The Role of Chemoprotectants in Cancer Supportive Care

By Masha S. H. Lam, PharmD, and Robert J. Ignoffo, PharmD, FASHP

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INTRODUCTION

Cytotoxic chemotherapy has a well-known low therapeutic index. No other group of drugs possesses the frequency, variety, and severity of side effects as the anticancer agents do. Toxicities resulting from chemotherapy may not only compromise a patient's quality of life, but also delay drug administration, lower drug intensity, and could ultimately affect outcome. To minimize treatment-related toxicities and to optimize chemotherapy, clinical research has largely focused on development of newer neoplastic agents and immunotherapy with comparable efficacy and fewer side effects. In addition, cytoprotectants—drugs with the ability to protect against cytotoxic effects—are playing an increasingly important role in cancer supportive care. An ideal cytoprotectant would be highly selective for normal tissues in all organs and produce minimal or tolerable side effects. While we have yet to develop the ideal cytoprotectant, major advances have resulted from the four Food and Drug Administration (FDA)-approved cytoprotectants: dexrazoxane, amifostine, leucovorin, and mesna. In 1999, the American Society of Clinical Oncology (ASCO) published practice guidelines on the use of cytoprotectants to assist healthcare providers in providing optimal supportive care in a cost-effective manner.[1]

This article will review the current understanding of the pharmacology and clinical utility of these chemoprotectants in oncology. Table 1 provides a summary of the indications, mechanisms of action, usual dose, pharmacokinetics, major toxicities, dosage forms, and costs of the commercially available cytoprotectants.

DEXRAZOXANE

Indication

The current FDA indication for dexrazoxane is to reduce the incidence and severity of doxorubicin-associated cardiomyopathy in women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m^2 and who, in their physician's opinion, would benefit from continuing therapy with doxorubicin.[2]

Anthracycline-Induced Cardiotoxicity

Cardiotoxicity has been reported with the use of all anthracyclines (doxorubicin, epirubicin, daunorubicin, and idarubicin) and the anthraquinone mitoxantrone.[3-8] The etiology of myocardial damage caused by anthracyclines seems to be multifactorial and complex. Several hypotheses have been proposed to explain the causes of anthracycline-induced cardiac damage. They include generation of highly cytotoxic intracellular free radicals with iron as a cofactor to cause lipid peroxidation of mitochondrial membranes and endoplasmic reticulum in the heart tissues[9-11]; selective inhibition of cardiac muscle gene expression that results in myofibrillar loss[12]; changes in calcium homeostasis in myocardial tissues[13]; accumulation of a toxic metabolite of doxorubicin, doxorubicinol[14,15]; excessive endogenous histamine release that results in calcium influx at the histamine-receptors[16]; and myocardial concentration of glutathione peroxidase suppressed by doxorubicin.[17,18] Of all these proposed mechanisms, free radical-mediated myocardial injury has been the most widely studied and accepted explanation for the pathogenesis of cardiotoxicity by anthracyclines.

Clinical manifestations of cardiac toxicity can be categorized as acute and subacute/chronic or late-onset types.[19] Electrocardiographic changes, ischemia, pericarditis, arrhythmias including atrial flutter or fibrillation, and ventricular premature contractions have all been reported in acute cases.[3-8,20,21] However, major cardiac toxicity, ie, chronic cardiomyopathy, raises particular concern because it can lead to congestive heart failure and mortality.[21,22] The incidence of cardiac mortality associated with the use of anthracyclines has been reported to range from 0.36% to 3%.[21-24]

The most important risk factor associated with anthracycline-induced cardiomyopathy is cumulative lifetime dose of the drug. Von Hoff et al first reported that the risk of doxorubicin-induced cardiomyopathy was directly correlated to its accumulated dose.[22] They demonstrated that the incidence of congestive heart failure increased significantly from 3% at 400 mg/m^2 to 18% at 700 mg/m^2. More importantly, at cumulative doses of 550 mg/m^2, the probability of developing heart failure was 7% and continued to rise in a disproportionate manner. Peak plasma concentrations of

At the time of this writing, Dr. Lam was an oncology pharmacy specialty resident at the California School of Pharmacy in the Department of Clinical Pharmacy of the University of California at San Francisco. Dr. Ignoffo is clinical professor of pharmacy at the University of California School of Pharmacy, Department of Clinical Pharmacy, and a member of the NCI-designated Cancer Center, University of California Mt. Zion, in San

TABLE 1. SUMMARY OF CLINICAL PHARMACOLOGY OF CHEMOPROTECTANTS[2,71,147,177,192]

Cytoprotectants Indications	Mechanism of Action	Usual Dosage	Pharmacokinetics	Major Toxicities	Dosage forms/AWP*
Amifostine To reduce nephrotoxicity of cisplatin and alkylating agents, and radiation toxicity	An organic sulfhydryl compound that reduces the generation of free radicals produced by chemotherapy or radiation	740–910 mg/m^2 given in 15 minute infusion, starting 30 minutes before chemotherapy	Oral absorption: poor Vd=3.5 L $T_{1/2}\alpha$ =0.9 minutes; $T_{1/2}\beta$=8.8 minutes. Metabolism: dephosphorylated hepatically to WR-33278 and WR-1065 Elimination: renal. No dosage adjustment for renal/hepatic dysfunction	Transient hypotension, moderate to severe N/V; hypocalcemia	500 mg/vial for powder for injection (50 mg/mL when reconstituted) 500 mg/vial= $412.69
Dexrazoxane To reduce cardiomyopathy in patients who received >300 mg/m^2 of doxorubicin or other equivalent doses of anthracyclines	A heavy metal chelator that binds to iron intracellularly to inhibit oxygen free radicals generated by doxorubicin	Administered in a 10:1 ratio with doxorubicin or other anthracyclines	Oral bioavailability: poor Vd=0.8-2.1 L/kg; $T_{1/2}\alpha$=0.5-1.5 hours; $T_{1/2}\beta$=2.0-5.1 hours Elimination: renal (48%) No dosage adjustment fore renal/hepatic dysfunction	Myelosuppression; alopecia; Mild N/V	250, 500 mg/vial for powder for injection (10 mg/mL when reconstituted) 250 mg/vial= $178.06 500 mg/vial= $356.10
Mesna To prevent ifosfamide- or cyclophosphamide-induced hemorrhagic cystitis	As a sulfhydryl compound, and binds with acrolein, a urotoxic metabolite which is produced by CTX or ifosfamide to form a nontoxic substance	60% of ifosfamide dose given in three divided doses IV just before, and 4 and 8 hours after ifosfamide or CTX; can be given orally, double the IV dose (bioavailability only 50%). Oral mesna can be prepared by mixing the drug (oral dose should be twice IV dose) with a ratio of 1:2 or 1:5 of grape or orange juices or 1:1 to 1:10 in cola drinks	Oral bioavailability: 50–75%; Vd=0.65 L/kg 10% bound to plasma protein. Metabolism: oxidized in blood to dimesna, then partially reduced back to mesna in kidney $T_{1/2}$: mesna 22 minutes; dimesna 1.2 hours. Elimination: renally (33–53%) No dosage adjustment for renal/hepatic dysfunction	Altered taste, N/V, diarrhea, abdominal pain (occurs more often in doses >80 mg/kg)	100 mg/mL injection; packaged in 2, 4, and 10 mL vials 10 mL/vial= $212.88
Leucovorin To reduce incidence of myelosuppression and mucositis from high-dose methotrexate	As a reduced folate that can bypass the inhibition of dihydrofolate reductase induced by MTX, thereby rescuing normal tissues after cytotoxic effects on tumor cells have occurred	10–100 mg/m^2 q6h until MTX level <0.1μM Doses >25 mg should be given parenterally due to bioavailability	Oral bioavailability: 98% with doses of 25 mg and ↓ to 31% after single dose of 200 mg IM=100% with doses of 25 mg $T_{1/2}$: 0.5–4 hours I-isomer= 30–40 minutes; d-isomer=7–8 hours; 5-methyltetrahydrofolate=3 hours	Rare	3 mg/mL as 1 mL injection; 50, 100, 350 mg/vial for powder for injection; Tablet form: 5, 10, 15, 25 mg. †5 mg/tab=$2.03; 10 mg/tab=$5.76; 15 mg/tab=$8.15; 25 mg/tab=$19.0 50 mg/vial=$18.4; 100 mg/vial=$35.0; ‡200 mg/vial=$78.0; 350 mg/vial=$137.95

*AWP (average wholesale price) based on *Drug Topics Red Book* 2001.
†Based on Roxane brand.
‡Based on Bedford brand.
Vd=volume of distribution; $T_{1/2}$=half life; CTX=cyclophosphamide; MTX=methotrexate; IM=intramuscular.

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doxorubicin have also been suggested to be another causal factor for cardiomyopathy.[25] The incidence of doxorubicin-associated cardiotoxicity can be decreased with the use of weekly lower dose regimens or of prolonged continuous intravenous (IV) infusion instead of the traditional larger single boluses given every 3 weeks.[26-28] Other risk factors include mediastinal irradiation to the chest wall,[29,30] age (young children and elderly),[23,31] female gender,[32] preexisting heart disease,[23,33] type of anthracycline,[34,35] and concurrent use with other cardiotoxic agents (taxanes and trastuzumab).[36,37]

Clinical strategies, such as close monitoring of cardiac function in patients with one or more cardiac risk factors,[1] alteration of dosing schedule or administration, and use of other less cardiotoxic anticancer agents, eg, liposomal anthracyclines,[38,39] have been suggested to ameliorate toxicity. Studies have also recommended limiting the use of doxorubicin to a lifetime-accumulated dose of 360 to 450 mg/m^2 if other factors, such as combined chemotherapy or history of prior mediastinal radiation, are present.[1,40,41] In addition, such agents as probucol,[42] N-acetylcysteine,[18,43] alpha-tocopherol,[44] cromolyn sodium,[45] and dexrazoxane (DZR)[46-57] have been studied. Only DZR has been extensively investigated to prevent anthracycline-induced cardiomyopathy. Its pharmacology, evidence-based clinical trial results, and safety issues will be discussed next.

Pharmacology

DZR, previously known as ICRF-187 (chemical name (+)-1,2-bis (3,5-dioxopiperazinyl-1-yl) propane), was originally designed as an antineoplastic agent with cytostatic activity.[58] The active metabolite of DZR, ICRF-198 formed after hydrolysis, is a derivative of ethylenediaminetetraacetic acid (EDTA), which binds to intracellular iron from doxorubicin-iron complexes and thereby inhibits the conversion of superoxide anions and hydrogen peroxide to toxic superhydroxide free radicals.[59,60] The cardioprotective effects of DZR may be associated with its ability to upregulate transferrin receptor expression by activating binding affinity of iron regulatory protein, which results in increasing iron uptake into cells.[61,62]

Some clinical studies have shown that DZR may inhibit the catalytic activity of topoisomerase II by binding and stabilizing the protein/DNA complex, as opposed to other traditional topoisomerase II inhibitors, such as etoposide, which prevents resealing of DNA strand breaks via the enzyme.[63,64] These mechanisms may possibly explain the cytotoxic effects as well as the dose-limiting side effects of DZR-associated myelosuppression.

Pharmacokinetics

The pharmacokinetics of DZR are best fitted using a 2-compartment kinetic model with first-order elimination.[53,56,65] The distribution and elimination half-lives were reported as 0.17–0.4 hour and 1.86–2.5 hours, respectively.[2,53,65] DZR is primarily distributed in total body water with an estimated volume of distribution of 25 L/m^2.[2] Up to 42% of unchanged drug was eliminated in urine when 500 mg/m^2 of DZR was given to patients with normal renal and hepatic function.[2] Although no dosage adjustment is recommended by the manufacturer, dosing of DZR may need to be adjusted in patients with renal dysfunction to minimize the adverse effects of drug-induced myelosuppression. Phase I pharmacokinetic studies have shown that the pharmacokinetics of DZR was unchanged when it was used in combination with doxorubicin or epirubicin.[56] DZR used in patients with advanced breast cancer did not appear to alter the pharmacokinetics of paclitaxel and doxorubicin.[66]

Clinical Trials in Metastatic Breast Cancer

Preclinical studies have demonstrated the efficacy of DZR in the prevention of anthracycline-induced cardiotoxicity.[46-48] In humans, most data come from breast cancer studies where patients received doxorubicin-based chemotherapy. Speyer et al[50] studied 150 women with advanced breast cancer who were randomized to receive a doxorubicin-containing regimen at a dose of 50 mg/m^2 ± DZR 1000 mg/m^2. The DZR-treated group received more cycles (11 vs 9) and a greater cumulative doxorubicin dose (median 500 mg/m^2 vs 441 mg/m^2) than the group that did not receive DZR (P<.05). In this study, DZR seemed to offer the best cardiac protection when accumulated doxorubicin doses were between 275 and 399 mg/m^2 and 600 and 699 mg/m^2. The number of patients who were withdrawn due to median decrease in left ventricular ejection fraction (LVEF) determined by multigated radionuclide scan was significantly greater in the control arm (37 vs 5). DZR given at a dose of 1,000 mg/m^2 (20:1 dose ratio) did not statistically influence overall objective response rates, time to disease progression, or progression-free survival. However, the degree of leukopenia and thrombocytopenia was slightly greater in the DZR arm even though no statistically significant differences were observed in other adverse effects (death, fever, infection, alopecia, nausea, vomiting, mucositis) between arms. This may be attributable to an intrinsic myelosuppressive nature of DZR or the high doses given.

Two phase III, randomized, double-blind, placebo-controlled studies conducted in the US confirmed the cardioprotective effect of DZR and led to FDA approval.[51,52] Swain et al[51] randomized patients with advanced breast cancer to receive 500 mg/m^2 fluorouracil (F), 50 mg/m^2 doxorubicin (A), and 500 mg/m^2 cyclophosphamide (C) with either DZR at 1000 mg/m^2 (dose ratio of 20:1) or placebo every 3 weeks. Since myelosuppression and premature death occurred more frequently in the DZR arm during the first 9 months of the study, the FDA's Oncology Drug Advisory Committee recommended that the dose ratio of the study drug to doxorubicin be reduced to 10:1. The results showed that the hazards ratio of placebo to DZR for a cardiac event were 2.63 and 2.00 in both trials. However, the objective response rates in the DZR group were 14% lower than in the placebo group (P=.019) in one trial. No

statistical differences in terms of time to progression and survival were observed between groups. The investigators concluded that, while DZR was the first agent to demonstrate cardioprotection against doxorubicin, its potential effect on the response rate to chemotherapy was a concern.

This concern led Swain et al[52] to conduct an open-label study. All patients who were initially randomized to the FAC chemotherapy for 6 courses (a cumulative dose of doxorubicin) plus placebo were further randomized to placebo or DZR. With regard to all cardioprotection-associated endpoints (any cardiac event, ejection fraction changes, congestive heart failure), the hazards ratio of placebo to DZR was 3.5. Compared with the DZR group, the placebo-treated patients had 13 times the risk of developing congestive heart failure. The overall incidence of congestive heart failure was 3% in the DZR vs 22% in the placebo group ($P<.01$). Median survival of the DZR group (882 days) was almost twice that of the placebo group (460 days). This survival advantage led to FDA approval for the use of DZR in the prevention of cardiomyopathy in advanced breast cancer patients who received a cumulative doxorubicin dose of 300 mg/m^2.[2] This survival benefit has been attributed to the fact that DZR inhibits topoisomerase II, which may delay development of multidrug resistance by the cancer.[67]

Use With Other Anthracyclines/Taxanes

Although DZR is approved only in the prevention of doxorubicin-induced cardiomyopathy, its efficacy with other anthracycline analogs has been studied. In a multicenter, randomized, controlled study, Venturini et al[54] gave DZR (in a dose ratio of 10:1) to 162 patients with advanced breast cancer randomized to receive epirubicin-based chemotherapy with or without DZR. The patients who were previously exposed to anthracycline received combination chemotherapy (epirubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2, fluorouracil 600 mg/m^2) ± DZR. Patients who were anthracycline-naive received a single high dose of epirubicin (120 mg/m^2) ± DZR. The primary endpoint was cardiac toxicity, defined as clinical congestive heart failure, reduction of resting LVEF to 45%, or decrease from baseline resting LVEF of 20 ejection fraction (EF) units. The control arm's overall cardiotoxicity was 3 times that of the DZR arm (23.1% vs 7.3%). There were no significant differences in terms of noncardiac toxicities, objective response, progression-free and overall survival between the two arms.

Lopez and colleagues[55] investigated the efficacy of DZR (dose ratio of 6:1) against epirubicin cardiotoxicity in patients with advanced breast cancer and soft tissue sarcomas. As with the study by Venturini et al, Lopez et al showed cardioprotection of DZR in patients receiving epirubicin-based chemotherapy, but no survival benefit.

DZR's cardioprotective effect in patients with metastatic breast cancer receiving a combination of taxanes and anthracyclines has also been evaluated. In a nonrandomized phase I study, 25 patients with advanced breast cancer received 600 mg/m^2 of DZR, followed by doxorubicin 60 mg/m^2 and paclitaxel 150 or 175 mg/m^2.[66] This study sought to determine the maximum tolerable dose of paclitaxel given over a 3-hour IV infusion that could be combined with doxorubicin and DZR. Using endpoints similar to previous studies, the results showed that no patients developed clinical congestive heart failure or a decrease in LVEF below normal after receiving a median cumulative doxorubicin dose of 360 mg/m^2 with a maximum tolerated dose of paclitaxel of 150 mg/m^2. The authors concluded that, since patients treated with DZR in this trial had no cardiac toxicity, as compared with those who experienced a 20–50% decrease in LVEF below normal in other trials, DZR may reduce cardiac toxicity associated with this chemotherapy combination in the dose schedule studied.

Adjuvant Use in Breast Cancer

Use of DZR in an adjuvant setting in breast cancer remains controversial. In one clinical study, there was evidence of a reduced response rate in patients with metastatic disease, and the issue of diminishing effectiveness in adjuvant settings is of particular concern. Since there have been no published randomized, controlled trials to support the use of DZR in this setting, its use in other than a clinical trial should be avoided.

Other Uses

Data regarding the use of DZR in other settings are limited. The Pediatric Oncology Group/Children's Cancer Group Intergroup is currently conducting pilot studies to test the cardioprotective effects and safety of DZR in patients with newly diagnosed nonmetastatic osteosarcoma who receive doxorubicin in combination with cisplatin or cisplatin/ifosfamide.[68] A recent preclinical study has demonstrated efficacy of DZR in the treatment of anthracycline extravasation.[69]

Adverse effects

The most common adverse effects associated with the use of DZR in clinical studies include pain on injection, mild nausea and vomiting, alopecia, transient, reversible elevations of serum transaminases, and increased risk of myelosuppression.[2,49-56,65,70] The latter toxicity is primarily dose-limiting and was demonstrated with doses >4,000 mg/m^2 in Phase I clinical trials.[65,70] One Phase I pharmacokinetic study showed a decrease in the area under the concentration-time curve (AUC) of epirubicin AUC resulting from increased systemic clearance in patients who received DZR doses at 900 mg/m^2 (ratio range 6–7.5:1) and 1,200 mg/m^2 (ratio 9:1), but not at 600 mg/m^2 (ratio 5:1) or in the epirubicin-alone treatment group.[56] In the same study, gastrointestinal toxicity (severe vomiting and stomatitis) but not myelosuppression occurred less frequently in patients who received epirubicin and DZR. It is uncertain whether the decreased effect on epirubicin AUC was due to inactivation of the cytotoxic drug by DZR or some other factor. Lopez et al[55] noted a lower incidence of vomiting and stomatitis with the combination of high-dose epirubicin (160 mg/m^2) and DZR (1,000 mg/m^2) vs epirubicin alone.

Dosage Administration and Pharmacy Issues

Based on the results of clinical trials, the manufacturer recommends that DZR be given within 30 minutes of the start of anthracycline infusion at a dose ratio of 10:1 to doxorubicin or epirubicin.[2] Dexrazoxane is available as lyophilized powder for injection of 250 mg and 500 mg. The vials must be initially reconstituted with 0.167 mol/L sodium lactate injection to a DZR concentration of 10 mg/mL of sodium lactate and then further diluted with normal saline or 5% dextrose injection to a concentration of 1.3 to 5 mg/mL in IV infusion bags. The stability of reconstituted and diluted solution is 6 hours at room temperature or under refrigeration.[2] The calculated dose of DZR may be rounded to a vial size to minimize the drug costs and drug waste.

AMIFOSTINE

Indication

Amifostine is FDA-approved for prevention of cumulative nephrotoxicity associated with repeated administration of cisplatin in patients with advanced ovarian cancer or non-small–cell lung cancer. It is also indicated for reducing the incidence of radiation-induced xerostomia.[71] Only the protective effect of amifostine on chemotherapy-induced toxicities will be discussed here.

Cisplatin-Induced Nephrotoxicity

Platinum analogs have been extensively used in the treatment of various types of tumors for more than two decades. Platinum can cause a wide range of toxicities, and nephrotoxicity is especially problematic because of its substantial negative impact on quality of life. The exact cellular mechanism of cisplatin-induced renal damage is unknown; however, clinical evidence can occur in acute and chronic forms.[72-74] The proximal and distal renal tubules are the primary targets of cisplatin.[72,75,76] The glomerular filtration rate decreases by 20–40% in patients treated with high-dose cisplatin.[77,78] Renal damage associated with cisplatin is most often intrinsic, dose-limiting, and cumulative. Yet toxicity has also been reported with administration of a single dose.[74,79] In addition, renal damage can be reversible or irreversible.[79,80] Clinical evidence of cisplatin-induced nephrotoxicity is manifested by increased blood urea nitrogen (BUN) and serum creatinine, azotemia, renal electrolyte wasting (magnesium, potassium, calcium, and sodium), proteinuria, and oliguria.[77-83] Other nonintrinsic factors that may predispose a patient to an increased risk of cisplatin-induced nephrotoxicity include hypomagnesemia, inadequate hydration, hyperuricemia, hypoalbuminemia, and concomitant use of other potentially nephrotoxic agents (aminoglycosides, amphotericin B, IV radiographic contrast media).[73,83,84] It is uncertain if age is associated with an increased risk of cisplatin nephrotoxicity because there have been conflicting data from different studies.[85,86] Aggressive pre- and posthydration, use of mannitol or loop diuretics, use of hypertonic saline solution, and modification of cisplatin dosing schedule and administration have all been used to minimize cisplatin-induced renal damage.[87-91]

More than 20 drugs that specifically modulate the toxicity of platinum have been tested in animal models and clinical studies.[92] Among all these agents, amifostine, sodium thiosulfate, diethyldithiocarbamate, and dimesna have been extensively evaluated in preclinical and human studies for their potential to safely increase the therapeutic index of platinum drugs without worsening their toxicities or compromising their antitumor effects.[92-120] Currently, only amifostine, a first-generation platinum-protecting agent, is approved by the FDA to reduce the cumulative renal toxicity associated with repeated administration of cisplatin in patients with advanced ovarian cancer or non-small–cell lung cancer.[71]

Pharmacology

Amifostine, also known as WR-2721, with a chemical name of S-2-[3-aminopropylamino] ethyl-phosphorothioic acid, was originally selected from over 4,000 cytoprotectants by the Walter Reed Army Institute of Research due to its superior radioprotective and safety profile.[96] It is a prodrug enzymatically converted to a free thiol active substance, WR-1065, by alkaline phosphatase.[71] Compared with tumor cells, normal cells possess better vascularity, higher pH, and higher capillary alkaline phosphatase activity, which make amifostine capable of differentially protecting normal cells.[96] The active metabolite, WR-1065, acts as a scavenger of free radicals that are formed by cell damage from radiation and alkylating agents such as cisplatin, and that ultimately cause damage.

Pharmacokinetics

Amifostine's pharmacokinetics have been extensively studied both preclinically and clinically.[121-125] There is an oral formulation, but due to its high toxicity, other formulations and schedules have been explored.[126] Preliminary studies have demonstrated that amifostine 500 mg/m^2 administered subcutaneously, is at least comparable and may be even superior to a 200 mg/m^2 IV schedule.[122] Utley et al observed that after IV injection, amifostine is enzymatically converted to an active free thiol metabolite via alkaline phosphatase, followed by rapid tissue uptake.[123] Alkaline phosphastase is found on the plasma membrane surface of endothelial cells lining small blood vessels and on the surface of proximal renal tubular epithelium.[127] Less than 10% of parent drug is found in the plasma 6 minutes after administration.[71] Amifostine is distributed biphasically with a distribution half-life of <1 minute and an elimination half-life of 8 minutes.[125] Amifostine exhibits nonlinear kinetic behavior.[125] Shaw and colleagues reported that the AUC of amifostine for patients who received the drug at 910 mg/m^2 was 2.6-fold higher than in those who received the 740 mg/m^2 dose.[121,122] Further studies demonstrated that patients receiving the IV dose of amifostine at 910 mg/m^2 excreted a significantly higher amount of the active metabolites vs patients receiving a 740 mg/m^2 dose.[122]

With higher doses of amifostine, a greater amount of unmetabolized drug underwent glomerular filtration followed by tubular epithelial metabolism and excretion into urine.[122] This suggests that doses >740 mg/m^2 may not provide additional therapeutic benefits and would increase dose-related side effects.

Clinical Trials of Nephrotoxicity Prevention

The largest efficacy trial of amifostine was conducted by Kemp et al in a randomized, controlled study in patients with stage III and IV ovarian cancer.[101] More than 200 patients were randomized to receive six cycles of cyclophosphamide (C), 1000 mg/m^2, and cisplatin (P), 100 mg/m^2, with or without amifostine. Amifostine, 910 mg/m^2, was given as a 15-minute infusion prior to chemotherapy. The study endpoints included the incidence of hematologic, renal, neurologic, and ototoxicity and antitumor efficacy. This study has two important findings: 1) for patients who completed all six cycles of chemotherapy (cumulative cisplatin dose of 600 mg/m^2), the percent of patients in the CP arm who experienced >40% reduction in creatinine clearance was more than twice as that in the CP plus amifostine arm (30% vs 13%; P=.001); 2) amifostine did not adversely affect the chemotherapy's antitumor efficacy, and, in fact, this finding confirmed the results of preclinical studies.[98]

Another pivotal trial was conducted by Schiller et al.[102] In this Phase II nonrandomized trial, amifostine in doses of 910 mg/m^2 or 740 mg/m^2 was given to 25 chemotherapy-naive patients with metastatic non-small–cell lung cancer who were treated with 120 mg/m^2 of cisplatin on day 1 every 4 weeks and 5 mg/m^2 of vinblastine weekly. A 64% response rate was achieved with an estimated median survival of 17 months during the 19-month follow-up. Three of 25 patients (12%) developed grade 3 renal toxicity, but only 1 of 13 (7%) receiving more than four cycles had >40% reduction in creatinine clearance, consistent with the result of the Kemp et al trial.

Since the FDA approval of amifostine, new data have been published that appear to diminish its role in ovarian and non-small–cell lung cancers: 1) cisplatin, often considered the standard of care for the treatment of ovarian cancer and non-small–cell lung cancer, has been largely replaced by carboplatin because of its improved renal toxicity profile[128-130]; 2) the high doses (100–120 mg/m^2) of cisplatin that were used in those studies and subsequent clinical trials have demonstrated no survival benefit and a significant increase in toxicity with higher doses of cisplatin.[131-134] Currently, the most commonly used chemotherapy regimens in both disease settings are a lower-dose (50–75 mg/m^2) cisplatin-based regimen or a combination chemotherapy of carboplatin and taxanes.[128,129]

Several small clinical trials have also demonstrated the nephroprotective effect of amifostine in patients with other types of cancers receiving cisplatin-containing regimens.[98,100,103,105,106] Hartmann et al evaluated the efficacy of amifostine during 3-day, high-dose chemotherapy with carboplatin, ifosfamide, and etoposide (HD-VIC) and autologous bone marrow transplant in 40 patients randomized to receive HD-VIC with or without amifostine at a dose of 910 mg/m^2 given as a 15-minute infusion prior to carboplatin/ifosfamide daily for 3 days.[103] Amifostine decreased the drop in glomerular filtration rate by 27% from baseline vs the control group (P<.01).

In summary, amifostine at a dose of 740 mg/m^2 to 910 mg/m^2 seems to be effective for the prevention of cumulative renal toxicity induced by cisplatin in different oncology disease settings. Further studies evaluating the dose intensity of cisplatin-based regimens in cancers that are most platinum-sensitive (eg, germ cell tumors) seem warranted.

Neuroprotection

Chemotherapy-associated neurotoxicity occurs most commonly with the use of platinum analogs, taxanes, and vinca alkaloids.[136-140] The incidence has been reported to be as high as 76%.[138] Similar to cisplatin-induced nephrotoxicity, neural damage appears to be dose-related and cumulative.[137,138] Although several clinical trials have shown amifostine's potential neuroprotective role in patients receiving a cisplatin-based regimen,[101,102,105,107] it was not seen in patients receiving other neurotoxic chemotherapy, especially paclitaxel-containing regimens.[108,109]

In a well-designed, randomized, double-blind study by Leong et al,[108] 60 patients with unresectable stage III non-small–cell lung cancer received two cycles of paclitaxel at 175 mg/m^2 and carboplatin at an AUC dose of 6 mg/ml•min, followed by radiotherapy with a concurrent weekly dose of paclitaxel, 60 mg/m^2. All patients were randomized to either 740 mg/m^2 of amifostine or placebo given before each dose of paclitaxel and carboplatin. Neurotoxicity was objectively assessed by performing nerve conduction tests during each pre- and posttreatment. Amifostine decreased the severity of esophagitis, but it did not decrease significantly the incidence of neurologic toxicities. In a Phase II randomized trial, Gelmon et al[109] produced similar findings. They randomized 40 women with metastatic breast cancer to receive high-dose paclitaxel with or without amifostine 910 mg/m^2. There was no difference in the incidence of neurotoxicity between the amifostine and control arms. Different dosing schedules and intensities of chemotherapy as well as different neuropathologic mechanisms induced by the different anticancer agents may largely explain these conflicting data.

In summary, based on good neurologic assessment methods, amifostine does not appear to play a preventive role in paclitaxel-induced neuropathy. For cisplatin, until sufficient well-designed randomized clinical trials clearly define the neuroprotective role of amifostine against platinum analogs, its use should not be recommended outside the clinical trial setting.

Myeloprotection

Bone marrow suppression is one of the major dose-limiting toxicities for most chemotherapy agents. Among all classes of anticancer drugs, alkylating agents have the highest incidence of myelosuppression. Clinical strategies such as dose reduction or use of colony-stimulating factors are commonly used to decrease the risk of neutropenia.

Since preclinical evidence demonstrated amifostine's ability to selectively protect normal cells against the cytotoxicity of radiation and different alkylating agents, amifostine's myeloprotective effects have been studied in patients receiving cyclophosphamide and platinum-based regimens.[101,104-106,111-113] So far, only one randomized controlled trial[101] has shown a significant decrease in cumulative grade 4 neutropenia-associated events, including fever, infection, antibiotic use, and length of hospitalization, in patients receiving cisplatin, cyclophosphamide, and amifostine. Glover et al demonstrated the effectiveness of amifostine against cyclophosphamide-induced hematologic toxicity in their Phase II controlled trial.[104] Johnson and colleagues evaluated the cytoprotective efficacy of amifostine dosed at 740 mg/m^2 in a total of 84 patients with small-cell lung cancer receiving IV ifosfamide 3 g/m^2, carboplatin (AUC 6), and etoposide 50 mg orally twice daily for 7 days given in a once every 3-week cycle.[135] No significant between-group difference was observed in grade 3 or 4 neutropenia or thrombocytopenia. Leong et al also failed to show a myeloprotective benefit of amifostine.[108] Further, Malmstrom et al showed that amifostine did not influence the rate of topotecan-induced hematologic toxicities in advanced ovarian cancer patients.[110]

The myeloprotective effect of amifostine appears to be drug-specific. The current data only show a benefit for patients receiving cyclophosphamide-containing therapy.

Adverse Effects

Nausea, vomiting, and infusion-related hypotension are the most common side effects of amifostine reported in clinical trials.[71,101] Other side effects include flushing, malaise, hypocalcemia, hypomagnesemia, dizziness, metallic taste, hiccups, and sneezing.[71] Rare toxicities, such as Steven-Johnson syndrome, and a systemic inflammatory response syndrome have also been reported.[145,146] In doses 740 mg/m^2, the incidence of hypotension is 62%, with only 3% of patients requiring discontinuation of therapy.[101] Hypotension is thought to be secondary to the direct action of relaxing smooth muscle exerted by the active metabolite, WR-1065.[98] There is clinical evidence that the incidence of hypotension is related to the dose, duration of the infusion, and a patient's hydration status.[101,102,106,124] Doses >740 mg/m^2 given over 15 minutes produce a higher incidence of severe hypotension than lower doses.[102] In general, a longer administration time results in a greater risk of hypotension. Shorter infusion times (<5 minutes) are much better tolerated and the severity of hypotension is significantly decreased.[141] Nausea and vomiting associated with amifostine can be moderate to severe. In one randomized study, the incidence of severe nausea and vomiting on day 1 of cyclophosphamide-cisplatin chemotherapy was 19% in patients who received amifostine vs 10% in patients who did not receive the drug.[101] Nausea and vomiting are generally preventable with serotonin antagonists and corticosteroids given at least 30 minutes prior to administration.

Pharmacoeconomic Issues

Cancer is a chronic disease and is well known to cause a large healthcare burden due to high costs of antineoplastic agents and continuous supportive care. Some healthcare organizations have published clinical practice guidelines as strategies to improve quality of care and reduce medical costs in oncology. The pharmacoeconomics of amifostine use in advanced ovarian cancer patients receiving cisplatin and cyclophosphamide has been evaluated.[142,143] Both studies demonstrated amifostine's potential value in cost savings and quality of life.

Domagk and colleagues also performed a pharmacoeconomic study in which 125 male patients with head and neck cancer were randomized to receive radiotherapy (cumulative dose of 54 Gy with 1.5 Gy/daily 5 times weekly) or combination chemotherapy of cisplatin (80 mg/m^2 on day 1) and fluorouracil (12 mg/kg on day 2–6) given every 4 weeks for 3 cycles ± amifostine at 740 mg/m^2.[144] For patients in the amifostine arm, the cost saving was approximately twice that in the control arm. Cost savings were mainly due to reduction of toxicities and complications associated with radiochemotherapy. Based on these positive results, pharmacoeconomic benefits of amifostine in other cisplatin-based regimens seems likely.

Dosing Administration and Pharmacy Issues

The current FDA dosing recommendation for amifostine is 910 mg/m^2 given as a 15-minute infusion starting 30 minutes before chemotherapy.[71] However, controlled studies have shown that amifostine given at a dose of 740 mg/m^2 has produced equivalent cytoprotection with a lower incidence of severe gastrointestinal and vascular side effects.[102,106]

Amifostine is available as lyophilized powder of injection of 500 mg. It is reconstituted with 9.5 mL of sterile 0.9% normal saline to a final concentration of 50 mg/mL.[71] After direct reconstitution or further dilution at concentrations ranging from 5 mg/mL to 40 mg/mL, the drug solution is chemically stable for up to 5 hours at room temperature and up to 24 hours at 2° C to 8° C.[71]

Patient Monitoring

To avoid or minimize hypotensive episodes, a baseline measurement of the patient's supine and standing blood pressures and hydration status should be obtained before every treatment course. Those with a history of hypertension should be advised to stop taking any antihypertensive medications 24 hours before amifostine treatment. Patients should be adequately hydrated with 1 L of fluid orally or IV before and during amifostine administration. In addition,

the patient should be supine at all times during infusion. Blood pressure should be closely monitored for infusion times >5 minutes and the infusion stopped if a 20% drop in systolic blood pressure occurs. If the patient's blood pressure returns to normal within 5 minutes, the infusion may be restarted and completed if tolerated. If blood pressure does not normalize in 10 minutes, dose reduction in the subsequent cycles should be considered in patients who experience severe side effects of amifostine during the first cycle. An alternate is to give a shorter infusion of 5 minutes.[141] Table 2 lists the manufacturer's guidelines for interrupting amifostine infusion due to decrease in systolic blood pressure.[71] Antiemetics, including serotonin receptor antagonists and corticosteroids, can significantly reduce the incidence of severe nausea and vomiting.

LEUCOVORIN

Indication

Leucovorin calcium is FDA-approved for reduction of bone marrow and gastrointestinal toxicity after high-dose methotrexate therapy in osteosarcoma; treatment of megaloblastic anemias due to folic acid deficiency when oral therapy is not feasible; and in combination with 5-fluorouracil in the treatment of colorectal cancer.[147] The use of leucovorin rescue for high-dose methotrexate will be the only topic discussed here.

In 1966, Goldin and colleagues developed the concept of leucovorin rescue.[148] They showed that delayed administration of leucovorin (folinic acid) could prevent severe toxicity after methotrexate therapy without inhibiting therapeutic effect. This work, along with several subsequent studies on tumor resistance to conventional doses of methotrexate, has provided the pharmacologic rationale for high-dose methotrexate (HDMTX) followed by leucovorin rescue.[149] HDMTX with leucovorin rescue was first used in 1967 for children with childhood leukemia.[150] Over the last 20 years, HDMTX plus leucovorin rescue has been established for a few tumors, especially osteogenic sarcoma and childhood acute lymphoblastic leukemia (ALL). However, HDMTX has not been shown to improve the outcome in other common tumors (eg, breast, lung, and colon) vs lower doses.

Pharmacology of Leucovorin Rescue

Leucovorin exists in a racemic form as both D- and L-isomers, but the latter is the active form. After oral or IV administration, leucovorin is converted to 5-methyl tetrahydrofolate (5-MTH4). Membrane transport of 5-MTH4 is critical for adequate rescue of normal cells, as it must compete with methotrexate for entry into the cell. Within the cell, 5-MTH4 has two major effects: 1) it competes with MTX for binding to the enzyme dihydrofolate reductase (DHFR); and 2) it displaces MTX from DHFR.[151,152] Thus, leucovorin rescue bypasses the MTX block and replenishes the intracellular folate pool thereby allowing resumption of DNA synthesis.[153,154] However, the ability of leucovorin to rescue normal cells is dependent on the duration of methotrexate exposure, the dose and duration of rescue treatment, and the interval between MTX and leucovorin rescue administration.[155] Methotrexate concentrations >5 x 10^{-8} mol/L (0.05 μM) are considered cytotoxic to normal cells. Concentrations above this for 48 hours or longer may produce irreversible cell damage. Thus, leucovorin rescue should begin within 48 hours of the start of HDMTX, but is usually started 24 hours afterward to ensure adequate rescue of normal cells.

The definition of HDMTX varies substantially depending on the reference source. Ackland and Schilsky suggest that a dose >1 g/m^2 be considered HDMTX.[149] In addition to the dose and schedule of methotrexate, the infusion duration, which ranges from 4 to 42 hours, will also affect plasma MTX levels. For any high-dose regimen of methotrexate, standard care is to obtain a patient's plasma MTX levels at 24 and 48 hours after the start of infusion and then to dose leucovorin according to a guideline (Table 2). For 24- or 48-hour levels >1mmoL, proportionately higher doses of leucovorin are required to achieve adequate rescue.[156] Leucovorin should be initiated shortly after MTX infusions lasting 36 to 42 hours are completed to ensure adequate rescue. This will also necessitate monitoring 60- or 72-hour MTX levels.

Pharmacokinetics

Nixon and Bertino have shown that about 90% of calcium leucovorin is absorbed after oral administration.[156,157] After IV administration, about 60% of the drug appears in

TABLE 2. GUIDELINE FOR INTERRUPTING AMIFOSTINE INFUSION DUE TO DECREASE IN SYSTOLIC BLOOD PRESSURE

Baseline SBP (mm Hg)	<100	100–119	120–139	140–179	180
Decrease in SBP during infusion (mm Hg)	20	25	30	40	50

Note: If the patient's blood pressure normalizes within 5 minutes and the patient is asymptomatic, the remainder of the amifostine infusion may be administered at the previous rate. **Do not prolong the duration of amifostine infusion**. If the patient is unable to receive the complete amifostine infusion, the dosage of amifostine may be decreased from 910 mg/m^2 to 740 mg/m^2 for subsequent infusions.[71]

SBP=systolic blood pressure.

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the plasma as the active metabolite, 5-MTH4, compared with 100% after oral or intramuscular administration. Leucovorin is commercially available as a racemic mixture of L- and D- folinic acid. The L-isomer is considered the active form.[158] The L-isomer has much shorter half-life than the D-isomer because the former is rapidly converted to 5-MTH4.[159] In addition, a higher optimum ratio of the 5-methyl metabolite to parent compound is observed after oral vs IV administration.[159] Thus, oral administration might be the preferred route for methotrexate rescue.[159] For leucovorin doses 25 mg given orally, absorption was 100% compared with IV administration. However, in doses 50 mg, the oral absorption of leucovorin was dose limited and did not result in any higher levels of the active metabolite. Thus, leucovorin doses >50 mg should be given IV, especially when needed to rescue very high MTX levels. After IV administration, the plasma half-life of the parent compound was 30 minutes while that of the 5-methyl metabolite was about 4 hours.[159] Thus, to achieve therapeutic concentration throughout the day, leucovorin should be given every 4–6 hours. After IV administration, free 5-methyl THF and L-isomer are excreted in the urine similar to creatinine clearance.[159] Therefore, renal insufficiency will result in higher levels of both the L-isomer and the active metabolite.

Leucovorin in Malignant Disorders

The two major oncologic indications for the use of leucovorin are 1) combined therapy with fluorouracil in advanced colorectal cancer, and 2) prevention and treatment of toxicity associated with folate antagonists, particularly methotrexate. Several regimens of HDMTX with leucovorin rescue are shown in Table 3. Leucovorin has been given in conjunction with HDMTX for the treatment of metastatic or high-risk osteosarcoma, CNS lymphoma, and acute leukemia of adults or children. Leucovorin rescue allows for an increase in the therapeutic index of methotrexate. Extremely high peak MTX levels (>700 (mol/L) have been shown to improve the prognosis of patients with high-risk osteosarcoma, especially those with localized disease.[160] In addition, complete responses were observed in almost 30% of patients who achieved extremely high peak MTX levels. Other examples of therapeutic peak levels have been demonstrated in acute childhood lymphoblastic leukemia. Evans and colleagues showed that a HDMTX regimen producing a peak steady state concentration of 16 µM resulted in a lower probability of relapse.[161] This study formed the basis for an MTX-containing regimen currently used in the treatment of adult acute lymphoblastic leukemia at our institution.[162] Further studies are needed to determine if achieving a threshold MTX level improves outcomes in this setting.

In other tumors, such as metastatic head and neck cancer, breast cancer, and cervix cancer, HDMTX has not been shown to improve outcomes vs conventional doses of methotrexate.[163,164] Furthermore, in reversing the cytotoxic effect of MTX, leucovorin may also reverse the antitumor effect of conventional doses of MTX.[165]

Rescue of Extremely High Concentrations of Methotrexate

The most common risk factor associated with extremely high MTX levels is methotrexate-induced renal failure. This is often managed by increasing the dose and duration of leucovorin rescue. Pinedo and colleagues have shown that exposure of mouse bone marrow cells to extremely high concentrations of methotrexate (>100 µM) cannot be adequately rescued even with high doses (>1 g/m^2) of leucovorin.[166] However, Flombaum et al reviewed their clinical protocol at Memorial Sloan-Kettering Cancer Center for treating extremely high methotrexate concentrations.[167] They showed that, in 13 patients, early initiation of high-dose leucovorin rescue in IV doses ranging from 240 mg to 8 g daily could result in adequate methotrexate rescue without use of other measures. Median MTX levels were 164 µM at 24 hours (range, 102–940 µM, 16.3 µM at 48 hours (range, 10.5–190 µM, and 6 µM at 72 hours (range, 1.35–39 µM, which fell to nontoxic levels at a mean time duration of 11 days.[167] For patients developing acute renal failure at high MTX levels (>100 µM, some clinicians recommend hemodialysis with or without hemoperfusion to lower the level such that an effective leucovorin rescue dose can be given.[168-171] Other therapies include carboxypeptidase or thymidine.[172,173]

TABLE 3. LEUCOVORIN DOSING RELATIVE TO 24- AND 48-HOUR METHOTREXATE CONCENTRATIONS

Plasma Level of MTX at 24 or 48 hours (µmol)	LV dose starting at Hour 24	Duration/Comment
0.1 to 1	10 mg/m^2 PO q3 to 6 hours	Usually 48 hours or until MTX level <0.1µM
1–10	10 mg/m^2 PO q6 hours	Usually 48 hours or until MTX level <0.1µM
>10–200	100 mg/m^2 IV q4 to 6 hours; continue urinary alkalinization	Repeat serum MTX concentration and continue LR until MTX level <0.1 µM
>200	100 mg/m^2 IV 4 hours; continue urinary alkalinization	Hemodialysis and hemoperfusion until MTX level <100 µM

MTX=methotrexate; LV=leucovorin.

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Other factors that may play a role in the delayed clearance of methotrexate include pleural and peritoneal effusions and use of concurrent interacting drugs, such as aspirin, nonsteroidal anti-inflammatory agents, penicillins, doxycycline, and probenecid.[174]

Special Circumstances: Intrathecal Methotrexate

Leucovorin is generally not used for most patients receiving intrathecal methotrexate except for those with decreased renal function. Prolonged cytotoxic methotrexate concentrations can be achieved in childhood leukemia patients with acute renal insufficiency.[175] The terminal half-life of methotrexate in these patients ranged from 19 to 44 hours.[175] Patients with renal dysfunction should have 24-hour plasma MTX levels monitored and leucovorin given to prevent systemic side-effects.

Malignant Effusions

Pleural and peritoneal effusions act as a depot for methotrexate and will delay the drug's body clearance.[176] Such patients may have prolonged cytotoxic concentrations of methotrexate and may require leucovorin to prevent serious side effects. The management of patients with effusions is to remove as much fluid as possible prior to administration of methotrexate. In the event of an effusion, leucovorin should be instituted 24 hours after administration of methotrexate.

Adverse Effects

Calcium leucovorin is remarkably devoid of side effects with either oral or parenteral administration. After IV injections, acute allergic reactions have been reported rarely.

Dosage Administration and Pharmacy Issues

As described above, the usual rescue dosage of leucovorin is 10–15 mg orally or IV given every 6 hours until serum concentrations of methotrexate fall to nontoxic levels. In the setting of accidental overdose or an acute increase in serum creatinine concentration, the dose of leucovorin should be increased to 100 mg/m^2 (about 150 mg) and given parenterally because of dose-limited bioavailability. Calcium leucovorin is available in a variety of dosage forms including injection: 10 mg/mL; powder for injection: 50 mg, 100 mg, 200 mg, 350 mg; and tablet: 5 mg, 10 mg, 15 mg, 25 mg.

MESNA

Indications

Mesna is FDA indicated for prevention of hemorrhagic cystitis induced by ifosfamide. It is also used to prevent toxicity from high doses of cyclophosphamide as is used in several high-dose programs for both hematologic and solid tumors. Mesna, when administered concurrently with any dosage of ifosfamide, significantly reduces urinary symptoms of dysuria and the incidence of hematuria.[177]

Pharmacology and Pharmacokinetics

An acronym for methane ethylsulfonate sodium, mesna is a thiol that binds chemically and directly to the urotoxic metabolites of ifosfamide and cyclophosphamide, acrolein, and the hydroxyl metabolites of ifosfamide and cyclophosphamide. After IV administration, mesna is rapidly converted to an inactive dimer, dimesna. Upon reaching the renal parenchyma, dimesna is converted by glutathione

TABLE 4. HIGH-DOSE METHOTREXATE AND LEUCOVORIN RESCUE REGIMENS IN SYSTEMIC MALIGNANT DISORDERS

Investigator	MTX dose	Duration of Infusion	LV Rescue Dose	Start time of Leucovorin after MTX (hours)
Rosen[185]	8–12 g/m^2	4 hours	10 mg orally every 4 hours depending on MTX level	24
Frei[186]	3–7.5 g/m^2	20 min	10 mg/m^2 IV x 1, then PO every 6 hours x 12	24
Evans[187]	1 g/m^2	24 hours	15 mg/m^2 IV 6 hours x 2, then 3 mg/m^2 q 12 hours x 3	36
Stoller[188]	50–200 mg/kg	6 hours	15 mg/m^2 IV q6 hours x 8	8
Balis[189]	33.6 g/m^2	24 hours	200 mg/m^2 x 1, 12 mg/m^2 q3 hours x 6, then 12 mg/m^2 q 6 hours until MTX <0.1 µmol	12
Taylor[190]	1,500 mg/m^2	24 hours	25 mg PO x 2, then 10 mg PO q 6 hr x 8	6
Tetef[191]	700 mg/m^2 load followed by 2,800 mg/m^2 continuous IV	24 hours	400 mg/m^2 x 1, then 200 mg/m^2 for doses 2–5, then 100 mg/m^2 until MTX level <0.1 µmol	6

MTX=methotrexate; LV=leucovorin.

Modified from Ackland and Schilsky.[149]

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back to the active form of mesna, which then binds to the urotoxic metabolites (acrolein) present in the bladder or ureter. The mesna-acrolein complex is soluble and rapidly excreted in the urine.

Mesna was originally developed as an injectable solution for IV use. The half-life of the parent compound is 17 minutes. Recently, a tablet form was developed and is used in countries outside the US. After oral administration, the bioavailability ranges from 50% to 90%. The mean residence time of mesna is longer after oral than IV administration, which suggests that oral therapy may provide adequate protection for longer periods.[178,179]

Use in Prevention of Ifosfamide Uropathy

Prior to the development and use of mesna, severe urologic toxicity occurred in a high percentage of patients treated with ifosfamide, and the drug had to be withdrawn from clinical trials. Today, ifosfamide plus mesna is a mainstay in the treatment of soft tissue sarcoma and refractory germ cell tumors. The combination is also effective in osteosarcoma, lymphoma, and ovarian cancer. The recommended total daily IV dose of mesna is 60% of the ifosfamide dose. It is given in three equal doses before drug administration, and 4 and 8 hours after drug administration. In the ambulatory setting, the 4- and 8-hour doses are often given orally at 40% of the ifosfamide dose.[181] In a follow-up study, Goren and colleagues showed that the combination of IV and oral mesna is at least as effective as IV mesna as a urologic prophylaxis for ifosfamide.[182]

Use With High-Dose Cyclophosphamide

High doses of cyclophosphamide used in preparative regimens for allogeneic bone marrow transplantation are associated with a high risk of urinary and bladder toxicity. The usual prophylactic therapy is hyperhydration. Since the same urotoxic metabolite (acrolein) is produced in large amounts and can appear in the bladder and ureter after high-dose cyclophosphamide, mesna has also been tried in conjunction with forced hydration and shown to be effective.[183] Shephard and colleagues compared mesna to hyperhydration and showed that mesna was equally effective but much better tolerated.[184] Concerns that mesna might abrogate the effect of cyclophosphamide and increase the risk of graft rejection have been allayed with the results of recent clinical trials showing no effect.[184] Mesna prophylaxis is now considered the preferred method of urinary protection for high-dose cyclophosphamide therapy.

Adverse Effects

Side effects include metallic taste and nausea and vomiting after rapid IV administration.

Dosage Administration and Pharmacy Issues

Mesna is usually given in doses as described above for ifosfamide or cyclophosphamide. The drug is available in 200-mg ampules or 1-g vials. It may be given as a bolus over 15 minutes or mixed with ifosfamide or cyclophosphamide in the same solution and given as a continuous infusion. Mesna is incompatible with cisplatin and carboplatin and should be not admixed with these agents.

CONCLUSIONS

Cytoprotective drugs are a new class of agents that will allow patients to receive chemotherapy at close to the intended dose intensity and density to achieve optimal outcome. Pharmacoeconomic studies have shown that certain cytoprotectants may not only save overall healthcare costs, but may also have a positive impact on patients' quality of life. Nevertheless, in terms of efficacy of the currently available chemoprotective agents, randomized clinical trials have demonstrated only a relatively narrow spectrum of toxicity protection. By definition, the ideal cytoprotective agent should "prevent all toxicities, from non-life-threatening side effects (alopecia) to irreversible morbidities (hearing loss, neurotoxicity) to potentially fatal events (severe cardiomyopathy, severe thrombocytopenia), without adversely affecting the antitumor efficacy of the cancer therapy, and would be easy to administer and relatively nontoxic in its own right."[1] Thus, the currently FDA-approved cytoprotectants are still far from ideal with regard to efficacy and safety profiles. More well-designed controlled clinical trials are urgently needed to demonstrate the value of newer cytoprotectants in oncology supportive care. OS

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