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The potential of amifostine: from cytoprotectant to therapeutic agent

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ABSTRACT

Background and Objectives. **Amifostine is an inorganic thiophosphate cytoprotective agent known chemically as ethanethiol, 2-[(3-aminopropyl)amino]dihydrogen phosphate. It is a pro-drug of free thiol that may act as a scavenger of free radicals generated in tissues exposed to cytotoxic drugs, and binds to reactive metabolites of such drugs. Amifostine was originally developed as a radioprotective agent in a classified nuclear warfare project. Following declassification of the project it was evaluated as a cytoprotective agent against toxicity of the alkylating drugs and cisplatin. In fact, pretreatment with amifostine was well tolerated and reduced the cumulative hematologic, renal and neurological toxicity associated with cisplatin, cyclophosphamide and vinblastine therapy of advanced and metastatic solid tumors. The objective of this review is to focus the importance of amifostine as a myeloprotective and cytoprotective drug during treatment with chemotherapeutics, presenting the most recent results, and to discuss the application of amifostine in the therapy of myelodysplastic syndromes.**

Evidence and information sources. **The material analyzed in this study includes data published or under publication by the authors as full papers or clinical protocols. Articles and abstracts published in Journals covered by Medline constitute the other source of information.**

State of the art and Perspectives. **Amifostine, formerly known as WR-2721, is an organic thiophosphate that was developed to protect normal tissues selectively against the toxicities of chemotherapy and radiation. Amifostine is a pro-drug that is dephosphorylated at the tissue site to its active metabolite by alkaline phosphatase. Differences in the alkaline phosphatase concentrations of normal versus tumor tissues can result in greater conversion of amifostine in normal tissues. Once inside the cell the free thiol provides an alternative target to DNA and RNA for the reactive molecules of alkylating or platinum agents and acts as a potent scavenger of the oxygen free radicals induced by ionizing radiation and some chemotherapies. Preclinical animal studies demonstrated that the administration of amifostine protected against a variety of chemotherapy-related toxicities including cisplatin-induced nephrotoxicity, cisplatin-induced neurotoxicity, cyclophosphamide- and bleomycin-induced pulmonary toxicity, and the cytotoxicities (including cardiotoxicity) induced by doxorubicin and related chemotherapeutic agents. Amifostine was shown to protect a variety of animal species from lethal doses of radiation. Studies in tumor-bearing animals demonstrated that the administration of amifostine results in cytoprotection without loss of antitumor activity. Multiple phase I studies were carried out with amifostine in combination with chemotherapy for various neoplasms. Appropriate doses of amifostine resulted to be 740-910 mg/m² in a single dose regimen, and 340 mg/m² in a multiple dose regimen. Amifostine afforded not only hematologic protection, but also other organ protection from cytotoxic agents such as nephrotoxicity, mucositis and peripheral neuropathy from cisplatin. Many studies have been performed to investigate cytoprotective efficacy of amifostine. In brief, amifostine gives hematologic protection from cyclophosphamide, carboplatin, mitomycin C, fotemustine and radiotherapy; renal and peripheral nerve protection from cisplatin; mucosa, skin, and salivary gland from radiotherapy. In phase I/II studies these properties have been confirmed, together with a generally good tolerability of the drug, hypotension being the most common side effect. It has been observed that amifostine possibly enhances the anti-tumor effect of carboplatin, nitrogen mustard, melphalan, and cisplatin combined with 5-FU or vinblastine. For all these characteristics, amifostine is at present broadly used as supportive treatment during chemotherapy, in lymphomas and solid tumors, and its spectrum of possible applications is enlarging. As data have been provided indicating that amifostine stimulates hematopoiesis, it has been proposed as a possible therapeutic agent in myelodysplasia, in which most clinical complications are related to cytopenia. Several trials have been performed and are at present on-going with the purpose of elucidating the real efficacy of amifostine in restoring effective hemopoieisis. The first observations reported are generally in agreement, indicating a partial response to amifostine, especially in low-risk MDS. Although synthesized several years ago, amifostine has entered into clinical use only recently. Its broad cytoprotective effects seem beneficial, particularly in view of the widespread and increasing application of high-dose chemotherapy, even in elderly patients. Amifostine possibly parallels the action of growth factors as supportive agents, with which it also shares a relatively limited toxicity. In fact, it can reduce both neutropenia and thrombocytopenia induced by cytotoxic therapy. In this sense, the use of this cytoprotectant should be encouraged. Challenging data came from the early application of amifostine as a single therapeutic agent in myelodysplastic syndromes. Although at present only partial responses have been reported, in the near future the real significance of this compound will be clarified thanks to large and complete clinical trials, and its importance finally discussed and defined.**

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The relatively non-selective effects of most antitumor agents adversely influence the quality of life of patients, increase therapy-related mortality and also limit the dose of chemotherapy and radiation. In the last decade, several agents have been developed to protect or rescue normal tissues from these adverse effects including dexrazoxane (cytoprotectant against cardiotoxicity), mesna (reduction of alkylator-associated hemorrhagic cystitis), amifostine (broad-spectrum cytoprotectant), leucovorin (rescue agent for high-dose methotrexate), and growth factors (erythropoietin, GM-CSF, G-CSF).[1-3]

The ideal properties of a potential cytoprotectant are: 1) selectivity, i.e. ability to protect non-neoplastic tissues from the toxicity of antitumor therapies without protecting the tumor cells; 2) broad-spectrum activity, i.e. should protect a range of normal tissues from adverse effects of a wide array of cytotoxic agents, with differing mechanisms of action; 3) minimal adverse effects.[3,4]

These same characteristics and properties can, on the other hand, be exploited in the attempt to overcome ineffective hemopoiesis, a condition typical of myelodysplastic syndromes.

Molecule and mechanism of action

Amifostine, formerly known as WR (Walter-Reed)-2721, was developed originally during the Cold War by the Walter Reed Army Institute as a radioprotectant.[4-7] After that, this drug was studied for a potential role in therapeutic radiation, as well as chemotherapy especially with alkylating agents, organoplatinum agents and anthracyclines.[1,5,7-9] This review examines the cytoprotective and therapeutic properties of amifostine in hematologic neoplasms, its mechanism of action, adverse event profile and specific areas of current investigation.

Amifostine is an organic thiophosphate cytoprotective agent known chemically as ethanethiol, 2-[(3-aminopropyl)amino]-, dihydrogen phosphate (ester), and it has the following structural formula:

$$H_2N(CH_2)_3NH(CH_2)_2S\text{-}PO_3H_2$$

Amifostine is a phosphorylated pro-drug. It is rapidly dephosphorylated by alkaline phosphatase (a plasma membrane enzyme) into the free thiol WR-1065 that is its active form.[11-13] WR-1065 is consequently oxidized to a symmetrical disulfide of WR-1065 (WR-33278) or mixed disulfides with endogenous thiols and thiol-containing proteins.[4,11,14]

This drug is rapidly cleared from plasma, less than 10% of the drug remaining in the plasma 6 minutes after intravenous administration.[6,12,15,16] The rapid disappearance of amifostine from the plasma may be due to its rapid conversion into WR-1065 that is also rapidly cleared from the circulation by its fast uptake in normal tissues or by its conversion into disulfides.[12,17,18] The peak tissue concentration of WR-1065 is achieved 10-30 minutes after injection.[16,17]

WR-1065, an active form of amifostine, produces cytoprotective effects by binding to and detoxifying directly the active forms of chemocytotoxic drugs, scavenging free radicals, and donating hydrogen ions for DNA repair.[3,4,6,18,19] Free radicals are thought to be a factor of toxicity induced by radiation and some chemocytotoxic drugs.[5-7,9]

Amifostine has the unique ability to protect normal tissues but not tumor cells from radiation or chemotherapy.[3,7,11, 21-25] The selective cytoprotection derives from several mechanisms, as follows: first, the concentration of membrane-bound alkaline phosphatase (amifostine-activating enzyme) is 275-fold greater in normal than in tumor tissues; second, this drug is absorbed by active transport in normal tissues but by passive diffusion in tumor cells; third, the lower blood supply in tumors as compared with normal tissues may result in minor delivery of the drug to tumor cells; fourth, the neutral pH of normal tissue results in a greater uptake of the drug than that possible in the acidic environment of tumor tissue.[1,3,4,6,26] These mechanisms cause higher (about 50-100 fold) drug concentrations in normal organs than in tumor tissue. Organs with high amifostine uptake include kidney, salivary gland, bone marrow, liver, heart, lung and small intestine, whereas low amifostine concentrations were observed in the brain and spinal cord because of the negligible passage of the drug through the blood-brain barrier.[4,5,7,10,25]

Evidence of hematologic protection

Chemotherapy and radiotherapy intensification is often limited by hematologic toxicity. Myelosuppression is usually manifested as symptomatic neutropenia and thrombocytopenia. Hematopoietic growth factors (HGFs), the most used being GM-CSF and G-CSF, can reduce the duration of neutropenia, the frequency of infections and thus allow a modest escalation of chemotherapy, but until now HGFs have not been able to resolve therapy-induced thrombocytopenia. Moreover, there is evidence that the efficacy of HGFs decreases with repeated courses of chemotherapy.[2,28,29] In contrast, both preclinical and clinical studies have shown that amifostine can reduce both cytotoxic therapy-induced neutropenia and thrombocytopenia.[3,4,6,7,26]

Preclinical studies

In extensive preclinical studies, amifostine showed significant protection of hematopoietic progenitors from a broad range of cytotoxic agents, including daunorubicin, mitoxantrone, paclitaxel, cisplatin, doxorubicin, diaziquone, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, mitomycin-C, BCNU, 5-FU and radiation as well.[4,8,30-36] In 1981, Wasserman *et al.*[31] demonstrated cytoprotective effects of amifostine on mouse bone marrow colony-forming units exposed to cytotoxic agents and radiotherapy. They showed that the dose-modifying factors for

bone marrow protection were 4.6, 3.2, 2.4, 1.5, 2.7, 2.4 for nitrogen mustard, cisplatin, cyclophosphamide, BCNU, 5-FU and radiation, respectively (the ratio was determined from the CFU survival curve and when the ratio was > 1 protection was assumed to be present). List *et al.* showed multilineage cytoprotection by amifostine *in vitro*.[9] According to these observations, amifostine was able to protect CFU-GEMM against daunorubicin-, mitoxantrone- and paclitaxel-induced cytotoxicity, and could also protect BFU-E against doxorubicin-, mitoxantrone-, paclitaxel-, cisplatin- and diaziquone-induced toxicity.[9] van Laar *et al.* evaluated the cytoprotective effect of amifostine on animals treated with the combination of carboplatin and 5-FU, and tentatively rescued by intraperitoneal injection of 200 mg/kg amifostine 5 minutes prior to chemotherapy administration. They found that amifostine had protective ability against thrombocytopenia.[34]

Evidence of general cytoprotection

Preclinical animal studies also demonstrated that the administration of amifostine can protect against a variety of chemotherapy-related toxicities, including cisplatin-induced nephrotoxicity and neurotoxicity[35,36] and cyclophosphamide-induced pulmonary toxicity.[37] Amifostine has been shown to protect a variety of animal species from lethal doses of radiation.[38] It has also been shown to protect rat salivary glands, oral mucosa, and hair follicles (stopping alopecia) from the effects of radiation.[38,39] Studies in tumor-bearing animals have demonstrated that the administration of amifostine results in cytoprotection without loss of any antitumor activity.[40]

Clinical studies

The results of preclinical studies have influenced the development of clinical trials with amifostine as a cytoprotective agent.

A phase I study was conducted by Kligerman *et al.*[41] to determine the maximal tolerated dose (or an acceptable tolerated dose) and side effects of amifostine. In this study, 121 patients with advanced malignancies received a single dose of amifostine (escalated from 25 to 1330 mg/m^2) before administration of cyclophosphamide, nitrogen mustard, cisplatin or before radiation. The maximum tolerated dose was not determined, but an acceptable tolerated dose was established to be 740 mg/m^2. The most serious and life-threatening side effect was hypotension. However, only 5% of the patients had severe hypotension (drop in systolic blood pressure more than 20 mmHg for at least 5 minutes). The second important side effect was emesis. Hypotension and emesis were the causes of incomplete infusion of amifostine in about 6% of the patients. No death occurred in relation to toxicity. Kligerman *et al.* performed another phase I trial of multiple doses of amifostine, administered before protracted fractionated radiation therapy.[42] They concluded that the maximum tolerated dose of this drug for patients receiving fractionated radiation was 340 mg/m^2.

Glick *et al*. conducted a phase I controlled trial of amifostine and cyclophosphamide.[43] In this study, 15 patients received amifostine 450-1,100 mg/m^2 prior to cyclophosphamide 1,200-1,800 mg/m^2 and 4 weeks later (after full hematologic recovery), they were treated with cyclophosphamide alone. With amifostine pretreatment, 11 of 15 patients (73%) had improved nadir WBC counts (p=0.008) and 7/11 (64%), who had nadir differential counts performed, had improved nadir granulocyte counts (p=0.05). The mean WBC nadir with combined drugs was 2,700/mm^3, but only 1,800/mm^3 when cyclophosphamide was employed alone (p=0.008). The mean granulocyte nadir with amifostine plus cyclophosphamide was 1,274 /mm^3, compared to 765/mm^3 with cyclophosphamide alone.

Constine *et al.* provided data from a phase I/II trial.[44] They showed that patients to whom amifostine was given prior to hemibody irradiation (HBI) had a more rapid and complete return of WBC normal counts than the control group (HBI alone). No life-threatening toxicity was seen in the amifostine-group, compared with 2 life-threatening events in the control group. There were no significant differences in the platelet nadir and platelet recovery time between the two groups. This study suggested that the optimal dose of amifostine was 750-900 mg/m^2.[44]

From multiple phase I studies, the appropriate doses of amifostine were determined to be 740-910 mg/m^2 in single-dose regimens, and 340 mg/m^2 in multiple-dose regimens.[38-44] Results of preclinical and phase I trials suggested that amifostine is quite safe and has potential broad spectrum cytoprotection against many cytotoxic agents. All the above results should encourage further phase II and phase III trials.

Avilés *et al.*[23] conducted a clinical trial of amifostine and intermediate doses of cyclophosphamide. Forty patients with previously untreated high-risk diffuse large cell lymphoma were randomly assigned to four groups (10 patients in each group). Group 1 patients received amifostine 910 mg/m^2 prior to cyclophosphamide 1500 mg/m^2 for two cycles. Group 2 and group 3 patients received amifostine/cyclophosphamide only in one cycle and cyclophosphamide alone in the other cycle (their control). The patients of the last group received cyclophosphamide alone for two cycles. Patients treated with amifostine had fewer days of severe granulocytopenia (grade III or IV) and no infections were observed in amifostine plus cyclophosphamide groups, whereas four infective episodes occurred in the cyclophosphamide alone-treated group. The mean delay to treatment was 0.8 days in the amifostine plus cyclophosphamide group and 6.3 days in the cyclophosphamide alone group.[23] Glover *et al.*[43] provided data from a phase II trial on the effect of amifostine on cyclophosphamide-induced

myelotoxicity. Twenty-one patients with diverse malignancies were treated initially with 1,500 mg/m^2 of cyclophosphamide alone and 4 weeks later, after complete hematologic recovery, patients received 740 mg/m^2 of an intravenous infusion of amifostine over 15 minutes, followed 15 minutes later by the same dose of cyclophosphamide. The mean WBC nadir was 1,760/mm^3 and 2,500/mm^3 in the cyclophosphamide alone and the amifostine plus cyclophosphamide groups, respectively (p<0.0005). Like the mean WBC nadir, the mean granulocyte nadir was lower in the cyclophosphamide alone group compared with the group pre-treated with amifostine (541/mm^3 vs 1,247/mm^3, p=0.0005). Although thrombocytopenia was found only in patients treated with cyclophosphamide alone (9.5% vs 0%), this difference was not statistically significant.[43]

Amifostine was shown to decrease both the degree and duration of granulocytopenia during cyclophosphamide therapy.[46-49] These results led to the development of a phase III trial of amifostine used to protect against toxicity induced by the combination of cyclophosphamide and cisplatin (CP).[22] The study randomized 242 women with advanced ovarian cancer to receive six cycles of cyclophosphamide 1000 mg/m^2 and cisplatin 100 mg/m^2 every 3 weeks with or without amifostine 910 mg/m^2 given prior to chemotherapy. One hundred and twenty-two patients were randomized to receive amifostine plus CP and 120 patients were randomized to receive cisplatin alone.[22] The two groups were matched with respect to age, race, FIGO stage, extent of residual disease and performance status. Patients enrolled in the amifostine plus cisplatin-group significantly less frequently discontinued treatment because of hematologic toxicity (p=0.016). Pre-treatment with amifostine reduced the incidence of neutropenia associated with fever and/or infections requiring antibiotics (p=0.005), days in hospital (p=0.019) and days on antibiotics (p=0.031). Additionally, pre-treatment with amifostine resulted in an 88% reduction (p=0.169) in the number of platelet units transfused and a 29% reduction in the RBC units transfused (p=0.230).

Evidence of general cytoprotection

The above described trial showed not only the hematologic protection exerted by amifostine, but it also confirmed amifostine's protective effects against cisplatin-induced nephrotoxicity, neurotoxicity and ototoxicity (p=0.003, 0.029, 0.108, respectively). Moreover, pre-treatment with amifostine before the cisplatin regimen did not produce tumor cell protection.[22] Amifostine was further confirmed to decrease non-hematologic toxicities, such as nephrotoxicity, and neurotoxicity, during cisplatin therapy in other clinical studies.[46-49]

Many clinical trials have been performed to investigate the efficacy of amifostine as a cytoprotectant against various cytotoxic agents in patients with neoplasms of different origin and type.[22,24,43-59] In summary, amifostine has a broad spectrum cytoprotective properties as follows: 1) hematologic protection against cyclophosphamide, carboplatin, mitomycin C, fotemustine and radiotherapy; 2) renal and peripheral nerve protection against cisplatin; 3) mucosa, skin, and salivary gland protection from radiotherapy-induced damage; 4) absence of tumor cell protection. However, amifostine can not prevent hematologic toxicity induced by melphalan.[59]

Chemotherapy- or radiotherapy-induced secondary malignancies are important late complications of cancer therapy. Preclinical studies demonstrated that amifostine is anticarcinogenic, antimutagenic, anticlastogenic and antitransforming.[30,55-59] In addition to its cytoprotective capacity, amifostine possibly enhances the anti-tumor effect of carboplatin, nitrogen mustard, melphalan, and cisplatin combined with 5-FU or vinblastine, as demonstrated in preclinical studies.[11,30,34,60-63]

At MD Anderson Cancer Center a clinical trial of amifostine in the treatment of chronic lymphocytic leukemia (CLL) is ongoing. The primary objective of this trial is to assess the efficacy of amifostine in decreasing the incidence of Grade 3 and 4 infections, and of fever associated with neutropenia in patients with CLL who are treated with the fludarabine and cyclophosphamide (FC) combination. Recent MD Anderson studies in CLL based on the addition of cyclophosphamide to fludarabine have shown very positive results.[64] The rationale behind the combination is: (a) both agents are active in CLL, (b) they have non-cross-resistance toxicities, and (c) fludarabine inhibits repair of DNA damage induced by alkylating agents *in vitro*. Nevertheless, substantial myelosuppression hampers complete success of this therapy. Neutropenia to a level of < 1×10^9/L was seen in 70% of the MD Anderson CLL patients at some time during the first 3 courses of FC. The incidence of Grade III or IV fever or infections, including pneumonia, was 55%. Amifostine may potentially reduce myelosuppression and thus the infections and fever associated with FC-related neutropenia. The protocol scheme is to give six cycles of FC/amifostine as follows: fludarabine 30 mg/m^2 IV over 30 minutes daily for 3 days (days 1, 2, and 3) (total dose 90 mg/m^2). Immediately after, amifostine 500 mg (fixed dose) IV over 5 minutes daily for 3 days (days 1, 2, and 3). Finally, cyclophosphamide 300 mg/m^2 IV is given daily for 3 days.

Amifostine in MDS

Myelodysplastic syndromes (MDS) are an heterogeneous group of neoplastic hematologic diseases[65,66] whose therapy has not yet been established. Efforts to tailor therapy according to cytogenetic and biological characteristics of the diseases have been so far frustrated.[67,68] At present, only bone marrow transplantation has revealed curative efficacy in

younger MDS patients.[69] For this reason an alternative therapeutic approach with amifostine in MDS has been of conspicuous interest.

Recently, List *et al.* demonstrated that amifostine could stimulate hematopoiesis, both in preclinical and clinical studies.[9,70,71] Its protective and supportive effect on hemopoiesis has been supposed to be particularly beneficial in myelodysplastic syndromes because of its ability to improve the inefficient bone marrow activity characteristic of this group of diseases. Amifostine has thus been proposed as a possible therapeutic agent in MDS, in which most clinical complications are related to cytopenia. A milestone work was a phase I/II study[70] in which 18 MDS patients (5 RARS, 7 RA, 4 RAEB, 2 RAEB-T) received intravenous treatment with 100, 200 or 400 mg/m^2 amifostine three times a week, or 740 mg/m^2 (i.e. the recommended radioprotective dose) once a week for three consecutive weeks. Seventeen of the 18 patients received more than one course of therapy. Single or multi-lineage hematologic response occurred in 83% of the patients treated with doses 100-400 mg/m^2 three times a week. There was no hematologic improvement in the cohort of patients who received the higher dose of amifostine once weekly. Seventy-eight percent of the patients treated three times a week had a 50% or greater increase in neutrophil counts; 6/14 patients with thrombocytopenia had an increase in platelets of more than 50% from baseline; 5/15 transfusion-dependent patients had a decrease in transfusion needs. Side and dose limiting effects were nausea and vomiting, but no severe hypotension occurred. Cytogenetic analysis prior to and after treatment with amifostine, demonstrated that only 2/18 cases had an increase in metaphases which originated from the normal clone; in all other cases there was no disappearance of the karyotypically abnormal clone, indicating that amifostine was acting as a differentiative agent on the myelodysplastic clone, an effect for which the mechanism of action should be clarified. Amifostine's trophic influence may be exerted via antioxidant activity or through polyamine-like effects, given its structural similarity to biologically active polyamines.[72] The results obtained in this phase I/II trial were promising, and there have been some development in therapeutic regimens including amifostine for the treatment of low-risk MDS in particular.

A poor response to amifostine was observed in a limited cohort of patients (i.e.,12) treated in a multicenter trial.[73] In this study, amifostine was given in an uninterrupted 8-week schedule of thrice-weekly i.v. infusions, at a dose of 300-450 mg/m^2. Of the 12 patients, 3 had a 5q– cytogenetic anomaly and 4/12 had intermediate risk MDS (RAEB and CMML). These characteristics, together with the limited number of cases and their heterogeneity, may account for the reported failure of the treatment.

Quite different results emerged from a broader study performed in the Department of Hematology of Florence.[74] In this trial, 26 patients with low-risk MDS (13 RA, 2 RARS, 2CMML, 9 RAEB) were treated with amifostine 200 mg/m^2 x 3/week for 4 weeks, and 5 high-risk MDS patients received the same dose of amifostine, combined with low-dose Ara-C (ldAra-C) 10 mg/m^2 twice a day. Of the 26 patients with low-risk MDS, hemoglobin level and retyculocyte, neutrophil and platelet counts increased in 6 (23%), 11 (42%), 13 (50%), and 9 (34%) patients, respectively. Red cell transfusions were reduced < 50% in 4/26 patients and abolished in 1/26. In high risk MDS patients, complete remission was reached in 1/5 cases, with normalization of the cytogenetic aberration and elimination of transfusion need. A bilineage improvement was obtained in 2 more patients. Unexpectedly, there was a decrease in soluble transferrin receptor levels in all patients after 4 weeks of therapy. This detail may be interpreted as a sign of restoration of effective hemopoiesis. Moreover, EPO and TPO serum levels were not significantly modified. Overall, amifostine was well tolerated, with negligible side effects. The disease in 8/31 patients evolved into overt AML. Several extended trials of amifostine alone or in combination with other drugs are ongoing,[75] the most relevant being an American multi-institution trial (*List and Bennet, personal communication*). This is a phase II study enrolling mostly low-risk, adult MDS patients. Scheduled treatment consists in administration of amifostine i.v., 3 times a week, for 3 weeks at escalating doses of 200- 400 mg/m^2. Up to now, about 100 patients have been treated, and 40% have had single or multi-lineage improvement, while there has been a 35% decrease in bone marrow blasts in high-risk MDS. Tolerance seems generally good. Definitive results of this trial are awaited to shed light on the importance of this drug in myelodysplastic syndromes and the possible positive influence of the drug on the natural history of the disease. At present, the rate of hematologic improvement obtained with amifostine may be compared to that obtained with various hematopoietic growth factors in MDS therapy, i.e. incomplete stimulation of residual normal hemopoiesis, accompanied by partial increase in maturation and function of the dysplastic clone.

We can conclude that amifostine may be an intriguing therapeutic tool, provided that we succeed in defining the biological features characterizing the subset of MDS patients responsive to this cytoprotectant.

Side effects

The two major side effects of amifostine that cause treatment discontinuation are vomiting and transient hypotension.[3,5,6,21,51] Nausea and vomiting are adverse events that may occur during or following treatment with amifostine and that increase both in frequency and severity with increasing doses. The concomitant administration of emetigenic chemotherapy, radiation therapy, or a history of prior chemotherapy may increase the frequency, severity, and duration of nau-

sea and vomiting as well. The incidence of vomiting may be reduced by pre-treatment with dexamethasone and serotonin antagonists.[5,22,76]

Amifostine administration has been associated with hypotension, particularly in patients who are dehydrated or otherwise predisposed (eg antihypertensive therapy). In addition, it has been suggested that patients who are dehydrated, even minimally, may have more severe nausea and vomiting. Transient hypotension occurs in about 60% of treated patients, but severe hypotension is rare.[5,21] Hypotension usually occurs at the end of the infusion of amifostine and lasts less than 10 minutes.[5,21]

Minor side effects include flushing, sneezing, sleepiness, dizziness, hiccups, chills, metallic taste, allergic reaction, and hypocalcemia.[3,4,5,22,44,76-79] Hypocalcemia was noted during clinical trials of amifostine, but required treatment in only 1/7 patients. Recently, during clinical studies of multiple consecutive daily administrations of amifostine at doses of 740-910 mg/m^2, severe hypocalcemia requiring aggressive IV calcium replacement was observed in patients known to be predisposed. Patients should be monitored carefully for the development of hypocalcemia, particularly if they are predisposed and/or receiving multiple doses of amifostine in a 24-hour period.[76]

Guidelines for amifostine therapy

Results of preclinical and clinical studies laid the basis for FDA approval, in 1995, of the use of amifostine as a cytoprotectant in patients treated with cyclophosphamide and cisplatin for advanced ovarian cancer.[6] The recommended dose for adult is 910 mg/m^2 administered as a 15-minute intravenous infusion 30 minutes before the initiation of chemotherapy.[6,22,76,77] The drug must be given daily for fractionated chemotherapy or radiotherapy.[5] Repeated doses may be required when combined with chemotherapeutic agents with a long half-life such as carboplatin.[1,6] The dose should be reduced to 740 mg/m^2 if patients experience significant hypotension. The dose used for radioprotection ranges from 200 to 910 mg/m^2.[5,7,55,56] Other guidelines are given to reduce or treat hypotensive events as follows: 1, all hypertensive drugs should be withheld for 24 hours prior to amifostine infusion; 2, patients should be hydrated before the amifostine infusion; 3, patients should be in a supine position during the treatment period; 4, the patient's blood pressure must be monitored every 5 minutes during the amifostine infusion; 5, if there is a significant drop in blood pressure or hypotensive symptoms develop, the drug must be stopped and the patients should receive normal saline and be placed in the Trendelenburg position.

Future directions

Amifostine has acquired credit among oncologists in the last few years.[79] The widespread use of aggressive chemotherapy regimens in increasing numbers of patients with various neoplasms requires a protective scheme to avoid general toxicity.[79] Amifostine may be such a tool; its use in combination with chemotherapy should become part of routine management of hematologic neoplasms such as lymphomas. In this context, important multi-institution trials are on-going and will definitively demonstrate the real efficacy of amifostine as a supportive, cytoprotectant agent.

At the same time, amifostine activity on hemopoiesis seems to be of possible benefit to a subset of patients with low-risk MDS. Combining amifostine and chemotherapy in patients with high-risk MDS is an intriguing therapeutic option which should be investigated carefully. Amifostine has few toxic and side effects, all of which can be rather easily controlled. Amifostine can be quite safely administered to elderly patients, who form the great majority of patients with MDS and who often cannot be treated with aggressive regimens.

The individuation of the optimal scheduling of amifostine to maximize its cytoprotective efficacy and the characterization of the biological profile of MDS cases potentially responsive to this drug (and also its mechanism of action) are important and urgent goals to fulfil in order to exploit the clinical potentials of amifostine completely .

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The two authors contributed equally to the paper.

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