Clinical Status and Optimal Use of Amifostine

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Amifostine (Ethyol) is an analog of cysteamine that selectively protects normal tissues in multiple organ systems against the toxic effects of radiation and various cytotoxic drugs while preserving the antitumor effects of these

Introduction

The recent decline in mortality observed among patients with cancer reflects not only improved methods for prevention and early detection of malignancy but also better treatments. The most striking therapeutic advances are the result of improved surgical techniques combined with cytotoxic radiation and/or drug therapy.

Historically, the notion of patients deriving potentially significant benefit from cytotoxic therapy was disparaged because of the presumption that cytotoxic therapies could not distinguish between normal and neoplastic tissues. However, the degree and duration of cytotoxic damage to normal and neoplastic tissue differ sufficiently to allow for clinically meaningful benefits in the palliation and cure of cancer. Whether the goal of therapy is palliation or cure determines the degree of risk and cost that the patient and health care system are willing to accept, since virtually all cytotoxic therapies have a narrow therapeutic index. This toxicity to normal organs not only limits the use and achievement of the full therapeutic potential of cytotoxic agents but also claims a cost in terms of patient morbidity and mortality.

Oncologists attempt to mitigate the toxic effects of chemotherapeutic agents by adjusting the dose and frequency of treatment. A major drawback to this strategy is insufficient control of the tumor. A growing area for new drug development is the evolving field of supportive care agents intended to avert or minimize treatment-limiting toxicities to normal organs. Historically, the oldest approach of this type was the use of rescue agents, such as leucovorin “rescue” following high-dose methotrexate.[1] This approach has been useful for the treatment of pharmacologic sanctuaries, such as the central nervous system (CNS),[2] as well as tumors that are relatively resistant to standard doses of methotrexate, such as osteosarcoma. Likewise, the use of marrow-stimulatory cytokines following moderately toxic doses of drugs has been useful.

An alternate approach to rescue techniques is the use of cytoprotective agents, or cytoprotectors. These drugs selectively protect normal tissues from the cytotoxic effects of drugs and/or radiation while preserving their antitumor effects. The ideal cytoprotector should be easily administered and should have a broad spectrum of activity; not only should it be able to protect multiple tissues, but also it should protect these tissues from diverse cytotoxic treatments. The agent also should have a reasonable safety profile. By improving patient tolerability to the therapy, the cytoprotector may provide multiple benefits: It may improve patient quality of life; allow for dose-inten-sification and, thus, improved response and/or cure rates; and decrease costs associated with other supportive care measures needed to treat treatment complications.

To date, three cytoprotectors have been approved by international regulatory agencies. Mesna (Mesnex) is approved for the protection of the bladder from the toxicity associated with ifosfamide (Ifex) and high-dose cyclophosphamide (Cytoxan, Neosar).[3] Dexrazoxane (Zincard) is used to protect the heart from the cardiomyopathy associated with the cumulative cardiotoxic effects of doxorubicin.[4] Both of these agents are drug- or drug class–specific and their protective effect is limited to specific organs—the urinary bladder for mesna and the heart for dexrazoxane.

Amifostine (WR-2721 [Ethyol]) is the first broad-spectrum cytoprotective agent to be approved by international regulatory agencies. In this context, broad spectrum refers to cytoprotection against a broad array of cytotoxic therapies, ie, multiple drug classes as well as radiation, in multiple organ systems. Laboratory and clinical studies have shown that amifostine protects cells in virtually all organ systems except the CNS, which is a target for both acute and cumulative (or delayed) cytotoxic damage. Because of poor tissue distribution pharmacokinetics in the CNS, this organ
system has not been effectively studied. This article will review preclinical and clinical studies of amifostine, as well as trials evaluating its chemoprotective and radioprotective effects. Studies suggesting that amifostine pretreatment may also enhance the antitumor effects of chemotherapy in certain settings and prevent secondary malignancies are also detailed.

**Preclinical and Early Clinical Trials**

Amifostine was originally synthesized under a classified project of the US Army aimed at developing agents to protect the military from the effects of radiation from a nuclear warhead. (Its military code name is WR [Walter Reed]-2721.) Amifostine was selected for further development from over 4,000 compounds because of its superior radioprotective and safety profile. The synthesis of this series of sulfhydryl-containing compounds was based on previous observations showing that the sulfhydryl-containing amino acid, cysteine[5] and, subsequently, cysteamine could protect rodents from lethal doses of radiation.

Amifostine (Figure 1), an analog of cysteamine, is a phosphorylated aminothiol prodrug that is dephosphorylated in the tissues by membrane-bound alkaline phosphatase to its active metabolite, WR-1065. A free thiol, WR-1065 is the form of the drug that is taken up into cells and is the major cytoprotective metabolite. Oxidation of WR-1065 forms the symmetrical disulfide, WR-33278, which not only is structurally similar to spermine, a naturally occurring polyamine, but also shares certain biochemical properties with the polyamines that may contribute to some of its pharmacologic properties.

**Pharmacokinetics**

The selective cytoprotection of normal tissue by amifostine stems from its unique systemic and tissue distribution pharmacokinetics. Following intravenous administration of the drug, the half-lives of both the distribution and elimination phases in humans are extremely short (alpha-half-life, < 1 minute; beta-half-life, 8.8 minutes). Most (90%) of the drug is cleared from the plasma within 6 minutes, and only a small amount of the prodrug is bio-converted to the free thiol in the systemic circulation relative to normal tissues.[6-9]

Generation of the free thiol, WR-1065, occurs primarily at the tissue site due to local dephosphorylation by membrane-bound alkaline phosphatase; this enzyme has relatively high specific activity in the endothelia of normal capillaries and membranes of normal cells but is relatively deficient in the neovascular endothelia and membranes of cancer cells.[10-12] Once inside the cells, WR-1065, the free thiol, provides protection from cytotoxic damage by acting as a scavenger of oxygen-free radicals generated by radiation[13] and anthracyclines,[14] and by binding to highly reactive nucleophiles that would otherwise cross-link and damage DNA.[15-17]

Recent studies suggest that amifostine or WR-1065 can up-regulate gene expression of p53[18]; this results in cell-cycle accumulation at the G1-S interface, which, in turn, may allow for more efficient DNA repair. Extensive preclinical studies, in both cell cultures and tumor-bearing rodents, have shown that amifostine selectively protects normal tissues without protecting a wide variety of murine and human carcinomas, sarcomas, and leukemias.[19]

Based on this preclinical profile, amifostine has been studied in a number of clinical trials. The combined laboratory and clinical experience to date has shown protection of the organs listed in Table 1 from cytotoxic damage. As a result of these studies, an expanded pharmacologic profile of amifostine is emerging (Table 2). The following summary will provide a brief overview of these areas.

**Studies of Chemoprotective Effects**

Following extensive controlled laboratory investigations and a series of phase I and II clinical trials, it was evident that pretreatment with amifostine could protect normal tissues from hematologic toxicity associated with cyclophosphamide (Cytoxan, Neosar) or high-dose cisplatin (Platinol)[20,21] and from nonhematologic toxicities associated with cisplatin, and that it could achieve this cytoprotection without any negative effects on the antitumor efficacy of these drugs.[20,22-24]

Amifostine-mediated cytoprotection against these hematologic and nonhematologic toxicities was evaluated in a multicenter, multinational, phase III clinical trial that enrolled women with stage III/IV ovarian cancer (Figure 2). Following surgery for tumor debulking and staging, patients were stratified based on residual tumor and cancer center and were randomly assigned to receive six cycles of cyclophosphamide plus cisplatin with or without amifostine, administered at 3-week intervals. Prior to receiving any chemotherapy, all patients were hydrated with 5% dextrose in 0.45% saline (200 mL/h) for 6 hours. Patients were to receive drug therapy only when urine output exceeded 150
40% reduction in creatinine clearance in the control arm of the ovarian cancer trial (22) The clinical end points of the trial included assessment of the expected toxicities—hematologic, renal, peripheral neuropathy, and ototoxicity, as well as antitumor efficacy.

Hematologic Toxicity
The major hematologic end point was the cumulative incidence of neutropenic events through the six cycles of therapy. Neutropenic events were defined as grade 4 neutropenia with fever and/or signs and symptoms of infection that usually require hospitalization, clinical and laboratory evaluation, and institution of empiric broad-spectrum antibiotic therapy. Pretreatment with amifostine resulted in a significant reduction in this potentially life-threatening event. As shown in Table 3, amifostine pretreatment significantly decreased all parameters of hematologic toxicity. Most notably, it reduced both the number of days the patient spent in the hospital and the cumulative number of days of treatment with broad-spectrum antibiotics as a consequence of neutropenic events.

Renal Toxicity
The protocol-defined renal end point to assess the ability of amifostine to protect against cisplatin-induced nephrotoxicity was the need to delay or discontinue cisplatin therapy because of elevations in serum creatinine > 1.5 mg/dL. If serum creatinine level was > 1.5 mg/dL at day 22, cisplatin was to be delayed for a maximum of 2 weeks; if it remained at a level exceeding 1.5 mg/dL at day 35 (defined as a protracted elevation of serum creatinine), cisplatin was to be discontinued. Cisplatin-induced nephrotoxicity was the need to delay or discontinue cisplatin therapy. Consistent with the cumulative nature of cisplatin-induced nephrotoxicity, by cycles 5 and 6 a significantly greater proportion of patients in the control arm compared to the amifostine arm could not receive cisplatin as scheduled because of elevated serum creatinine levels. These differences were statistically significant despite the fact that patients in both groups received comparable doses of cisplatin (median cumulative doses, 555 and 500 mg/m² for the amifostine and control groups, respectively).

Since, in most hospitals, the upper limit of normal for serum creatinine in women is 1.0 mg/dL, a rise in serum creatinine to 1.5 mg/dL would represent a substantial deterioration in renal function. Estimations of creatinine clearance utilizing serum creatinine, age, weight, and gender were calculated utilizing the formula of Cockcroft and Gault. As shown in Table 4, by the end of therapy, 33% of patients treated with chemotherapy alone had a ≥ 40% reduction in creatinine clearance. This was reduced to 10% in the amifostine-treated patients (P = .001). The 33% incidence of a ≥ 40% reduction in creatinine clearance in the control arm of the ovarian cancer trial is consistent with the incidence observed in women treated with up to six cycles of the same regimen in a trial conducted by the Southwest Oncology Group (SWOG). In this trial, after the last cycle of therapy, 40% of patients (51/127) sustained a ≥ 40% reduction in creatinine clearance from baseline. Similarly, in two other trials that used single-agent cisplatin (100 mg/m² for 5 monthly cycles) in previously untreated patients with advanced ovarian cancer, a ≥ 40% decrease in glomerular filtration rate, as measured by endogenous creatinine clearance or ethylene-dinitrilo tetraacetic acid (EDTA) clearance, was noted in 35% and 45% of patients, respectively.

Other reports have shown comparable cumulative nephrotoxic effects of cisplatin, as measured by progressive increases in serum creatinine values and progressive decreases in creatinine clearance measurements through five or six cycles of cisplatin (80 to 100 mg/m²). In contrast, in phase II clinical trials using monthly courses of amifostine (740 or 910 mg/m²) prior to cisplatin (120 mg/m²) in patients with non-small-cell lung cancer (NSCLC), melanoma, breast, or head and neck cancer, the frequency of a ≥ 40% reduction in creatinine clearance from baseline was 8%, which is consistent with the 10% incidence observed in the amifostine arm of the ovarian cancer trial (Table 5).
The literature shows that the cumulative nature of cisplatin nephrotoxicity is generally permanent. The data from the ovarian cancer trial support this conclusion. The reduction in glomerular filtration rate at the end of cisplatin therapy observed in the control arm of that trial persisted through a 30-month follow-up period (Figure 5). This loss in renal reserve will have an impact on further antineoplastic and other therapies that require renal elimination or that have intrinsic renal toxicity—a clinical concern that also pertains to the use of certain radiographic contrast agents.

**Clinical Neurotoxicity**

In the ovarian cancer trial, clinical neurotoxicity was scored in accordance with the National Cancer Institute (NCI) grading system. The higher grades include troublesome paresthesias and inability to perform fine finger motions. Treatment with amifostine resulted in a significant reduction in the severity of clinical neurotoxicity (Table 6).

This is consistent with amifostine neuroprotection reported by Mollman et al.[41] They found a 40% reduction in ototoxicity (defined as troublesome tinnitus and clinical hearing loss requiring a dose reduction or discontinuation of cisplatin) in the amifostine-treated patients compared to the control patients, although the difference was not statistically significant, as only 7% of control patients experienced this toxicity.

**Effects on Antitumor Efficacy of Chemotherapy**

Amifostine pretreatment did not affect the antitumor effects of cyclophosphamide-cisplatin, as assessed by response rates (determined at second-look surgery or by overall survival). The overall response rates (pathologic complete plus partial responses) were 75% in amifostine-treated patients and 65% in the control group. With a median follow-up of 41 months, comparable median survival times of 31 months were noted for patients in both treatment arms (Figure 6).[22]

**Hematoprotective Effects: Other Examples**

The selective hematoprotective effects of amifostine have been further explored in controlled laboratory experiments using an admixture of normal human marrow and human breast cancer. To a suspension of cells from normal human marrow, Sphall and colleagues added 10% breast cancer cells. This admixture was then treated with escalating doses of 4-hydroperoxy-cyclophosphamide (4-HC); an aliquot of the cell suspension was pretreated with amifostine for 15 minutes, following which the cells were washed and then treated with 4-HC similar to the control aliquot. Following treatment, the cell suspensions were washed free of drug and then cloned to assess viability of marrow progenitors (colony-forming unit-granulocyte-macrophage [CFU-GM]) and breast cancer. For all dose levels of 4-HC, pretreatment with amifostine enhanced the viability of the marrow progenitor cell population by 10- to 100-fold (1- to 2-log increase). In contrast, pretreatment with amifostine did not attenuate the cytotoxic effect of 4-HC on breast cancer cells.[42]

These laboratory observations have been applied in two randomized, phase II clinical trials in patients with breast cancer and non-Hodgkin’s lymphoma (NHL) treated with dose-intensive chemotherapy followed by 4-HC-purged autologous marrow transplantation. Table 7 shows the hematologic data for the breast cancer patients who received 4-HC-purged marrow with or without amifostine pretreatment. Patients who received amifostine-treated marrow had a significantly shorter time to recovery of neutrophil and platelet counts and a significant reduction in the need for platelet and red blood cell transfusions. In addition, three patients whose marrow was treated with 4-HC alone required the reinfusion of non-4-HC-purged back-up marrow because of failure of engraftment.[42] Comparable results have been reported in patients with NHL undergoing autologous bone marrow transplantation.[43]

Results consistent with the aforementioned study have been reported by a laboratory study that used normal human marrow and acute leukemia cells (acute myelogenous and lymphocytic leukemia [AML and ALL] and chronic myelogenous leukemia [CML] in blast crisis) taken from patients. These normal marrow and leukemia cells were treated in vitro with mafosfamide, an analog of cyclophosphamide, with or without preincubation with amifostine as described above. Amifostine pretreatment protected normal marrow progenitor cells at each concentration of mafosfamide. In contrast, pretreatment with amifostine sensitized the human acute leukemia cells to the cytotoxic effects of mafosfamide (Figure 7).[44]

These contrasting effects on human normal and malignant hematopoietic cells are similar to those reported by Valeriote and Tolen.[45] The cytotoxic effect of mechlorethamine (nitrogen mustard [Mustargen]) on pleuripotent hematopoietic murine progenitor cells was assayed as spleen colony-forming units (CFU-S). Mechlorethamine reduced the viability of CFU-S in a dose-dependent fashion. Pretreatment with amifostine protected CFU-S at each dose level of mechlorethamine (Figure 8).

In contrast, pretreatment of mice sensitized the AKR leukemia to the cytotoxic effects of
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As mentioned above, amifostine was originally developed to protect normal tissues against radiation. Initial laboratory trials in tumor-bearing animals showed selective protection of normal tissues. [55-57] Further laboratory studies showed reasonable protection from radiation damage for a...
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The results of randomized clinical trials confirm these laboratory observations. In one such trial, 100 patients with advanced, unresectable rectal cancer were randomized to treatment with daily external-beam fractionated radiation therapy with or without amifostine, 340 mg/m². Pretreatment with amifostine resulted in a significant reduction in late radiation toxicities to pelvic organs (p = .026).[59] This protection of normal tissues occurred with no reduction in antitumor efficacy. Median survival was 15 months for patients treated with amifostine and radiation vs 12.3 months for those patients treated with radiation alone.

Laboratory studies show that daily treatment with amifostine results in an accumulation of the drug’s thiol metabolites in the major salivary glands of mice.[60] A randomized, phase II clinical trial in patients with carcinoma of the head and neck treated with daily standard-fraction radiation and a 5-day course of carboplatin (administered on weeks 1 and 3 of radiation therapy) showed that administration of 500 mg of amifostine prior to each dose of carboplatin on days 1 to 5 and days 21 to 25 resulted in a statistically significant reduction in the incidence of grades 3 and 4 mucositis and symptomatic xerostomia using the World Health Organization (WHO) criteria. Of 14 patients treated with carboplatin-radiation without amifostine, 12 sustained grade 3 or 4 mucositis, compared to none of the 25 patients treated with amifostine (p < .0001). Symptomatic dry mouth was reported by all 14 patients in the control arm, as opposed to 3 of 25 amifostine-treated patients (p < .0001).[61]

In a recent report of 315 patients with squamous cell carcinoma of the head and neck treated with daily standard-fractionated doses of radiation with or without amifostine, there was a significant reduction in symptomatic xerostomia during and 1 year following radiation therapy in patients who received a single daily dose of amifostine (200 mg/m²) prior to each radiation treatment. Furthermore, the median cumulative dose of radiation at the onset of grade 2 (symptomatic) xerostomia was 42 Gy in the control (radiation alone) patients vs 60 Gy in the patients treated with amifostine (p < .0001).[62]

Tumor Sensitization

In the careful search to confirm the selective cytoprotection of normal tissues by amifostine, many controlled laboratory experiments have been conducted both in vitro and in vivo. In none of these carefully controlled laboratory studies has there been any evidence of tumor protection.[19] An incidental result of these laboratory studies has been evidence of tumor sensitization by amifostine pretreatment, ie, an actual enhancement of antitumor effects along with protection of normal tissues.

The two examples cited above with human[44]and murine[45] leukemia are examples of this phenomenon. Examples from other laboratories include amifostine-mediated enhancement of carboplatin cytotoxicity on human ovarian cancer,[46] doxorubicin cytotoxicity on human breast cancer,[48] paclitaxel cytotoxicity on human NSCLC,[47] and the cytotoxic effect of photodynamic therapy on human small-cell lung cancer (SCLC).[64]

Cytostimulation

In studies designed to evaluate the cytoprotection of normal human marrow, the capacity of amifostine to stimulate multipotent human marrow progenitor cells became evident (Figure 10).[65] Similar stimulation of multipotent marrow progenitor cells was demonstrated in vitro by amifostine treatment of marrow taken from patients with myelodysplastic syndrome (MDS).[66] This marrow-stimulatory property of amifostine was tested in 18 patients with various defined subtypes of MDS. Encouraging elevations of neutrophil and platelet counts and a reduction in red blood cell transfusion requirements were reported.[66] Results of this trial are summarized in Table 11. Tolerance to amifostine (200 mg/m² IV three times weekly) has been excellent.[66] These initial marrow-stimulatory effects of amifostine in patients with MDS have been confirmed by other investigators.[67,68]
Prevention of Secondary Tumors

An unfortunate delayed effect of certain forms of chemotherapy and radiation therapy may be the development of secondary malignancies due to damage of DNA. Preclinical studies have demonstrated that amifostine can protect cells from the mutagenic effect of cisplatin, cyclophosphamide, bleomycin, mechlorethamine and radiation at the hypoxanthine guanine phosphoribosyl transferase (HGPRT) locus.[69-75] In addition, pretreatment with amifostine (400 mg/kg intraperitoneally) 30 minutes prior to gamma-irradiation (3,400 to 3,700 cGy) of the hind limbs of mice resulted in the development of significantly fewer sarcomas. Based on Kaplan-Meier estimates, 87% of the mice irradiated without amifostine developed tumors, as compared with 26% of the mice pretreated with amifostine.[76] Thus, amifostine may reduce the carcinogenicity of anticancer modalities in addition to decreasing their acute and chronic toxicities. As modern cancer therapies improve the survival of patients, especially children with certain tumors, prevention of secondary cancers becomes increasingly important.[77]

Amifostine Dose and Tolerance

At doses of 740 to 910 mg/m², amifostine has demonstrated the ability to reduce hematologic toxicities, nephrotoxicity, and neurologic toxicities associated with certain forms of chemotherapy with full preservation of antitumor efficacy.[20,22-24] These amifostine doses are administered as a 10- to 15-minute infusion just prior to chemotherapy. With drugs such as carboplatin that have a long half-life, two 600- to 740-mg/m² doses of amifostine have been administered, the first just prior to each dose of carboplatin and the second 2 hours afterward. Data from controlled clinical trials have shown that amifostine significantly reduces the neutropenia and thrombocytopenia associated with carboplatin.[51,78,79] Clinical trials have found that amifostine doses of 200 to 340 mg/m²/d (administered as a 3-to 5-minute intravenous push) reduce acute and late xerostomia and mucosal damage from fractionated radiation therapy while preserving its antitumor efficacy.[59,61,62] In clinical trials evaluating amifostine as a treatment for patients with MDS, doses of 200 mg/m² have also been administered three times per week for 3 weeks followed by a 2-week rest.[66] The principal toxicities associated with amifostine are nausea and vomiting and hypotension, typically characterized by a transient reduction in blood pressure (Table 12). These toxicities are dose-related, occurring at a much lower frequency and severity with daily doses of 200 to 340 mg/m².

Clinical trials of paclitaxel and amifostine have shown that standard paclitaxel premedications, in particular, high-dose dexamethasone and serotonin receptor antagonists, have ameliorated the emesis and hypotension associated with higher doses of amifostine administered prior to chemotherapy (Table 13).[80] With amifostine doses of 200 to 340 mg/m²/d administered prior to fractionated radiation, oral serotonin receptor antagonists, such as ondansetron (Zofran) and granisetron (Kytril), alone or in combination with other oral antiemetics, have effectively ameliorated nausea and vomiting (data on file, US Bioscience).

It is recommended that all patients be hydrated adequately prior to amifostine administration and that they be maintained in a supine position during the amifostine infusion. Blood pressure should be measured prior to the infusion and monitored at 5-minute intervals during and at the completion of the infusion. If hypotension occurs, the infusion of amifostine should be interrupted, in accordance with the guidelines in the package insert, and the patient should receive an infusion of normal saline solution. If blood pressure recovers within 5 minutes and the patient remains asymptomatic, the amifostine infusion can be restarted.

Conclusions

The emerging clinical profile of amifostine is unique and complex. Originally developed to protect the military in the event of a nuclear war, amifostine has emerged as an effective protector of normal tissues in patients receiving various cytotoxic agents and therapeutic radiation. To date, amifostine has been shown to protect against the toxic effects of alkylating agents, organoplatinums, anthracyclines, taxanes, and radiation. Importantly, the broad-spectrum cytoprotective properties for cytotoxic drugs and radiation are selective for normal tissues. Other laboratory and clinical investigations indicate a potential role for amifostine in the treatment of the ineffective
hematopoiesis characteristic of MDS.

References:


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