

ADVANCES IN SUPPORTIVE CARE

Current Developments in Side Effect Management, Palliative Care, and Quality of Life

Cytoprotectants in Supportive Care

Brian L. Abbott, MD
Medical Director
Hematology Program
Big Sky Oncology at Sletten Cancer Institute
Great Falls, Mont.

H&O What is the importance of cytoprotectants in cancer care?

BA Looking back over the past several decades of cancer treatment, some of the improvements in survival can be attributed to not only better chemotherapy regimens but also an improved ability to tolerate chemotherapy as a result of cytoprotectants. Also, more aggressive treatments are enabled by improvements in supportive care. The concept of dose density is emerging as an important aspect of improving treatment outcomes with more and more diseases. Cytoprotectants may play some role in allowing higher density and/or higher doses of cancer treatments.

H&O Could you discuss mesna?

BA Mesna is one of the oldest cytoprotectants in use. It has an established history of preventing hemorrhagic cystitis associated with cyclophosphamide and ifosfamide. Mesna works as a scavenger that binds to acrolein, a toxic byproduct of these chemotherapeutic agents. Though this agent is highly effective in this regard, it does not have broader application due to its relative specificity against acrolein. However, it could provide a model for the future development of other cytoprotectants in cases where non-therapeutic molecular byproducts are the cause of certain chemotherapy toxicities.

H&O What are the other approved cytoprotectants?

BA The first to discuss is dexrazoxane HCl (Zincard, Pfizer), which has an emerging role in cardioprotection

from anthracycline-associated damage. This role has been established by guidelines on cytoprotectants released by the American Society of Clinical Oncology (ASCO) in 2002. The risk of cardiomyopathy increases with cumulative anthracycline doses above 300 mg/m². At this time, the mechanism of such cardiomyopathy is not known. It is hypothesized that this condition results from oxidation due to iron chelation, which makes the heart susceptible to damage. Below the threshold dose of 300 mg/m², anthracyclines appear relatively safe, and it is not understood why this risk occurs mainly above that dose.

The research that led to the recommendations of the ASCO guidelines was originally conducted in patients with metastatic breast cancer who have received at least 300 mg/m² of doxorubicin. Trials in lung cancer have shown that similar doses are associated with higher risk of congestive heart failure and a decrease in ejection fraction, which can be prevented to some extent with the use of dexrazoxane.

Adequate long-term pediatric data do not yet exist, and research is ongoing in this setting (Table 1). Children more frequently have curable malignancies; thus, any long-term cardiac damage resulting from anthracyclines could affect many more decades of a cancer survivor's life. Because we hope these survivors will have a normal lifespan, as they get older and suffer from common comorbid conditions such as coronary vascular disease, they may be even more susceptible to long-term effects of anthracyclines than we currently realize. Thus, determining whether cytoprotectants like dexrazoxane may prevent these effects in children is a top priority.

H&O How is amifostine used?

BA Amifostine (Ethyol, MedImmune) is used to prevent acute and chronic xerostomia in patients receiving

Table 1. Selected Ongoing Clinical Trials Investigating the Use of Cytoprotectants as Supportive Care in Cancer Therapy

Sponsor(s)	Identifier	Title	Phase
<i>Amifostine</i>			
Beth Israel Medical Center	NCT00206752	Phase III [Trial] of Unilateral Neck Irradiation With Amifostine in Patients With SCC of the Head and Neck	III
Gynecologic Oncology Group, National Cancer Institute	NCT00058071	Amifostine in Treating Peripheral Neuropathy in Patients Who Have Received Chemotherapy for Cancer	III
Fred Hutchinson Cancer Research Center, National Cancer Institute	NCT00217438	Melphalan and Amifostine Followed By One or Two Autologous or Syngeneic Stem Cell Transplants and Maintenance Therapy in Treating Patients With Stage II or Stage III Multiple Myeloma	III
Children's Oncology Group, National Cancer Institute	NCT00274937	Radiation Therapy, Amifostine, and Chemotherapy in Treating Young Patients With Newly Diagnosed Nasopharyngeal Cancer	III
<i>Dexrazoxane HCl</i>			
The University of Texas M.D. Anderson Cancer Center	NCT00038142	Vincristine, Doxorubicin, Cyclophosphamide and Dexrazoxane With or Without ImmTher for Newly Diagnosed High Risk Ewing's Sarcoma	II
National Cancer Institute	NCT00019864	Combination Chemotherapy Before and After Surgery in Treating Patients With Osteosarcoma	II
Memorial Sloan-Kettering Cancer Center, National Cancer Institute	NCT00077285	Irinotecan and Carboplatin as Upfront Window Therapy in Treating Patients With Newly Diagnosed Intermediate-Risk or High-Risk Rhabdomyosarcoma	II
Dana-Farber Cancer Institute, National Cancer Institute	NCT00084838	Intrathecal and Systemic Chemotherapy Combined With Radiation Therapy in Treating Young Patients With Newly Diagnosed Central Nervous System Atypical Teratoid/Rhabdoid Tumors	II
Children's Oncology Group, National Cancer Institute	NCT00334867	Combination Chemotherapy With or Without Topotecan in Treating Patients With Newly Diagnosed Localized Ewing's Sarcoma	III
Dana-Farber Cancer Institute, National Cancer Institute	NCT00400946	Pegasparaginase or Asparaginase and Combination Chemotherapy in Treating Young Patients With Newly Diagnosed Acute Lymphoblastic Leukemia	III
<i>Milk Thistle</i>			
National Center for Complementary and Alternative Medicine Office of Dietary Supplements	NCT00200798	An Assessment of Milk Thistle Pharmacokinetics and Drug Interactions	II

radiation for head-and-neck cancer. Amifostine is an antioxidant that scavenges free radicals and other reactive products produced during radiation and alkylating-agent therapy. This agent is also used along with chemotherapy, particularly platinum-based regimens. The ASCO guidelines recommend its use to prevent cisplatin-associated nephrotoxicity. Another emerging use for amifostine is protection from paclitaxel-associated neurotoxicity. Initial studies showed no significant benefit in this setting, but there was a trend noted toward reduction of the grade of

neurotoxicity. Additionally, research has assessed whether amifostine reduces neutropenia or thrombocytopenia; no benefits have been shown in terms of protecting hematopoietic stem cells in patients receiving platinum-based chemotherapy in ovarian and lung cancer or paclitaxel in metastatic breast cancer. Amifostine has also been studied in the pediatric setting for the prevention of ototoxicity. In this setting, there is an interest in using high-dose platinum-based regimens, but there are concerns about loss of high-frequency hearing.

H&O Has misoprostol been investigated as a cytoprotectant?

BA Yes. Misoprostol has been studied as a radioprotectant, and it is believed to have an anti-inflammatory mechanism. However, the research has not detected any significant benefits for patients. In rectal cancer, misoprostol was investigated in the prevention of radiation-related proctitis, without positive results. Another study of patients receiving misoprostol in combination with head-and-neck radiation failed to show benefit.

H&O What have been the findings with milk thistle?

BA Milk thistle (*Silybum marianum*) comprises a complex mix of different flavonoids and has been studied in a number of different settings. At present, it is still unclear what its role may be. For example, it has been studied as an antioxidant and a liver protectant. Lay articles exist attesting to its usefulness for protection of the liver and as a therapy for hepatitis C. In the setting of cancer, it may have direct antitumor effects in addition to cytoprotective properties. Milk thistle's mechanism of action may be the inhibition of cyclin-dependent kinases, downregulation of antiapoptotic genes such as *BCL2*, inhibition of cell-survival kinases such as *MAP*, downregulation of inflammatory transcription factors such as nuclear factor κ B, or downregulation of *MDR1*.

Milk thistle has been studied clinically in the settings of prostate, colon, and ovarian cancer. Single-agent phase I studies have not shown significant clinical efficacy, but safe dose ranges were established. Ongoing phase II studies are assessing whether milk thistle does indeed have antitumor activity. In the future, combination studies may be warranted.

H&O Can you summarize your research into ABCG2?

BA A great deal of basic research is ongoing with drug transport proteins, which belong to a family called ATP-binding cassette (ABC) transporters. It is thought that they may lead to protection of the tumor itself from chemotherapy. The first such transport gene described was *MDR1*, and its product is P-glycoprotein. More recently, multidrug resistance protein (MRP1) and ABCG2 (formerly called breast cancer resistance protein [BCRP]) have been described. These transport molecules are expressed on the cell surface and actively efflux many natural and synthetic genotoxic compounds. Some of these proteins are widely expressed in normal stem cell populations in

addition to malignant stem cells. The physiologic role of these proteins may be to protect stem cells from naturally occurring genotoxic substances. In the process of a cancer developing, these genes may be activated or overexpressed, thus protecting the tumor cells from genotoxic chemotherapy substances. Inhibitors of these proteins have thus been studied to overcome antineoplastic drug resistance. The earliest trials used high-dose cyclosporin as an inhibitor of *MDR1* in diseases like acute myeloid leukemia, but overall the trials failed to show a significant survival benefit, whereas additional toxicity was observed.

The primary, and highly speculative, concern with inhibiting these transport molecules is that they are often associated with the excretion of drugs, such as through the hepatobiliary system. Thus, if inhibited, the molecules may no longer protect normal stem cells, which would normally be relatively protected from standard chemotherapeutic treatments. The result of this inhibition may be a narrowing of the therapeutic window of chemotherapy by decreasing the normal physiologic protection from genotoxic substances that these molecules confer. As new inhibitors are developed and clinical trials proceed, I believe it would be wise to monitor the pharmacokinetics of the chemotherapeutic drugs to note any alterations due to these inhibitors or any increases in toxicities. For example, a study of the knockout mouse for ABCG2 showed exquisite sensitivity to substrate xenobiotics. Otherwise viable mice died from relatively low doses of topotecan and mitoxantrone, which are substrates of ABCG2. These transport molecules may not have an obvious effect in the normal setting, but in the setting of a relatively small dose of chemotherapy, or even a naturally occurring genotoxic substance, a large toxicity may be uncovered.

Suggested Reading

Schuchter LM, Hensley ML, Meropol NJ, Winer EP; American Society of Clinical Oncology Chemotherapy and Radiotherapy Expert Panel. 2002 update of recommendations for the use of chemotherapy and radiotherapy protectants: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol*. 2002;20:2895-2903.

Abbott BL. ABCG2 (BCRP): a cytoprotectant in normal and malignant stem cells. *Clin Adv Hematol Oncol*. 2006;4:63-72.

Munter MW, Hoffner S, Hof H, et al. Changes in salivary gland function after radiotherapy of head-and-neck tumors measured by quantitative pertechnetate scintigraphy: comparison of intensity-modulated radiotherapy and conventional radiation therapy with and without amifostine. *Int J Radiat Oncol Biol Phys*. 2006 Dec 14; [Epub ahead of print].

Dest VM. Radioprotectants: adding quality of life to survivorship? *Semin Oncol Nurs*. 2006;22:249-256.

Veness MJ, Foroudi F, Gebiski V, et al. Use of topical misoprostol to reduce radiation-induced mucositis: results of a randomized, double-blind, placebo-controlled trial. *Australas Radiol*. 2006;50:468-474.

Lalla RV, Schubert MM, Bensadoun RJ, Keefe D. Anti-inflammatory agents in the management of alimentary mucositis. *Support Care Cancer*. 2006;14:558-565.