiation, facilitating access to deep-seated tumors and reducing scattering to adjacent normal tissues.

Variation of radiation schedules, including the simultaneous decrease of the dose while increasing the number of daily fractions (hyperfractionation), has improved response rates in some settings.[1-3] Three-dimensional conformal radiotherapy (3D-CRT)[4] and stereotactic radiotherapy[5] are both aimed at reducing damage to surrounding normal tissue while concentrating the radiation to the tumor.

Although these advances have reduced the possibility of damage to normal tissue, further improvements are still needed. Certain cancers with proximal tumor spread (such as Hodgkin’s disease and lung cancer) require large-field radiation therapy, which increases the potential for injury to normal tissue.

Protecting the body from the toxicities of radiation has been a major concern since the effects of radiation were graphically demonstrated at the end of World War II.

Radiation-Induced Cellular Damage and Toxicity

Since rapidly dividing tissues are more vulnerable to lethal DNA injury,[6] manifestations of radiation toxicity include oral and gastrointestinal mucositis and hematologic toxicity. When radiation is administered with chemotherapy, multiple toxicities may result. In addition to acute toxicity, radiation injuries may become permanent. Toxicity is often confined to the site of radiation. Because a linear relationship exists between radiation dose and permanent cell damage, more intensive radiation is more likely to be effective against cancer cells. Consequently, to maximize the therapeutic benefit to the patient and minimize the adverse effects on normal tissues, a delicate balance must be established between radiation dose and target volume.

The benefits of protecting normal tissues from the adverse effects of radiation therapy include the prevention of debilitating toxicities, maintenance of an effective immune system, improved DNA repair, and reduction of the mutagenic potential of irradiation. Protection should decrease the occurrence of toxicities, which should increase a patient’s quality of life.

While secondary tumors may take many years to develop and the incidence resulting from radiation may be low, the increased risk of secondary neoplasms is a concern for patients whose cancer has a good chance of long-term remission (as in Hodgkin’s disease).[7]

Clinical Trials

Developed by the Army as 1 of 4,400 compounds tested, amifostine (Ethyol) remains the best drug to date to be tested as a radioprotector.[8,9] It is unlikely that further drug development will occur. Studies began at the National Cancer Institute in 1973, and the drug was eventually licensed to US Biosciences[9] now Medimmune Oncology[8] with sales agreements with Alza and Schering.

A number of thio-organic compounds have been developed as adjuncts to radiotherapy. Among these, amifostine is currently approved as a protector against cisplatin (Platinol)-induced toxicity in the United States and cisplatin- and cyclophosphamide (Cytoxan, Neosar)-induced toxicities in Europe. It is also used for radioprotection against xerostomia.

In the United States, phase I trials of amifostine (originally known as WR-2721) were performed by
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In the single-dose toxicity study of amifostine, 201 patients were entered. Drug doses were escalated between 25 and 1,330 mg/m² according to a modified Fibonacci schedule. Toxic reactions in the single-dose study included hypotension, emesis, somnolence, sneezing, metallic taste, and hypocalcemia. The two major toxicities were emesis and hypotension, and their incidence increased with dose. It was concluded that the dose-limiting toxicity for a single dose of amifostine is emesis and that 740 mg/m² delivered in 15 minutes represents the maximum tolerated dose. No clinical evidence of tumor protection was seen in any of these patients, and no drug-related deaths occurred.

Eighty-four patients were entered into a multiple-dose trial. Doses were escalated from 100 mg/m² once a week to 450 mg/m² four times a week for 5 weeks. It was concluded that 340 mg/m² four times per week for 5 weeks before radiation therapy was the maximum tolerated dose. This dose in humans corresponds to a dose level in mice at which effective radioprotection was observed. No long-term chemical, hematologic, or enzymatic changes were observed in any patients treated with amifostine, and there were no drug-related deaths.

In another more recent trial, twice-daily amifostine was poorly tolerated when used with accelerated radiation.

Phase I/II Studies

In 1980, Tanaka reported a phase II clinical study of amifostine with radiotherapy, which demonstrated that amifostine protected nearly 60% of patients receiving radiation therapy for cancer of the head and neck, lung, breast, and uterus from increased toxicity. Subsequently, amifostine was used with radiation therapy in various phase II trials (Table 1). A direct comparison of these results is difficult because of differences in the drug and radiation regimens that were used. However, these studies show that amifostine can provide protection against radiation therapy toxicities.

Head And Neck Cancers

Radiotherapy of the head and neck commonly results in dose-limiting mucositis. Radiation to this region can also cause significant acute and chronic dysfunction of the salivary gland (xerostomia). Collectively, these effects can lead to severe secondary complications, including pain and difficulty in speaking and swallowing, decreased appetite, and weight loss. Clinical studies were conducted to determine the usefulness of amifostine as an adjunct to radiotherapy of the head and neck. Büntzel studied the protective effect of amifostine against concurrent chemoradiotherapy in head and neck cancer. This was a small randomized study of 39 stage III/IV head and neck cancer patients. Amifostine was given at 500 mg IV, but only on days when carboplatin (Paraplatin) was administered along with radiation. Patients receiving amifostine had significantly reduced mucositis and xerostomia in comparison with patients receiving radiochemotherapy alone. The patients treated with amifostine also had significantly less thrombocytopenia and leukocytopenia. There was no reduction in disease control when the two arms were compared. At 12 months after treatment, there was no evidence of disease in 79% of the amifostine-pretreated group vs 64% of the control group.

Busch et al demonstrated the ability to deliver salvage radiation with amifostine pretreatment in patients with recurrent head and neck cancer. Salvage radiation is often precluded because of the severity of radiation-induced toxicity. Thyroid cancer can be effectively treated with high-dose iodine-131, but treatment often results in a reduction in salivary gland function. In a recent prospective, double-blind, placebo-controlled trial, patients receiving amifostine (500 mg/m²) before radiiodine therapy exhibited no significant decrease in efficacy (P = .878) and no xerostomia, whereas control patients experienced a significant reduction in parotid (37%) and submandibular (31%) function, as measured by pertechnetate scan uptake (P = .01). Grade 1 xerostomia developed in 33% of patients in the iodine-131 group only.

Tumors of the Cervix and Pelvis

Data from a New York Gynecologic Oncology Group study of patients with cervical cancer who received amifostine (340 to 910 mg/m²) before cisplatin and whole-pelvic irradiation suggest that, relative to historical controls, patients treated with amifostine had less radiation toxicity to the pelvic mucosa in particular, late toxicities such as rectovaginal fistula and proctitis.

Lymphoid Malignancies and Bone Marrow Metastases
Investigation of amifostine in hematologic malignancies is important because lymphoid malignancies and cancers that metastasize to the bone marrow usually require irradiation to large areas of the body. A phase I dose-ranging study in patients with indolent non-Hodgkin’s lymphoma or chronic lymphocytic leukemia tested the MTD of amifostine, 910 mg/m² twice weekly, in conjunction with total body irradiation, for at least five treatments.[26] The investigators noted that the induction of adverse side effects—primarily malaise and less often hypotension and nausea and vomiting—appears to be related to the cumulative dose of amifostine.[27] The ability of amifostine to reduce bone marrow toxicity from radiation was demonstrated in a study of patients undergoing hemibody irradiation at a dose of 60 or 70 Gy. Patients pretreated with amifostine had no grade 4 bone marrow toxicity, compared to 10% in patients receiving hemibody irradiation alone (Table 1).[24]

**Phase III Studies**

**Head and Neck Cancer**

Amifostine was tested as a radioprotector in head and neck cancer in a phase III randomized trial initiated in September 1995.[20] Accrual was completed in August 1997, with 315 patients entered into the trial. The patients were stratified according to treatment center, site of disease (oropharynx or nasopharynx vs oral cavity), nodal status (N0 vs N+), performance status, and type of radiation (postoperative vs definitive or inoperable). Patients received 200 mg/m² of amifostine over 3 minutes before each dose of radiation (Table 1). The patients in the control arm received radiation alone. In each arm, the radiation dose schedule was the same, at 1.8 to 2 Gy/d for 35 fractions (54 Gy postoperatively or 70 Gy definitive radiotherapy). A 200 mg/m² dose of amifostine was chosen because of the known increased uptake of this drug in the parotid gland. The study required that at least 75% of the parotid glands receive treatment.

The results showed that pretreatment with amifostine significantly reduced the incidence of acute grade 2 xerostomia from 76% to 54% (P = .0004) and, importantly, that a significantly higher median dose of radiation (60 vs 42 Gy) was required to produce xerostomia (P = .0002). Data also showed a significant reduction in chronic grade 2/3 xerostomia (ie, moderate-to-severe xerostomia) 1 year after radiation therapy.

The quality-of-life effect of amifostine on head and neck cancer patients treated with radiation was assessed as part of the salivary protection study.[28] The clinical benefit was measured using an eight-item validated patient benefit questionnaire (PBQ) during and up to 11 months after radiation. Amifostine patients had significantly better PBQ scores and controls. The PBQ scores were most significant during the chronic xerostomia phase. The improvement in xerostomia led to improvements in factors such as diet, nutrition, weight, and sleep.

The results above demonstrate that amifostine can protect patients with head and neck tumors receiving radiotherapy or chemoradiotherapy against the dose-limiting effects of xerostomia.

**Non-Small-Cell Lung Cancer**

In an in-depth review of the nonoperative management of lung cancer, Green[29] stressed the importance of new strategies for treating advanced lung cancer and suggested that two to three cycles of chemotherapy combined with radiotherapy improves both the median and overall survival times for patients with advanced (stage III) disease. Tannehill et al[21] showed that pretreatment with amifostine resulted in less esophagitis than would be expected with chemotherapy and radiation alone.

In a laboratory model, Vujaskovic et al[30] showed that amifostine can protect against lung parenchymal toxicities as well as esophagitis.

A randomized phase III trial in 146 patients with lung cancer, conducted by Antonadou et al from Greece,[31] compared conventional radiation with or without amifostine at 340 mg/m² IV. The percentage of clinical grade 2 pneumonitis at 2 months was significantly reduced from 49% to 16%. The incidence of x-ray evidence of grade 2 or more pneumonitis was also significantly reduced, from 43% to 9%. The incidence of fibrosis at 6 months was significantly reduced from 53% to 28%. In addition, this study showed a statistically significant reduction in esophagitis at weeks 3, 4, 5, and 6 of radiation therapy. The rate of complete and partial response at 2 months was equivalent in the two treatment arms.

Antonadou and colleagues also treated 68 patients with localized advanced non-small-cell lung cancer in a small phase III randomized study of amifostine at 300 mg/m² in conjunction with radiation and paclitaxel (Taxol) or carboplatin.[32] Amifostine reduced the incidence of esophagitis and lung parenchymal toxicity in all settings.
The RTOG is conducting a phase III study in patients with stage III lung cancer who are receiving chemotherapy plus twice-daily radiation with or without amifostine. The study (RTOG 9801) opened in September 1998 and has enrolled 136 patients to date. The end points of the study are the esophagitis rate and quality of life. A minimum of 146 patients will need to be enrolled for a toxicity analysis. The goal is to decrease the esophagitis rate from 35% (the historical rate with chemotherapy and radiation) to 17%.

**Rectal Cancer**

A trial in 100 patients with advanced, inoperable rectal cancer investigated the resectability of previously inoperable tumors after radiation therapy and the radioprotective potential of amifostine.[22] Patients were randomized to receive pelvic irradiation (2.25 Gy 4 d/wk for 5 weeks, for a total of 45 Gy), either alone or following amifostine, 340 mg/m² IV, given 15 minutes before radiation therapy (Table 1). Each treatment group, including inoperable and unresectable cases, subsequently received an additional 7.2 Gy of radiation. Among patients receiving amifostine, there was no moderate or severe radiation toxicity to normal pelvic tissue, whereas 14% of patients treated with radiotherapy alone experienced such toxicity (P = .03). Complete tumor responses were seen in 16% of the group treated with amifostine and radiation, compared with a 10% response in the group irradiated without amifostine. Follow-up was 13 to 30 months, with a median of 24 months, and 12 of 100 patients became operable after treatment; 7 of the 12 had received amifostine. Median survival was 15 months in the amifostine arm and 12 months in the radiation-alone arm.

**Subcutaneous Administration of Amifostine**

The administration of subcutaneous amifostine has been tested in Greece.[31] Pharmacologic studies comparing IV to subcutaneous administration showed that the bioavailability was approximately 72% with the subcutaneous administration.[33] The logistics of the subcutaneous formulation are obviously much easier than the IV formulation, and this reduces the cost and manpower required for administration. Hypotension was rare. New infrequent toxicities were asthenia, fever, and a rash. Nausea and vomiting occurred but was diminished from the IV preparation. The preparation used was a flat dose of 500 mg amifostine diluted in 2.5 mL of normal saline injected subcutaneously in one site 20 minutes before radiotherapy. A total of 60 patients treated with thoracic tumors, 40 patients treated with head and neck tumors, and 40 patients with pelvic tumors were enrolled in randomized phase II trials. Comparative data showed decreased mucosal toxicity at each site for the patients who received the amifostine and a decrease in the days of radiotherapy delay that resulted from the toxicity. There was no clinical evidence of tumor protection. Local toxicity, such as pain, erythema, and rash, was seen with the subcutaneous injections. This may have resulted from the large volume of solution (2.5 mL) and the use of the shoulder area as the single injection site. Phase III trials of subcutaneously administered amifostine in head and neck and lung cancer patients are being planned.

**Discussion**

In a review of the use of chemotherapy and radiotherapy protectants, the American Society of Clinical Oncology (ASCO) concluded that there was no evidence from the available clinical data to demonstrate that amifostine leads to tumor protection.[34] In its clinical practice guidelines, ASCO gave amifostine the highest recommendation (IA) for use as a radioprotectant to decrease the incidence of acute and late xerostomia in patients who undergo fractionated radiation therapy in the head and neck region. The Society felt that current data on the role of amifostine in protection from mucositis was interesting but insufficient to recommend its use at this time. Results of further clinical trials will lead to a more definitive conclusion regarding protection of radiation-induced mucositis in the head and neck, thorax, and pelvic areas. The ASCO panel will review the developing clinical data in May 2002. Future and developing changes in the administration of amifostine include the subcutaneous formulation, dose increases to 340 mg/m², and possible changes in dose frequency. As new radiation therapy delivery techniques, such as 3D-CRT, lead to higher doses of radiation, protection against normal tissue toxicity becomes more important. An economic study of amifostine in head and neck cancer showed that its use cut the costs of overall toxicity management to the patient because it eliminated the frequency of hospitalizations for toxicity management.[35] This is
one reason that toxicity prevention may be preferable to toxicify management. That said, amifostine may prove to be protective against the toxicities associated with multiple chemotherapy agents, as well as radiation, and in multiple normal tissues.

Conclusions

A major dose-limiting effect of radiotherapy is damage to normal tissue. Protection of normal tissue against side effects secondary to radiotherapy or chemoradiotherapy will permit dose escalation, increase patient survival, and provide better quality of life for patients undergoing cancer treatment.

References:


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