The administration of intensive chemotherapy according to a rigid schedule improves response rates and duration of response. However, dose-limiting toxicities and resulting delays in therapy often interfere with therapy.

**Introduction**

New regimens of cancer chemotherapy combine drugs that have the potential to produce additive or synergistic antitumor effects without treatment-limiting overlapping toxicities. These regimens have been designed to maximize antitumor effects while maintaining an acceptable safety profile. Although this approach has achieved long-term disease-free survival in many children with malignant tumors and in adults with leukemia, lymphoma, and germ-cell neoplasms, success has been limited in the epithelial tumors more commonly seen in adult patients.

Extended analysis of clinical trials of chemotherapy with and without radiation therapy in patients with a variety of relatively responsive neoplasms, including lymphoma, germ-cell tumors, and ovarian and breast cancer, has revealed that administration of a high percentage of the planned treatment dose according to the planned schedule produces an improved response rate and duration of response.[1-3] As a result, there is great interest in developing supportive therapy that will permit a higher percentage of patients to receive their planned therapy or even to permit the administration of a higher cumulative dose or greater dose intensity so as to achieve improved response rates and survival duration.

The development and potential application of agents that can reduce toxicity to normal tissues but not to malignant cells are the subject of intense investigation. Two different approaches are actively undergoing evaluation: (1) administration of cytoprotective agents before chemotherapy or irradiation, and (2) administration of rescue agents, such as bone marrow colony-stimulating factors (CSFs), after therapy. This review will explore the differences between these two approaches (ie, protection vs rescue), their advantages and limitations, and the possibility of their complementary use.

**Cytotoxicity**

Chemotherapy may produce toxicity in a broad range of normal tissues and organs. The bone marrow, gastrointestinal (GI) epithelium (including the oral mucosa), kidney and urinary bladder, peripheral nerves, central nervous system, and heart and lungs have proved to be of primary concern with regard to dose-limiting toxicity. Acute drug effects on the bone marrow and gut typically determine the timing of repeated courses or cycles of treatment.

Cumulative injury to the bone marrow from alkylating agents, such as nitrosoureas and mitomycin (Mutamycin), or parenchymal toxicities, such as nephrotoxicity, peripheral neuropathy, and ototoxicity (cisplatin [Platinol]), cardiotoxicity (anthracyclines), lung and vascular endothelial cell toxicity (bleomycin [Blenoxane]), and lung and kidney toxicity (mitomycin) affect the ability to deliver the full, scheduled course of therapy without producing persistent or irreversible toxicity. In combined-modality regimens, cardio-pulmonary and mucosal toxicities are further exacerbated when the affected organs are within the radiation field.

In oncologic practice, cumulative toxicities are minimized by setting an upper limit for the total cumulative dose and by controlling individual doses, dosing frequency, and concomitant therapies. It is in this context that a broadly applicable cytoprotectant would be of great value if it could selectively protect normal organs but not the neoplastic cells.

**Cytotoxic Mechanisms of Anticancer Treatments**

Anticancer agents exert their therapeutic benefits by inducing cytotoxic effects or initiating apoptosis (programmed cell death) in neoplastic cells (Table 1). Cytotoxicity results from the action of chemotherapeutic agents that undergo chemically or...
enzymatically induced transformation to highly reactive species. These species, in turn, react with DNA (alkylating agents, organoplatinum compounds) or generate superoxide or hydroxyl free radicals, which are damaging to DNA, cellular lipids, and cell membranes (anthracyclines, bleomycin).[4,5] In addition, some agents interfere with the biochemical processes that regulate normal cellular activity. Vinca alkaloids and taxanes prevent microtubule formation and dissolution, respectively, disrupting cytoskeletal integrity. Antimetabolites, such as methotrexate, trimetrexate (Neutrexin), fluorouracil, and cytarabine, interfere with the synthesis of DNA.

Dysregulation of apoptosis is now regarded as an important factor in the development of carcinogenesis. Some investigations suggest that tumor growth is more a function of reduced rates of cell death than of enhanced proliferation.[6] Repressed apoptosis has been attributed to a mutation of the tumor-suppressor protein p53,[7,8] overexpression of the bcl-2 apoptosis-inhibitor gene,[9-11] or alteration in the expression of other apoptosis-related proteins or oncogenes, such as c-myc, APO-1, Fas,[12] and BAX.[13]

Chemotherapeutic agents can facilitate apoptosis under certain conditions.[14] For instance, hydroxyurea (Hydrea) and doxorubicin induce changes characteristic of apoptosis in chronic myelogenous leukemia.[15] DNA topoisomerase I and II inhibitors, cytarabine, and paclitaxel (Taxol) also trigger changes characteristic of apoptosis in various types of leukemia.[16] Tamoxifen (Nolvadex), an antiestrogen, induces morphologic and biochemical changes typical of apoptosis in human breast cancer cells,[17,18] and 4-hydroperoxycyclophosphamide (perfos-famide [Pergamid]), cisplatin, and paclitaxel also cause apoptosis-related changes in ovarian cancer cell lines with p53 mutants.[19]

The physiologic manifestations of cytotoxicity relate to the cytotoxic mechanisms of the various chemotherapeutic agents used. Bleomycin damages the lung by injuring alveolar cells and vascular endothelial cells via oxygen radical species. Anthracycline cardiotoxicity results from free-radical injury produced by a drug-iron conjugate. Cisplatin nephrotoxicity[20] and the urotoxic effects of alkylating agents, such as cyclophosphamide (Cytoxan, Neosar)[21] and ifosfamide (Ifex), probably result from the renal excretion of highly reactive, aquated platinum species and toxic metabolites, respectively.

Strategies to overcome unwanted cytotoxic effects have been developed from our understanding of the mechanism of action of anticancer agents. For example, elucidation of the enzymatic inhibitory effect of methotrexate and trimetrexate permitted identification of leucovorin as a rescue agent to bypass the enzymatic blockade.

All current active cancer treatments produce injury to both neoplastic and normal cell populations. Cytoprotective strategies attempt to protect normal cells and tissues from injury without protecting cancer cells. Cytoprotective agents are administered before the anticancer therapy. In contrast, cytokine rescue strategies do not protect normal cells, but rather, attempt to accelerate the production of hematologic elements from surviving stem cells to replace those killed or damaged during chemotherapy. Cytokines are administered after cytotoxic therapy in order to prevent accentuated toxicity to stem cells forced into DNA synthesis while being exposed to chemotherapy.

### Cytoprotective Agents

Table 2 lists the protective agents that are currently available or under-going clinical evaluation. The cyto-protective agents currently in use are amifostine (Ethylol), dexrazoxane (Zinecard), and mesna (Mesnex). Amifostine has the potential to protect a range of normal tissues against the toxicities of radiation and chemotherapy drugs that alter the structure and function of DNA (eg, platinum agents, alkylating agents). Dexrazoxane is specific for doxorubicin-related cardiotoxicity, and mesna is specific for bladder toxicity from ifosfamide or cyclophosphamide.

#### Amifostine

Amifostine, formerly known as WR-2721, is a naturally occurring thiol that can protect against cell damage by binding to the active species of alkylating agents or platinum or by scavenging free radicals. This drug arose from a classified nuclear warfare project sponsored by the US Army and was ultimately selected from more than 4,400 chemicals screened because of its superior radioprotective properties and safety profile.[22-24] Subsequently, amifostine was evaluated for its potential role in reducing the toxicity of chemotherapeutic drugs that alter the structure and function of DNA, such as alkylating agents and organoplatinum agents, as well as radiation therapy. Preclinical studies have demonstrated that amifostine can selectively protect a broad range of normal tissues, including bone marrow, gastric epithelium (including oral mucosa), heart, intestine, kidney, lungs, and salivary glands--but not neoplastic tissues--from the cytotoxic effects of
chemotherapy and radiation.[25-27]

**Mechanism of Action**—Amifostine is a prodrug that is dephosphorylated by plasma membrane alkaline phosphatase to the free thiol WR-1065. It is postulated that WR-1065-mediated cell protection occurs through its binding to active species of platinum drugs or alkylating agents, scavenging of oxygen-free radicals, and donation of hydrogen to DNA radicals.[22]

The mechanism by which amifostine selectively protects normal tissue is based on the higher concentration of free thiol achieved in normal organs than in tumors. Differences in the microenvironment of normal tissues and tumors result in differential uptake of the free thiol into normal tissues relative to tumor masses.[22] Tumors are relatively hypovascular, with resulting tissue hypoxia, anaerobic metabolism, and a low interstitial pH. The combined hypovascularity and low pH result in low rates of prodrug activation by alkaline phosphatase. In addition, the distribution of alkaline phosphatase in normal and malignant tissue differs; high concentrations of this enzyme are found in the capillaries and cell membranes of normal cells. The selective protection of normal tissues results from reduced conversion of amifostine to the active protector WR-1065 and low uptake of WR-1065 by tumors.[28] Consequently, the steady-state concentration of the free thiol is as much as 100-fold greater in normal organs, such as bone marrow, kidney, and heart, than in tumor tissue (Figure 1).[23] Once the free thiol WR-1065 has entered a normal cell, it is available to detoxify the active species generated by alkylating agents, platinum agents, or radiation therapy (Figure 1).

In addition, because of the similarity of its propylamine structure to polyamine precursors, the free thiol may concentrate around DNA and confer preferential protection to this molecule.[29] Studies with Chinese hamster ovary cells have shown that WR-1065 protection is not related to fluctuating intracellular glutathione or cysteine levels, but rather, may be related to inhibition of an inducible error-prone repair system or to the induction of phase II detoxification enzymes.[30]

In addition to protecting against the immediate effects of cytotoxic chemotherapy, sulphydryl compounds such as amifostine may have important antimutagenic properties. Investigators have reported that amifostine protects against the formation of radiation-induced tumors in rodents.[31] In addition, whereas exposure to cisplatin, bleomycin, nitrogen mustard, and gamma- or neutron-irradiation can introduce mutations in the hypoxanthine-guanine phosphoribosyl transferase (hprt) gene locus of V79 Chinese hamster lung fibroblast cells, incubation of these cells with WR-1065 (the active metabolite of amifostine) before administration of the cytotoxic agent significantly reduced mutation, resulting in calculated mutation protection factors of 7.1 for cis-platin, 2.8 for bleomycin, and 3.4 for nitrogen mustard. Such benefit could be significant, considering the potential for development of secondary malignancies from chemotherapy.[32,33]

Human pharmacokinetic studies of amifostine and its active metabolite WR-1065 demonstrate that more than 90% of the parent compound is cleared from the plasma within 6 minutes.[28] These data are extremely important in scheduling the administration of amifostine. Given its extremely short half-life, amifostine should be administered within 30 minutes of chemotherapy or radiation therapy, and several doses may be required to protect against cytotoxic drugs that have a long half-life and drugs that require a prolonged infusion time.

**Clinical trials** with amifostine were initiated in the 1980s. Early phase I trials were designed to determine dose-limiting side effects and the maximum tolerated dose of amifostine.[22,34] A maximum tolerated dose was not reached, but an acceptable tolerated dose, 740 mg/m², was established for use in phase II studies.[35] Subsequent clinical trials utilizing vigorous hydration and improved antiemetics determined that 910 mg/m² was the maximum tolerated dose of this drug.[36]

Initial clinical trials focused on the protective effects of amifostine against alkylating agent-induced hematologic toxicity and platinum-induced nephrotoxicity and neurotoxicity. In one such trial, amifostine, 740 mg/m², was administered before cisplatin was given at doses that escalated from 50 to 150 mg/m². Transient nephrotoxicity was observed in 40% of patients treated with 150 mg/m² of cisplatin plus amifostine but in none of the patients given 120 mg/m² of cisplatin plus amifostine.[34] Compared with published clinical trials in which cisplatin alone was used, trials that added amifostine to cisplatin-based regimens appeared to offer protection against cisplatin-induced nephrotoxicity and neurotoxicity.[37,38] In addition, a controlled trial demonstrated that amifostine pretreatment decreased both the degree and duration of neutropenia associated with cyclophosphamide.[39] More recently, a randomized, phase III study designed to evaluate the protective effects of amifostine in patients receiving cyclophosphamide and cis-platin was completed. A total of 242 patients with advanced ovarian cancer were randomized to receive six cycles of cyclophosphamide (1,000 mg/m²) and cisplatin (100 mg/m²), either alone or preceded by amifostine (910 mg/m²). Pretreatment with amifostine reduced cumulative treatment-related toxicities; specifically, the
amifostine-treated patients had significantly fewer episodes of grade 4 neutropenia associated with fever or infection requiring hospitalization and antibiotics, as well as a reduction in cumulative neurotoxicity and nephrotoxicity associated with cisplatin. Tumor response rates were equivalent in the two treatment arms, as documented at the time of second-look surgery. Median survival was comparable (31 months for both amifostine plus chemotherapy and chemotherapy alone), thus demonstrating a selective protective effect of amifostine against myelotoxicity, nephrotoxicity, and neurotoxicity with full preservation of tumor response.[40]

The preliminary results of a phase I study of patients with advanced malignancy treated with amifostine and escalating doses of paclitaxel administered as a 3-hour infusion suggests that, in the presence of amifostine pretreatment, paclitaxel can be escalated beyond previously neurotoxic doses. Patients are currently receiving 310 mg/m² and thus far have not experienced significant neurotoxicity or arthralgias.[41]

The ability of amifostine to reduce treatment-limiting neurologic toxicity associated with both cisplatin and paclitaxel has important medical benefits in view of the increasing use of this combination in the treatment of ovarian cancer and other solid tumors. A planned randomized clinical trial will confirm the cytoprotective effects of amifostine against paclitaxel-induced toxicity. Extensive preclinical studies showed that amifostine protects normal jejunum, colon, lung, and bone marrow tissues against the acute and late toxicities of radiation therapy. The radioprotective effects of this drug have now been demonstrated in a number of clinical studies.[25,35,42]

In a randomized trial, Liu et al compared the use of amifostine plus radiotherapy with radiotherapy alone in the treatment of rectal cancer.[42] They randomized 100 patients with inoperable, unresectable, or recurrent rectal carcinoma to receive equivalent doses of radiation with or without amifostine pretreatment. The incidence of moderate or severe late toxicities (alterations in bladder and GI mucosa) was significantly lower in the amifostine-plus-radiation arm than in the radiation-alone arm (0% vs 14%; P = .03). With a median follow-up of 2 years (range, 13 to 30 months), median survival is 15 months for the amifostine-plus-radiation arm, compared with 12.6 months for the radiation-alone arm.

In vitro studies have shown that amifostine pretreatment protects normal bone marrow progenitor cells from the cytotoxicity of the marrow-purging agent perfosfamide or mafosfamide (the active metabolite of cyclophosphamide) without protecting breast cancer cells or leukemia cells. On this basis, Shpall et al conducted a small randomized trial in patients with breast cancer undergoing high-dose chemotherapy followed by autologous bone marrow transplantation. Patients' bone marrows were purged by perfosfamide in the ex vivo setting, with or without preincubation with amifostine. When given before marrow purging, amifostine significantly shortened the time to engraftment, from 36 to 26 days (P = .042), decreased the number of platelet transfusions (P less than .017), and lessened the mean number of days patients required antibiotics (P less than .012).[43]

In a study conducted by Gorin, Douay, et al, amifostine enhanced the antitumor effect of mafosfamide against leukemia cells while simultaneously protecting bone marrow progenitor cells. This resulted in a sixfold increase in the therapeutic index.[44]

**Clinical Use**--Amifostine is generally well tolerated, but transient side effects include nausea, vomiting, hypotension, sneezing, a warm or flushed feeling, mild somnolence, a metallic taste during infusion, and occasional allergic reactions.[22,25] Emesis associated with amifostine is clearly dose-related and can be severe. Clinically, the most significant adverse effect associated with amifostine is transient hypotension. Decreases in systolic blood pressure of more than 20 mm Hg that last longer than 5 minutes and symptomatic hypotension occur in fewer than 5% of patients. The median time to onset of hypotension is 14 minutes. The mechanism by which amifostine causes hypotension is unclear. Transient hypocalcemia has been reported rarely. It is due to inhibition of parathyroid hormone secretion and direct inhibition of bone resorption.[45]

Amifostine is infused intravenously over a 15-minute period 30 minutes before chemotherapy or radiotherapy. Antihypertensive drugs should be withheld for 24 hours prior to amifostine therapy. Before amifostine administration, patients should be hydrated and treated with antiemetics (dexamethasone, 20 mg IV, and a serotonin antagonist) and IV fluids. Administration of amifostine requires close patient monitoring. Blood pressure should be measured every 5 minutes during the 15-minute infusion. In the event of a significant drop in blood pressure (eg, less than 20 mm Hg) or the occurrence of symptoms associated with low blood pressure, the amifostine infusion should be interrupted. The patient should receive saline and be placed in the...
Trendelenburg position. Clinicians must be aware of the importance of hydration and be familiar with the use of appropriate antiemetics before administering amifostine. In a recent trial of paclitaxel with amifostine cytoprotection in patients with advanced malignancies, pretreatment with dexamethasone (20 mg), ondansetron (Zofran) (.15 mg/kg IV), cimetidine, diphenhydramine, and lorazepam resulted in no interruption of amifostine infusion, no hypotension, and no significant nausea or vomiting in 42 cycles of therapy.[41]

In clinical trials involving drugs with relatively long half-lives (eg, carboplatin [Paraplatin]), administration of more than one dose of amifostine resulted in an increase in the maximally tolerated dose of carboplatin without additional myelosuppressive effects.[46]

**Dexrazoxane**

Preclinical studies suggest that the mechanism of antitumor activity of anthracyclines differs from the mechanism of cardiotoxicity, the dose-limiting toxicity of these agents. Cardiotoxicity is characterized by diffuse myocardial injury that can lead to chronic cardiomyopathy.[47,48] Two theories have been proposed to explain how anthracyclines alter mitochondrial membrane function, which leads to cardiac dysfunction. Both postulated biochemical mechanisms involve the production, through an iron-dependent process, of compounds with powerful oxidizing abilities. Cardiac myocytes are thought to be especially susceptible to this free-radical-mediated damage because they have lower levels of superoxide dismutase and catalase than other tissues.[47] These findings led to the development of dexrazoxane (ICRF-187; [+1,2-bis-[3,5 dioxopiperazinyl-1-yl] propane), a cyclized analog of ethylenediaminetetraacetic acid (EDTA) that could prevent toxicity by chelation of iron.[49] Distribution studies, conducted in animals with carbon-14-labeled dexrazoxane, demonstrated a lack of selective distribution to cardiac tissue, with the highest concentration in the kidney and liver.[48] In the myocardium, dexrazoxane undergoes hydrolytic ring-opening and chelates iron, reducing the amount available for the formation of oxygen radical-forming iron-doxorubicin complexes.[49] Furthermore, differences in the uptake and metabolism of dexrazoxane by cancer cells compared with myocardial cells may partially explain the differential protective effects of this agent.

**Preclinical Studies**--Substantial evidence from animal models supports the role of dexrazoxane in protecting against anthracycline-induced cardiomyopathy but not against other anthracycline-induced toxic effects.[48,50]

**Clinical Studies**--Dexrazoxane was initially evaluated as an antitumor agent. Its dose-limiting toxicities, observed in phase I trials, included transient leukopenia and moderate thrombocytopenia. Limited phase II studies showed only minimal antitumor activity.[48] On the basis of the preclinical data, dexrazoxane was evaluated as a cardioprotective agent against anthracycline-induced cardiotoxicity.

In a study conducted by Speyer et al,[51] 150 patients with metastatic breast cancer were randomized to receive chemotherapy with fluorouracil (500 mg/m²), cyclophosphamide (500 mg/m²), and doxorubicin (50 mg/m²), either alone or preceded by dexrazoxane (1,000 mg/m² administered intravenously over a 15-minute period 30 minutes before chemotherapy). Patients in the dexrazoxane group received more cycles than control patients (median, 11 vs 9 cycles; P less than .01), as well as higher cumulative doses of doxorubicin (median, 500 vs 441 mg/m²; P less than .05). The incidence of clinical congestive heart failure was significantly lower in the dexrazoxane group than in the control group (2 vs 20 patients, respectively; P less than .0001). There was also a significant difference (P less than .000001) in the number of patients who could not complete the study because of a decrease in resting left-ventricular ejection fraction (5 patients in the dexrazoxane group vs 32 patients in the control group).

There was little difference in noncardiac toxicities between the two treatment groups. The addition of dexrazoxane to the chemotherapeutic regimen caused, after two cycles of therapy, a more pronounced suppression of white blood cell count (2.3 ×10⁹/L, vs 2.6 ×10⁹/L in controls; P less than .05) and platelet count (187 ×10⁹/L, vs 226 ×10⁹/L in controls; P = NS). Complete responses were seen in 7 patients (9%) in the dexrazoxane group, as compared with 5 (7%) in the control group, and partial responses were noted in 21 patients (28%) in the dexrazoxane group and 25 (34%) in the control group. In addition, median time to progression of disease was 9.4 months in the group receiving chemotherapy alone, as opposed to 10.1 months in those receiving chemotherapy plus dexrazoxane. Median overall survival was 18.3 months in the dexrazoxane group vs 16.7 months in the control group. A higher percentage in the dexrazoxane group than in the control group were taken off the study because of disease progression (68% vs 31%).[51]
incidence and severity of cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m² and who would benefit from continuing therapy with doxorubicin. The dose of dexrazoxane is based on the dose of doxorubicin. The recommended dosage ratio of dexrazoxane to doxorubicin is 10:1 (500 mg/m² of dexrazoxane; 50 mg/m² of doxorubicin).

Dexrazoxane is administered as a slow IV push or rapid IV infusion 30 minutes before doxorubicin administration. It is recommended that dexrazoxane not be initiated at the same time as chemotherapy, because in one study, a lower overall response rate was observed in patients who received chemotherapy with dexrazoxane than in those treated with chemotherapy alone (41% vs 50%).[52]

Dexrazoxane therapy is associated with moderate myelosuppression affecting white blood cell and platelet counts.[48]

Mesna

The sulfhydryl compound, mesna (2-mercaptoethane sulfate, sodium salt), was developed as a prophylactic agent to prevent ifosfamide- and cyclophosphamide-induced hemorrhagic cystitis.[53]

The major source of urothelial toxicity is believed to be urinary excretion of acrolein, a metabolite of these chemotherapeutic agents. Mesna was designed to function in the urinary tract to detoxify urotoxic metabolites.

Following IV administration, mesna rapidly undergoes oxidation to mesna disulfide. In the urinary tract, the sulfhydryl groups of mesna react with the terminal methyl group of acrolein, forming a nontoxic thioether. The presence of mesna also inhibits spontaneous breakdown of cyclophosphamide to acrolein in the urine. Recent studies show, however, that mesna is only partially effective in protecting renal tubules from ifosfamide toxicity. The incomplete protection results in tubulotoxicity in the absence of urotoxicity.[54]

Mesna is generally administered intravenously, usually on a fractionated dosing schedule. One schedule is a loading dose, equivalent to 20% of the ifosfamide dose, given 15 minutes before ifosfamide administration and followed by two similar doses 4 and 8 hours after ifosfamide administration. Mesna doses as high as 60% to 120% of cyclophosphamide have been used and given at similar intervals. Since mesna is hydrophilic, it does not penetrate cells and thus does not interfere with the antitumor activity of the chemotherapeutic agents.

Rescue Agents

The rescue agents include CSFs, erythropoietin (Epogen, Procrit), and folinic acid (leucovorin). The available CSFs--granulocyte CSF, or G-CSF (filgrastim [Neupogen]), and granulocyte-macrophage CSF, or GM-CSF (molgramostim [Leucomax], sargramostim [Leukine, Prokine]), are lineage-specific for neutrophils and macrophages, respectively. Erythropoietin is specific for red blood cell production. Leucovorin is a rescue agent that bypasses the enzymatic blockade of the antifolates (methotrexate and trimetrexate).

Colony-stimulating factors, glycoproteins that stimulate the growth and differentiation of myeloid cells from the bone marrow, and cytokines, polypeptides that stimulate or inhibit the chemotaxis and proliferation of white blood cells involved in the immune response, have the potential to lessen the complications associated with chemotherapeutic agents. The identification, cloning, and industrial production of the hematopoietic CSFs have fostered an intense interest in their use to treat myelosuppression and to overcome the dose-limiting toxicity associated with some forms of chemotherapy. Current treatment regimens have focused primarily on G-CSF and GM-CSF. Erythropoietin is also widely used to treat anemia associated with renal disease and has recently been approved for chemotherapy-associated anemia.

Colony-Stimulating Factors

Clinical Trials--The ability of G-CSF and GM-CSF to reduce the duration of chemotherapy-induced neutropenia has been evaluated in clinical trials. In an open-label crossover trial of patients with transitional-cell carcinoma of the urothelium,[55] a randomized trial of patients with non-Hodgkin's lymphoma receiving chemotherapy alone or chemotherapy plus G-CSF,[56] and a randomized, placebo-controlled trial of patients with small-cell lung cancer,[57] G-CSF significantly reduced the incidence of febrile neutropenia and hastened neutrophil recovery following the first cycle of chemotherapy. In two of these studies, G-CSF resulted in a decrease in hospitalization and antibiotic use.[55,57]

The efficacy of G-CSF in reducing the duration of chemotherapy-induced neutropenia and resulting complications was assessed in a multicenter, randomized, placebo-controlled, double-blind study of
211 patients with small-cell lung cancer.[58] Patients received a combination of cyclophosphamide, doxorubicin, and etoposide (VePesid), with or without G-CSF. In addition to being well tolerated, G-CSF reduced the incidence of complications caused by neutropenia during the first cycle of therapy from 57% to 28% and decreased antibiotic use and hospitalizations by 47% and 45%, respectively.

Granulocyte CSF has also been used in the setting of high-dose chemotherapy and autologous bone marrow transplantation. In patients with Hodgkin's disease, G-CSF significantly accelerated the recovery of granulocyte counts.[59] In another study of patients receiving chemotherapy, G-CSF also hastened neutrophil recovery and reduced mucositis after autologous bone marrow transplantation.[60]

Randomized studies of GM-CSF have been conducted after myelosuppressive chemotherapy (standard-dose chemotherapy) and after myeloablative therapy (high-intensity chemoradiation followed by autologous bone marrow transplantation or peripheral stem-cell infusion).[61-65] In trials of myelosuppressive chemotherapy, GM-CSF has not consistently reduced febrile neutropenic events. In one such trial comparing GM-CSF vs placebo in patients with small-cell lung cancer treated with platinum and etoposide and concurrent chest irradiation, GM-CSF failed to cause significant differences in neutrophil recovery; furthermore, an increased incidence of fever and thrombocytopenia was noted in the GM-CSF-treated patients.[61]

Granulocyte-macrophage CSF has also been assessed in patients treated with myeloablative regimens. In several phase III trials evaluating the efficacy of GM-CSF in autologous bone marrow transplantation procedures, neutrophil recovery occurred 4 to 7 days earlier with GM-CSF than with placebo.[62] The incidence of infection, duration of hospitalization, and days of IV antibiotic use were significantly reduced in patients receiving GM-CSF.

The use of G-CSF or GM-CSF has allowed physicians to maintain chemotherapy doses. Trillet-Lenoir et al reported that only 29% of patients with small-cell lung cancer who received cyclophosphamide, doxorubicin, and etoposide with G-CSF support required reductions of 15% or more in their target dose, whereas 61% of patients in the control group required such reductions.[57] Similar results were achieved in a trial of patients with non-Hodgkin's lymphoma who received sequential combinations of vincristine, Adriamycin, prednisolone, etoposide, cyclophosphamide, and bleomycin (VAPEC-B), either alone or with G-CSF. Patients treated with G-CSF had significantly fewer dose reductions and treatment delays than did controls and maintained a median dosage intensity of 95% (as compared with 83% in controls).[56]

Despite these positive results with G-CSF and GM-CSF, none of the randomized trials has reported a significant difference in overall response rates or survival between CSF- and placebo-treated patients.

Clinical Use—Stimulation of myeloid progenitors by CSFs may increase the pool of granulocyte precursors susceptible to destruction by chemotherapeutic agents. Indeed, it has been shown that CSFs given concurrently with chemotherapy increases the severity of neutropenia and thrombocytopenia. As a result, administration of GM-CSF or G-CSF should not begin until at least 24 hours after the last dose of chemotherapy.[61,66,67] Recent data also show that the efficacy of CSFs decreases with repeated courses of chemotherapy.[68]

At currently used subcutaneous doses (5 mcg/kg/d of G-CSF and 125 mcg/kg/d of GM-CSF), the CSFs are well tolerated. The only common toxicity is medullary bone pain, which can usually be controlled with nonnarcotic analgesic agents. Medullary bone pain typically arises when CSF therapy is initiated and again just before the occurrence of neutrophil recovery.

Therapy with GM-CSF is often associated with low-grade fever, nausea, fatigue, chills, and myalgia. Other less common side effects with the first dose of GM-CSF include arthralgia, capillary leakage, and, rarely, dyspnea. It remains unclear whether the side-effect profiles of G-CSF and GM-CSF differ significantly from each other.

Leucovorin Leucovorin (folinic acid, citrovorum factor) is used as a rescue agent in patients receiving high-dose methotrexate or trimetrexate regimens. Methotrexate- or trimetrexate-induced cytotoxicity results from inhibition of dihydrofolate reductase (DHFR), followed by depletion of intracellular folate pools and impaired biosynthesis of purines and pyrimidines.

Leucovorin is a reduced folate that can prevent the toxic effects of methotrexate or trimetrexate, including myelosuppression and GI toxicity.[69] The mechanism of leucovorin rescue of normal cells is repletion of reduced intra-cellular folate levels. In addition, leucovorin competes with methotrexate polyglutamates to overcome the inhibition of thymidylate synthetase. The timing of leucovorin administration relative to methotrexate or trimetrexate is critical to avoid tumor cell rescue. Leucovorin is available for both oral and IV use. To prevent toxicity from high-dose methotrexate,
leucovorin, 15 mg (approximately 10 mg/m²) is administered every 6 hours for 10 doses beginning 24 hours after the initiation of the methotrexate infusion. In the presence of nausea or vomiting, leucovorin should be administered parenterally. Serum creatinine and methotrexate levels should be determined once daily. Leucovorin should be continued until the serum methotrexate level is less than 45 \times 10^{-8}$ M (0.05 mcM). Additional modification of the leucovorin dose and duration of therapy may be necessary depending on methotrexate levels.

**Current Status, Future Directions**

The major question that arises with the use of any chemoprotective agent is whether the protection of normal tissues extends to protection of tumor cells from the cytotoxic effects of chemotherapy and radiotherapy. Similarly, with cytokines, one must address the question of whether they stimulate the growth of both tumor cells and stem cells. Obviously, there is little benefit to be gained from a drug that protects or stimulates normal tissue and tumor tissue comparably.

**Cytoprotective Agents**

Several large, randomized clinical trials have evaluated the use of amifostine with chemotherapy and/or radiotherapy. In these studies, amifostine selectively protected against hematologic and nonhematologic adverse events without compromising the efficacy of the anticancer therapies.[24,40]

More recently, amifostine has been combined with cisplatin, vinblastine, and irradiation to treat advanced non-small-cell lung cancer. Patients with stage IV disease who received amifostine had a response rate of 64% and median survival of 17 months.[70] This high tumor-response rate in non-small-cell lung cancer when amifostine is given with platinum is significantly better than response rates customarily seen with traditional therapies.

Dexrazoxane is currently indicated for use as a cytoprotector against anthracycline-induced cardiotoxicity. However, this drug was originally tested as an anticancer agent. Its weak activity in this domain is apparently related to the ability of certain bisdioxopiperazines to inhibit DNA topoisomerase II.[71]

Recent studies have focused on the potential use of this class of compounds as facilitators of cancer therapies. In vitro assays have demonstrated that dexrazoxane can enhance the antiproliferative effect of cisplatin on ovarian cancer cells in a synergistic and dose-dependent manner, resulting in a decrease in cisplatin inhibitory concent (IC$_{50}$).[72] In addition, dexrazoxane has been used recently with good results as a sensitizer of radiation therapy in patients with inoperable rectal cancer.[73] This suggests that this agent may, under certain circumstances, be used as both a cardioprotector and a facilitator of therapy in cancer cells.

Mesna has been tried successfully as an orally administered uroprotective agent.[74,75] This type of administration is advantageous in therapeutic settings where outpatient chemotherapy is likely to increase.

**Colony-Stimulating Factors**

Colony-stimulating factors can reduce the incidence of febrile neutropenia after myelosuppressive chemotherapy. In addition, CSFs can shorten the period of neutropenia and reduce infectious complications after myeloablative therapy with autologous bone marrow transplantation or peripheral stem-cell transplantation and perhaps after allogeneic bone marrow transplantation. Overall, G-CSF and GM-CSF have little effect on platelet nadir or duration of thrombocytopenia. Colony-stimulating factors do not protect stem cells and are not to be given concurrently with chemotherapy or radiotherapy, as they have enhanced bone marrow toxicity in this setting. Recent clinical data obtained from patients with head and neck cancer who were treated with combination cisplatin-fluorouracil-leucovorin chemotherapy suggest that GM-CSF may reduce mucositis, another dose-limiting toxicity of chemotherapy.[76] There is increasing evidence that maintenance of GI epithelial structure and function is regulated by a cytokine network, analogous to that present in bone marrow.

Several cytokines with potential epithelial activity have been described, including GM-CSF, G-CSF, interleukin-1 (IL-1), IL-11, and transforming growth factor-beta (TGF-beta). These cytokines are now in preclinical or clinical development as mucosal protectants. Interleukin-11 has recently been shown to stimulate recovery of mucosal cells of the small intestine after cytoablative therapy.[77] Similarly, TGF-beta$_3$ slows the proliferation rate of mucosal cells, making them less vulnerable to chemotherapeutic agents.[78]

The use of hematopoietic CSFs in patients with myeloid malignancies (acute myeloblastic leukemia
and myelodysplastic syndromes) has been a concern because most myeloid leukemia cells express CSF receptors.[79] Several clinical trials that address this issue have been completed, and results vary with respect to the interference of CSFs with antitumor efficacy.[80,83] Evidence suggests that GM-CSF may also act as a growth activator on a variety of tumor cells of nonhematopoietic origin.[84] However, in a trial of patients with ovarian cancer receiving carboplatin-cyclophosphamide therapy and GM-CSF, the patients in the GM-CSF arm showed less severe neutropenia and thrombocytopenia but no difference in tumor response rate when compared with controls.[85]

**Cytoprotective Plus Rescue Agents**

Preclinical studies show that the combination of amifostine pretreatment, irradiation, and G-CSF after radiation enhances hematologic recovery.[86,87] Assessment of these combined effects merits clinical investigation. Cytoprotection with amifostine can reduce the extent of toxic damage to normal tissues, including proliferating cell populations, kidneys, and peripheral nerves. Once the chemotherapeutic or radiotherapeutic treatment phase has been accomplished, myeloid progenitors (now present at a higher baseline) can be stimulated by growth factors (CSFs or cytokines).

**Conclusions**

Cytoprotective and rescue agents can reduce the acute and cumulative toxicities associated with more intensive and more effective therapeutic regimens. Oncologists must learn how to use these agents in order to improve the quality and duration of life of cancer patients.

**References:**


30. Grdina DJ, Shigametsu N, Dale P, et al: Thiol and disulfide metabolites of the radiation protector and chemopreventive agent WR 2721 are linked to both its anti-cytotoxic and anti-mutagenic
Current Role of Protective Agents in Cancer Treatment
Published on Physicians Practice (http://www.physicianspractice.com)


49. Hasinoff BB: The iron (III) and copper (II) complexes of adriamycin promote the hydrolysis of the cardioprotective agent ICRF-187 \((+)-1,2\text{-bis}(3,5\text{-dioxopiperazinyl-1-yl})\text{propane}\). Agents Actions 29:374-381, 1990.


65. Gianni AM, Bregni M, Siena S, et al: Recombinant human GM-CSF reduces hematologic toxicity and widens clinical applicability of high-dose cyclophosphamide treatment in breast cancer and...


81. Estey E, Thall PF, Kantarjian H, et al: Treatment of newly diagnosed acute myelogenous leukemia...


Source URL: http://www.physicianspractice.com/review-article/current-role-protective-agents-cancer-treatment-0

Links: