

Uniting Medical and Radiation Oncology Nurses to Improve Patient Quality of Life: Achieving Success Through Team-Based Care



Based on the April 30, 2005, clinical congress satellite symposium held during the Oncology Nursing Society's 30th annual meeting at the Peabody Orlando Hotel, Orlando, Florida



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OVERVIEW

Toxicities associated with aggressive cancer therapies present a significant treatment challenge, impacting both therapeutic outcomes and patient quality of life. This monograph will review up-to-date clinical information on the use of cytoprotective agents and toxicity management, with a focus on head/neck, lung, and pelvic cancers. Critical dosing issues surrounding the use of cytoprotective agents will be reviewed, with attention paid to patient management. This monograph will also emphasize the need for a team-based, patient-engaged approach to improve patient quality of life after chemo- and/or radiation therapy. Throughout the monograph, special consideration will be given to advances in the management of mucositis with cytoprotective agents.

TARGET AUDIENCE

Medical oncology and radiation oncology nurses, including staff nurses, advanced practice nurses, case managers, educators, researchers, consultants, and other healthcare professionals dedicated to excellence in patient care will benefit from this educational activity.

LEARNING OBJECTIVES

After completing this CNE activity, participants should be able to:

- Apply the team-based, patient-engaged approach to improve patient quality of life after chemo- and/or radiation therapy
- Integrate new clinical information on the use of cytoprotective agents and chemotherapeutic/radiotherapeutic toxicity management in multiple forms of cancer, including head/neck, lung, and pelvic

- Describe critical issues regarding dosing administration of cytoprotective agents and patient management

ACKNOWLEDGEMENT

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MEDIUM

This monograph was adapted from the session entitled, "Uniting Medical and Radiation Oncology Nurses to Improve Patient Quality of Life: Achieving Success Through Team-Based Care," held during the Oncology Nursing Society's 30th Annual Congress, April 27-30, 2005, in Orlando, Florida. The instructional format of a monograph was chosen to accommodate the learning preferences of a significant portion of the target audience.

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This activity was approved for credit and released in June 2005. Effective July 1, 2007, the activity will no longer be eligible for contact hours but may still have value for the healthcare professional.

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Cytoprotective Agents and Toxicity Management of Radiotherapy and Chemotherapy in Selected Cancers

INTRODUCTION

Aggressive treatment protocols involving combinations of radiotherapy and chemotherapy are rapidly becoming standards of care for advanced cancers of the head and neck and the pelvic region, and for non-small-cell lung cancer. Hyperfractionated and accelerated fractionation modalities of radiotherapy, radiotherapy and sequential chemotherapy, and, particularly, combinations of chemotherapeutic agents and radiotherapy used concomitantly have resulted in improved local-regional tumor control and enhanced rates of both disease-free survival and overall survival when compared with standard treatments.^{1,2}

Superior therapeutic success, however, has not come without a price. That is, a considerable increase in normal tissue toxicity and a considerable reduction in patient quality of life may exist.^{3,4} Side effects associated with more aggressive cancer treatments include increased levels of pain and fatigue (when compared with side effects associated with standard regimens), decreased ability to perform activities of daily living, and, depending upon the site and type of

cancer, increased levels of mucositis and xerostomia, pulmonary toxicity and pneumonitis, and urinary/bladder dysfunction and colitis.^{3,5-6} These side effects, which may manifest during treatment and/or subsequent to the acute treatment phase, may persist long after treatment has been discontinued and may result in significant morbidity and mortality.

Onset of these toxicities may even interfere with the planned implementation of the treatment protocol. Acute toxicities associated with cancer therapy may necessitate treatment delays or prolongations and even require reductions in scheduled doses of radiotherapy and/or chemotherapeutic agents. Clinical trial data suggest that such protocol modifications can result in reduced therapeutic efficacy when compared with protocols that stay “on schedule” and at the maximum therapeutic dose.^{2,7} Fear of such toxicities may be built into treatment protocols, impeding dose escalation even in instances where higher doses of radiation, chemotherapy, or radiochemotherapy combinations could result in more optimal disease control and better survival rates.⁸⁻¹⁰

TEAM-BASED APPROACH TO CANCER TREATMENT

As aggressive therapies for cancer treatment have become more standardized, the need for a team-based approach to the delivery of cancer therapies has become more pronounced. In the instances of sequential or concurrent combinations of radiotherapy and chemotherapy, the value of multidisciplinary nursing teams, including both medical oncology nurses and radiation oncology nurses, is becoming more evident. Coordination of the administration of these powerful and often-toxic treatments, awareness of the side effects they can produce — and of the toxic synergies their combination can engender — and knowledge of palliative strategies and agents that may reduce these side effects can result in a more successful administration of the aggressive treatment protocol and in a better outcome for the patient. Thus, communication across treatment boundaries becomes essential: medical oncology and radiation oncology nurses must share their knowledge base in regard to each patient in whose care they are involved.

MINIMIZING TREATMENT-ASSOCIATED SIDE EFFECTS

The importance of treating the side effects that occur with more-aggressive cancer therapies has sparked considerable interest in the implementation of less-

toxic treatment strategies as well as in the development of cytoprotective agents and so-called “rescue” agents. Less-toxic treatment strategies include intensity-modulated radiation therapy (IMRT), which is designed to minimize the radiation dose to normal tissue and to restrict the area of normal tissue involvement.³ It has been suggested that IMRT has a better side-effect profile compared with conventional radiotherapy. However, in a study of IMRT vs conventional radiotherapy in patients with oropharyngeal carcinoma, Chao et al found that, while late salivary toxicity was improved with IMRT, moderate-to-severe acute complications (including mucositis) were both significantly high and comparable across both treatment modalities.¹¹

Cytoprotective agents, which are administered immediately prior to radiation therapy and/or chemotherapy, include amifostine, dexrazoxane, and mesna. Rescue agents, administered subsequent to chemotherapy or radio-chemotherapy, include leucovorin, granulocyte colony-stimulating factor (G-CSF), and granulocyte macrophage colony-stimulating factor (GM-CSF). Clinical trial data have indicated that these agents can protect normal tissue or particular types of normal tissue while also minimizing the severity and duration of chemotherapy-induced neutropenia. They can thus reduce side effects associated with aggressive radiochemotherapy in a variety of cancer types.²

CANCER TREATMENT

In addition to surgery, the most common therapeutic modalities used to treat a wide range of cancer types and severities are radiotherapy and chemotherapy. Surgery and/or radiation are the most common treatments for early-stage cancers; chemotherapy and/or radiotherapy with and without surgery are commonly recommended for more advanced-stage cancers. These treatments are administered according to a variety of protocols (radiotherapy) or choice of agents (chemotherapy) and may be used independently, in sequence, or concurrently.

RADIOTHERAPY

Radiotherapy involves the utilization of high-energy radiation to kill cancer cells and shrink tumors. Like surgery, radiotherapy has a local application and is used primarily for local/regional tumor control. A large number of clinical trials involving a wide range of cancer types and stagings have found that increasing the dose and frequency of radiotherapy (compared with standard, once-daily radiotherapy) improves hard-endpoint outcomes such as recurrence-free local control and survival rates.¹²⁻¹⁴

Several dose-escalation radiotherapy strategies have been developed. These include:

- Hyperfractionation, in which the size of the standard radiation dose is reduced (eg, from 2

Gy/fraction to 1.2 Gy/fraction), but the frequency is increased from once-daily (standard radiation therapy) to 2 to 3 times per day. Theoretically, a greater cumulative dose of radiation can be delivered via hyperfractionation, which should improve tumor control compared with standard radiotherapy. At the same time, the small doses, although more frequently delivered, could be more sparing of normal tissue than is standard therapy, thus reducing acute and late-stage toxicities.^{3,15}

- Accelerated fractionation (or accelerated hyperfractionation) maintains a more conventional therapy-like radiation fraction size (eg, 1.5-2 Gy/fraction) as well as the same cumulative dose as standard therapy. Accelerated-fractionation protocols differ from conventional treatments by shortening the overall treatment time; accelerated fractionation delivers multiple radiation fractions per day. The expectation is that the high dose delivered more frequently, over a shorter period of time, will better inhibit tumor cell proliferation. It is presumed that this proliferation, which results in poorer local control, occurs during the course of radiation therapy and that it may be facilitated by treatment delays or prolongations.^{7,15}

The key therapeutic question is, how aggressively can radiotherapy be dosed so as to balance

Side Effects of Chemotherapy

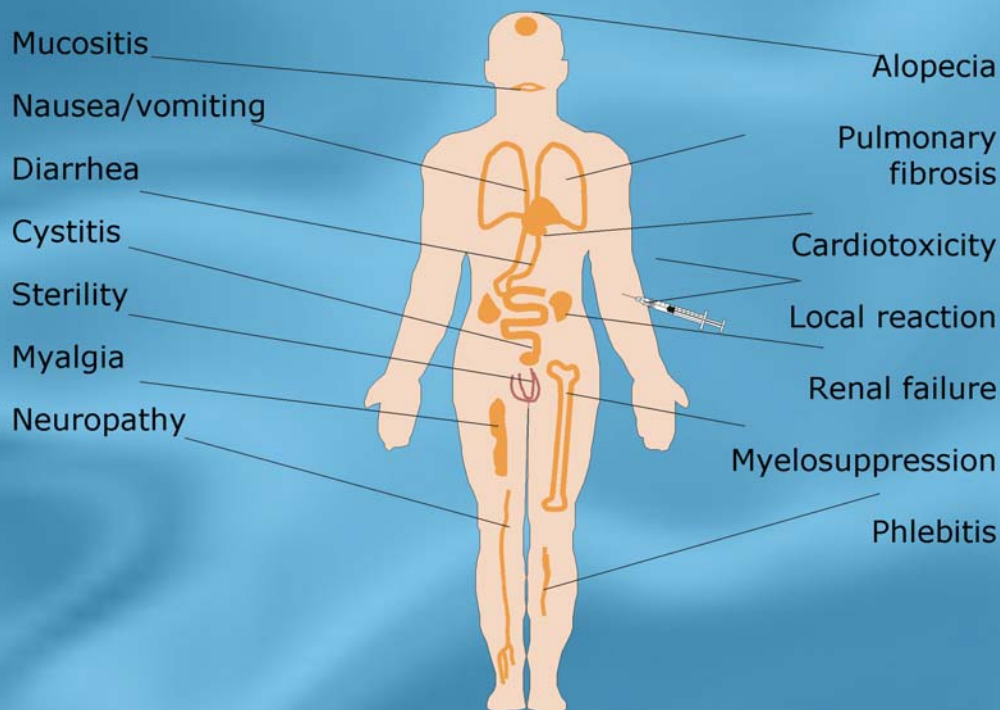


Figure 1

maximum cancer-killing properties with tolerable levels of side effects and normal-cell toxicities? Ku et al have shown that, while hyperfractionation and accelerated fractionation produce significantly improved local-regional tumor control in head and neck squamous-cell carcinoma compared with standard radiotherapy, acute side effects, particularly those affecting the mucous membranes and pharynx, were significantly more severe with both types of fractionated therapy.³ Similarly, Jen et al observed superior local control rates with altered fractionated, twice-daily radiotherapy vs standard, once-daily therapy. However, the incidence of acute toxicities was higher in the twice-daily group with more severe

mucositis and moist desquamation compared with the standard therapy group.¹³

CHEMOTHERAPY

Unlike radiotherapy, which is locally deployed, chemotherapy is a systemic cancer treatment that utilizes pharmacologic agents to destroy cancer cells by interfering with their ability to grow and multiply. Since cancer cells tend to grow and replicate more rapidly than normal cells, chemotherapy destroys more cancer cells than normal cells. But because all cells grow and replicate, chemotherapy's interference with normal cellular processes can cause significant toxicities and side effects (Figure 1).

For many cancers, standard chemotherapy regimens involve a combination of cytotoxic agents. For example, standard chemotherapy for aggressive non-Hodgkin's lymphoma includes 3 chemotherapeutic agents — cyclophosphamide, doxorubicin, and vincristine — and prednisone, a corticosteroid (this combination of therapies is known as CHOP).

Toxicities associated with CHOP include myelotoxicity, severe neutropenia, cardiotoxicity, and neurotoxicity. The severity of morbidity and mortality rates associated with these toxicities may cause physicians not to administer CHOP to certain subpopulations of patients with non-Hodgkin's lymphoma, such as the elderly, or those with comorbidities or poor functional status.¹⁶

COMBINATION RADIOCHEMOTHERAPY

The combination of radiotherapy with 1 or more chemotherapeutic agents administered either sequentially (induction therapy) or concurrently (concomitant therapy) is emerging as the new standard of care for a number of advanced cancers. Combination therapies may be used neoadjuvantly (preoperatively) for tumor downstaging and to devitalize margins and lymph node metastases prior to surgical resection. Postoperatively, combination therapies can help prevent recurrence and enhance disease-free and overall survival. Radiochemotherapy may also be indicated in cases where the cancer may not be resectable.¹⁷⁻¹⁸

The cytophysiologic rationale supporting the combination of radiotherapy and chemotherapy is the premise that chemotherapeutic drugs enhance the antitumor and cytotoxic effects of radiation. A number of mechanisms appear to be involved, including inhibition of cellular repair functions, targeting (by either treatment modality) of distinct subpopulations of cells within the tumor, and slowing tumor cell

repopulation in rapidly proliferating neoplasms.^{15,17,19}

Improved clinical outcomes provide rationale for the use of combination therapy rather than radiation alone. In a review of 10 recent clinical trials comparing various radiochemotherapy regimens (single/ multiple chemotherapeutic agents; various radiation fractionation options) vs radiation alone for head and neck cancer, Argiris found that, almost without exception, concurrent radiochemotherapy was significantly superior to radiation alone as determined by survival rates and local tumor control.¹⁹ For example, Calais et al randomized 226 patients with advanced-stage oropharynx carcinoma to receive identical radiotherapy (70 Gy in 35 fractions) while 1 group also received 3 cycles of a 4-day chemotherapy regimen containing carboplatin and 5-fluorouracil by continuous infusion. Overall 5-year survival rates were 51% for the radiochemotherapy group vs 31% for the radiotherapy-only group ($P=.002$).¹

Similarly, in recent clinical trials comparing radiochemotherapy with radiation alone for the treatment of lung cancer, both induction and concurrent radiochemotherapy demonstrated therapeutic superiority when compared with radiotherapy alone.¹⁷ In a clinical trial comparing these modalities, 331 patients with nonmetastatic, inoperable non-small-cell lung cancer were randomized to 1 of 3 treatments: radiotherapy for 2 weeks (3 Gy given 10 times, in 5 fractions a week), followed by a 3-week rest period and then radiotherapy for 2 more weeks (2.5 Gy given 10 times, 5 fractions a week); radiotherapy on the same schedule, combined with 30 mg of cisplatin per square meter of body-surface area, given on the first day of each treatment week; or radiotherapy on the same schedule, combined with 6 mg of cisplatin per square meter, given daily before radiotherapy. Survival was significantly improved in the radio-

therapy-daily-cisplatin group compared with the radiotherapy group ($P=.009$): 54% at 1 year, 26% at 2 years, and 16% at 3 years in the combination therapy group vs 46%, 13%, and 2% in the radiotherapy group.²⁰

Similarly favorable results for radiochemotherapy vs radiation alone have been found in trials involving a variety of other types of cancer. Results from the

United Kingdom Coordinating Committee on Cancer Research study on radiotherapy alone vs radiochemotherapy in patients with anal cancer found a 46% reduction in the risk of local failure in the radiochemotherapy arm. Risk of death from anal cancer also was significantly reduced in the radiochemotherapy group ($P=.02$).²¹

THE ROLE OF CYTOPROTECTIVE AND RESCUE AGENTS

Many side effects may be associated with cancer therapies; they may present acutely during treatment and/or even months after treatment cessation. In some instances, treatment-associated side effects may result in long-standing, even permanent, dysfunctions and debilitations (Table 1).

Common side effects associated with radiation treatment of advanced lung cancer include acute and late-stage esophagitis, acute pulmonary toxicity, late-stage pneumonitis, and organ fibrosis.⁵ In the treatment of oropharyngeal cancer with chemotherapy, common side effects include mucositis; hematopoietic suppression; and gastrointestinal, renal, neurologic, and otologic toxicities induced by cisplatin therapy.²² Xerostomia (dry mouth resulting from salivary impairment) is one of the most common side effects associated with radiotherapy for head and neck cancers. In some patients, xerostomia may resolve subsequent to treatment discontinuation, but in others, salivary gland impairment may become a lifelong problem, leading to oral mucositis, dysphagia, oral discomfort, dental caries, and increased risk of infection.²³ Oral and gastrointestinal mucositis are frequent side effects of both chemotherapy and radiotherapy. Symptoms range from mild dysphagia and hoarseness to anorexia, diarrhea, gastrointestinal bleeding, fistula, and bowel perforation. Some of these symptoms can become so severe as to become

life-threatening. Mucositis may occur regardless of the tumor location or target tissue since its etiology appears to involve chemo- and/or radiotherapy-induced generation of oxidative stress and reactive oxygen species.²⁴

The frequency and severity of cancer therapy-induced side effects increases as the therapies themselves become more aggressive, particularly when chemotherapy and radiotherapy are combined. In addition, the known toxicity of both chemotherapeutic agents and radiotherapy is enhanced by their use in combination.¹⁷ In their survey of the side effects of aggressive treatment of advanced head and neck cancer, List et al found that these side effects — including eating and speech dysfunction, residual pain, and xerostomia — can severely affect patient function and quality of life.²⁵ Argiris has noted that the level of toxicity associated with radiochemotherapy is such that careful patient selection is required.¹⁹ Indeed, in the oropharynx trial discussed above, the incidence of grade 3 and 4 mucositis was significantly higher in the combined therapy vs the radiation-only arm, 71% vs 39% ($P=.005$).¹ Significantly greater levels of side effects in the combination therapy group also were noted in the non-small-cell lung cancer trial. Cisplatin-induced nausea and vomiting occurred in 86% of the patients given it weekly and in 78% of those given it daily;

these effects were severe in 26% and 28%, respectively.²⁰ In the anal cancer trial, early-stage morbidity was found to be significantly more frequent ($P=.03$) in the combination-therapy patient group than in the radiation-only patient group.²¹

More aggressive therapies typically produce better treatment outcomes but at the cost of higher levels of side effects compared with standard treatments. The result is more patient toxicity, which may increase overall costs of therapy, as patients now need to be treated for the effects of their cancer treatments. These side effects also may introduce treatment

delays or prolongations, as patients may require time to recover. Grade 3-4 oral or gastrointestinal mucositis, a common side effect of many anticancer treatments, will cause a therapy treatment delay in approximately 35% of patients.^{2,3,7} Somewhat paradoxically, treatment delays associated with more aggressive therapy can result in poorer prognoses than might have been the case had the patient been administered standard therapy, delivered according to protocol.⁷ And, certainly, any increase in the incidence and severity of side effects will have a significant and negative impact on patient quality of life.^{4,25}



Toxicities Associated With Cancer Treatments

- **Chemotherapy**
 - **Pulmonary toxicity**
 - **Myelotoxicity**
 - **Neurotoxicity**
 - **Alopecia**
 - **Mucositis**
 - **Hematopoietic suppression**
 - **Cisplatin toxicities (gastrointestinal, renal, neurologic, and otologic toxicities)**
- **Radiation therapy**
 - **Xerostomia**
 - **Mucositis**
 - **Esophagitis**
 - **Acute and chronic pulmonary toxicity**
 - **Organ fibrosis (skin, muscle, breast, lung, GI)**

Antonadou D et al. *Int J Radiat Oncol Biol Phys.* 2001;51:915-922; Chin HW et al. *Fed Pract Suppl.* 2001;18:12-21; Cooper JS et al. *N Engl J Med.* 2004;350:1937-1944.

Analyses of a large number of clinical trials of chemotherapy, hyperfractionated and accelerated fractionated radiation therapy, and combination therapy have revealed that the ability to administer a higher cumulative dose and/or a greater-intensity dose can produce an improved rate of response and duration of response. Weighing against the administration of more aggressive treatment strategies is the fear of intolerable therapy-induced side effects. In addition, although these more aggressive strategies are associated with greater benefit, they also entail the possibility of treatment delays and prolongations, perhaps necessitated by the onset of intolerable side

effects. It has been shown that the benefit of these more aggressive therapies is contingent upon a high percentage of the planned treatment dose being delivered according to the planned treatment schedule. Unfortunately, the very aggressive nature of the treatment may interfere with the scheduled delivery of the treatment.²

The challenge of making aggressive cancer treatments more clinically practicable and tolerable has sparked a great deal of interest in development of supportive therapies. By increasing the tolerability of aggressive cancer treatments, supportive therapies can make

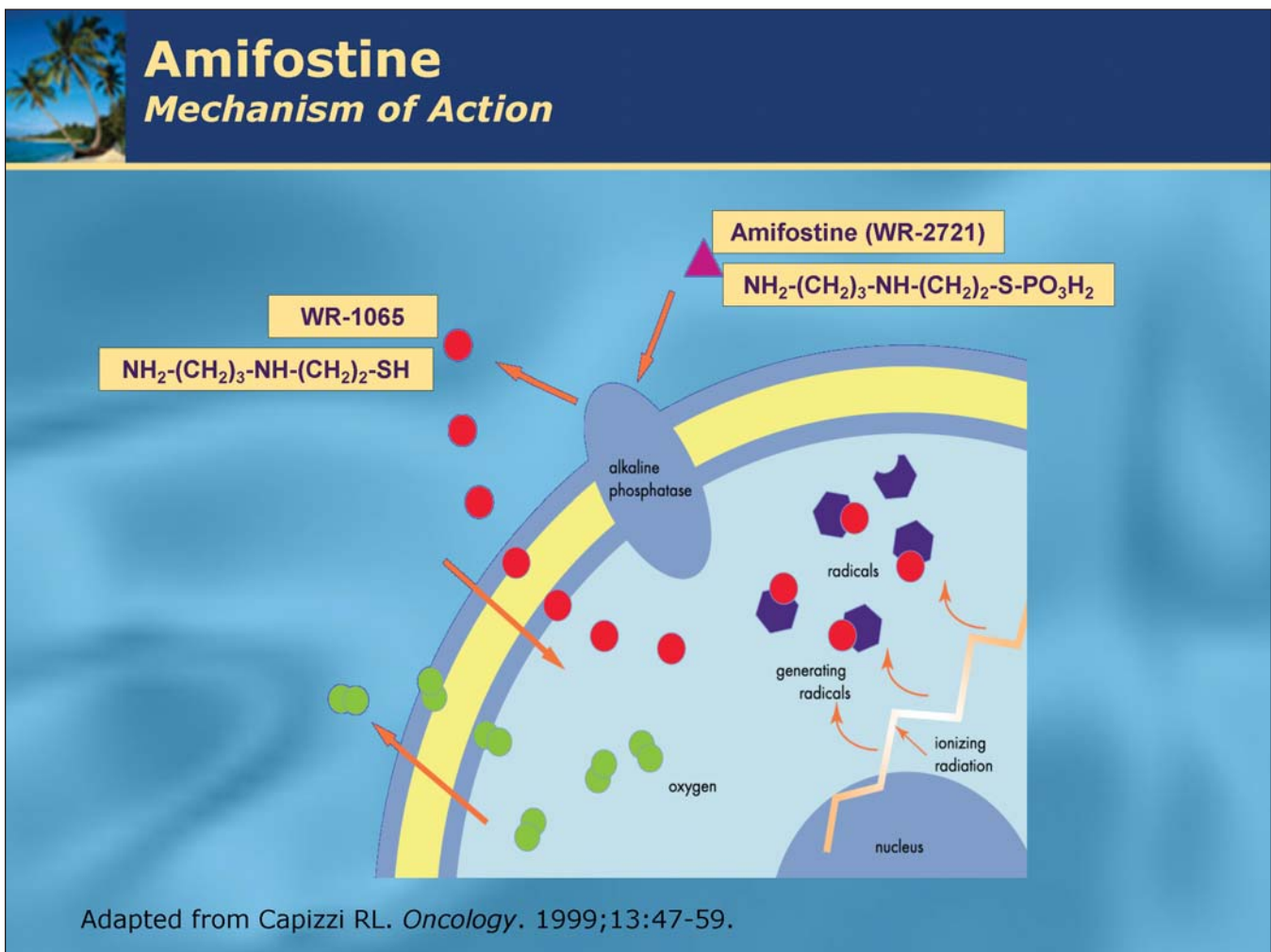


Figure 2

therapeutic improvements promised by such treatments more feasible. Specifically, supportive therapies can reduce or even eliminate treatment delays or prolongations associated with more aggressive therapies. In addition, supportive therapies confer the potential to increase the maximum therapeutic dose (of either radiotherapy or chemotherapy or both in combination) tolerable to normal tissue but lethal to cancerous tissue.

AMIFOSTINE

Amifostine is one of the most important of these supportive therapies, or cytoprotectants, having demonstrated favorable results in a number of clinical trials involving a variety of cancer types and treatment modalities. Amifostine is an organic thiophosphate cytoprotective agent known chemically as 2-[(3-aminopropyl) amino] ethanethiol dihydrogen phosphate (ester). Amifostine is dephosphorylated by alkaline phosphatase in tissues to a pharmacologically active, free-thiol metabolite.²⁶ It is believed that the free-thiol metabolite mediates cellular protection by binding to and detoxifying intracellular reactive oxygen species generated by alkylating agents and platin agents (chemotherapy) or by radiation therapy (Figure 2). The free-thiol metabolite is much more readily absorbed by normal tissue than by tumor tissue. In fact, micro-environmental differences between normal tissue cells and tumor tissue cells result in free-thiol concentrations 100-fold greater in the former. These higher concentrations of free thiol protect normal tissue, such as bone marrow, the kidneys, and the

heart, but not tumor tissue, from the destructive cellular effects of chemotherapy and radiotherapy.²

Amifostine is indicated for cumulative renal toxicity associated with chronic administration of cisplatin, as well as for moderate-to-severe xerostomia associated with postoperative radiotherapy in head and neck cancer. In a number of clinical trials, including chemotherapy for ovarian and non-small-cell lung cancer and radiotherapy for head and neck cancer, pretreatment with amifostine significantly reduced treatment-associated toxicities and side effects.²⁶

Prior to dosing with amifostine, patients should be adequately hydrated and should be kept in a supine position. Blood pressure should be monitored during the infusion and thereafter as long as clinically indicated. Possible adverse events associated with amifostine include hypotension, nausea, and vomiting. It is recommended that antiemetic medications be administered prior to and in conjunction with amifostine. For recommended amifostine dosing schedules please refer to the product insert.^{26*}

Recent dosing studies comparing standard infusion of amifostine with more rapid infusion of lower doses (eg, 200 mg/m² preradiation) both with and without antiemesis (eg, 5-minute infusion and rapid-push IV [1 minute]) have reported that the shortened infusion times show reduced toxicity and improved tolerability.²⁷

Although subcutaneous administration of amifostine is not currently approved, it would seem to have a number of advantages over IV administration,

*For chemoprotection, data now available suggest that the best success can be achieved with a dose of 740 mg/m² given by IV within 3 to 5 minutes. This dose provides the same protection as the higher, 940 mg/m² dose, while being associated with less risk of hypotension. [Schiller JH, Storer B, Berlin J, et al. Amifostine, cisplatin, and vinblastine in metastatic non-small-cell lung cancer: a report of high response rates and prolonged survival. *J Clin Oncol*. 1996;14:1913-1921.] For radioprotection, current data suggest that a bolus injection (delivered within 60 seconds) significantly reduces acute side effects compared with infusion delivery while demonstrating no decrease in radioprotection. [Wagner W, Radmard A, Schonekaes K-G. A new administration schedule for amifostine as a radioprotector in cancer therapy. *Anti-Cancer Res*. 1999;19:2281-2284.] Alternatively, a flat dose of 500 mg administered as a 10-second IV push has also been shown to be safe and well-tolerated when used as a radioprotectant. **(These are not FDA-approved dosages/administrations.)** [Boccia RV, Alster M, Houskamp E. Amifostine (ethyol) given by rapid IV push is safe and tolerable. *Proceedings of ASCO*. 2001;20:2953.]

including reduction in the time required and staff needed to administer it, as well as considerably reduced patient discomfort and risk.²⁷ Koukourakis et al recently tested the feasibility of amifostine administered by subcutaneous injection in 60 patients with thoracic tumors, 40 patients with head and neck tumors, and 40 patients with pelvic tumors. All patients were undergoing radiotherapy; 20 minutes prior to administration of each radiotherapy fraction, a 500-mg dose of amifostine diluted in 2.5 mL of saline was administered subcutaneously. The results showed that amifostine administered subcutaneously was well tolerated by 85% of patients. The incidence of side effects was low: Grade 1 nausea occurred in 29% of patients, grade 2 vomiting and hypotension in only 3%. Compared with a control group of patients treated with radiotherapy alone, amifostine significantly reduced the severity of side effects related to oral and gastrointestinal mucositis. Amifostine also reduced treatment delays, which were significantly longer ($P < .04$) in the radiotherapy only group; eg, 20% of patients being treated for head and neck cancer with radiation alone experienced treatment delays lasting between 8 and 14 days vs 0% of amifostine + radiotherapy patients.²⁸

OTHER SUPPORTIVE AGENTS

Other supportive agents used to mitigate cancer treatment–associated side effects and toxicities include:

- Dexrazoxane, a cytoprotective agent, is a cyclized analog of ethylenediaminetetraacetic acid (EDTA) that prevents cytotoxicity by chelation of iron. Data from preclinical and clinical studies suggest that dexrazoxane protects against anthracycline-induced cardiomyopathy but not against other anthracycline-induced toxic effects.
- Mesna is a sulhydryl compound that was developed as a prophylactic against ifosfamide- and cyclophosphamide-induced hemorrhagic cystitis. The major source of urothelial toxicity is believed to be a urinary excretion of acrolein, a metabolite of both ifosfamide and cyclophosphamide. Mesna was designed to function in the urinary tract to detoxify urotoxic metabolites.
- Leucovorin is the active form of the B complex vitamin folate. Leucovorin is used as an antidote to drugs that decrease levels of folic acid. In cancer-treatment regimens, leucovorin is used in patients receiving high-dose methotrexate and trimetrexate, the cytotoxic effects of which include myelosuppression and gastrointestinal toxicity. Leucovorin rescues normal cells threatened by such treatments by facilitating repletion of reduced levels of intracellular folate.
- Granulocyte Colony Stimulating Factors (G-CSF) and Granulocyte Macrophage Colony Stimulating Factors (GM-CSF)
 - Colony stimulating factors are groups of glycoproteins that stimulate the growth and differentiation of myeloid cells from bone marrow and cytokines that stimulate or inhibit the chemotaxis and proliferation of white blood cells involved in immune response. In patients with non–small-cell lung cancer, G-CSF has significantly reduced the incidence of febrile neutropenia following initial chemotherapy, thereby reducing the need for hospitalizations and antibiotics. GM-CSF has been demonstrated to accelerate neutrophil recovery subsequent to autologous bone marrow transplantation procedures.²

HEAD AND NECK CANCER: TREATMENTS, TOXICITIES, ROLE OF CYTOPROTECTION

The American Cancer Society estimates that the number of new cases of head and neck cancer will approach 50,000 this year; estimated mortality from both new and current cases in 2005 is 14,640. Head and neck cancers include cancer of the oral cavity and pharynx, as well as cancer of the tongue, pharynx, mouth, and other oral cavity cancers. By far, the most common kind of head and neck cancer is cancer of the oral cavity and pharynx; an estimated 29,370 new cases are expected to be diagnosed this year. Estimated deaths from oral cavity and pharynx cancer are expected to surpass 7300. The incidence of oral cavity and pharynx cancer is far higher in men than in women; men over the age of 50 are at greatest risk, particularly men who use tobacco and/or consume alcohol to excess. Signs and symptoms of oral cavity and pharynx cancer — indeed of most head and neck cancers — include persistent bleeding sore(s); persistent red and white patches; and difficulty chewing and swallowing. Treatments include radiation and surgery. In advanced disease, chemotherapy may be added to both surgical and radiotherapy treatments.²⁹

CLINICAL TRIAL DATA: OUTCOMES AND TOXICITIES

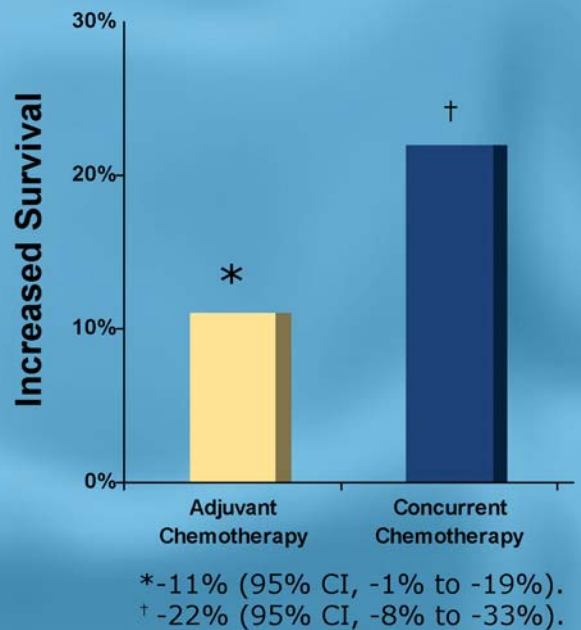
In an overview of clinical trial data of therapies for head and neck cancer, Dimery et al found a 40% survival rate for patients with advanced squamous-cell carcinoma whose tumors could be resected and a 20% survival rate for those patients with unresectable tumors treated with radiation alone. The addition of chemotherapy to radiotherapy significantly increased survival rates. In patients with advanced nasopharyngeal carcinoma, for example, radiotherapy alone produced a 5-year survival rate between 10% and 40%; the addition of neoadjuvant chemotherapy to radiotherapy boosted 5-year survival to over 80%.³⁰

A more recent meta-analysis of 25 clinical trials compared the addition of chemotherapy with local definitive treatment (surgery and/or radiotherapy) of head and neck squamous-cell carcinoma. Overall, the addition of chemotherapy — administered either prior to local definitive treatment, both prior and subsequent to local definitive treatment, or concurrently with local definitive treatment —



Head and Neck Cancer Radiochemotherapy Meta-analysis: 42 Studies

- Toxicity increased with addition of chemotherapy to RT (42 trials, 5079 patients)
 - HR 2.17 (95% CI, 1.84-5.26)
 - $P < .001$
- Survival improved (25 trials, 4076 patients)
 - 11% with adjuvant chemotherapy
 - 22% with concurrent chemotherapy



Adapted from El-Sayed S et al. *J Clin Oncol.* 1996;14:838-847.

Figure 3

reduced mortality rates by 11% vs local definitive treatment alone. In the concurrent therapy trials, the combination of radiochemotherapy reduced mortality by 22% when compared with local definitive treatment alone³¹ (Figure 3).

Toxicities and side effects associated with head and neck cancer treatments can be severe. Considering just radiation therapy alone, between 55% and 85% of treated patients will experience treatment-associated anorexia and weight loss, and between 75% and 85% will experience chronic pain; as many as 90% of patients will experience some level of mucositis, with grades 2 and 3 predominating^{4,32} (Table 2).

The addition of chemotherapy to radiotherapy in the treatment of head and neck cancers has been found to significantly increase treatment-associated toxicities, even though it increases long-term survival and improves other treatment goals.³¹ In a trial of radiotherapy alone vs concurrent radiochemotherapy used postoperatively for head and neck squamous-cell carcinoma, 77% of patients in the combined-therapy group experienced acute adverse events of grade 3 or higher (eg, hematologic, mucous membrane, and gastrointestinal events) compared with 34% of patients in the radiotherapy-only group.³³



Head and Neck Cancer Complications of Radiation Treatment

• Xerostomia (dry mouth)	78%-95%
• Dysgeusia (change in taste)	90%
• Anorexia/weight loss/malnutrition	55%-85%
• Chewing/eating difficulties	70%
• Mucositis/stomatitis	45%-93%
• Dysphagia	65%-100%
• Radiation necrosis (osteoradionecrosis)	5%-15%
• Pain	75%-85%

Brizel DM et al. *J Clin Oncol.* 2000;18:3339-3345; Epstein JB et al. *Head Neck.* 2001;23:389-398; Gal TJ et al. *Arch Otolaryngol Head Neck Surg.* 2003;129:72-76.

Table 2

THE ROLE OF AMIFOSTINE

In a small trial (N=39), patients with stage III or IV squamous-cell carcinoma of the head and neck were randomized to receive radiochemotherapy alone (daily fractions of 2 Gy, 5 days per week to a total dose of 60 Gy plus 70 mg/m² carboplatin on Days 1 through 5 and Days 21 through 26) or radiochemotherapy preceded by 500 mg of amifostine by IV infusion on the days when carboplatin was administered. Patients in the amifostine + radiochemotherapy arm (n=25) had significantly less xerostomia and mucositis ($P=.0001$ for both

conditions) compared with the therapy-only arm (n= 14) as well as significantly less thrombocytopenia and leukopenia ($P=.001$ for both conditions). Interestingly, more patients receiving amifostine + radio-chemotherapy were disease-free at the 12-month follow-up (79%) compared with the carboplatin therapy-only group (64%), suggesting amifostine may have enhanced the effects of radiochemotherapy.³⁴

A phase 3 trial of previously untreated head and neck squamous-cell carcinoma randomized 315 patients to receive once-daily radiotherapy (1.8 to 2.0 Gy) to

doses of 50 to 70 Gy (n=150), or the same radiotherapy dose + amifostine 200 mg/m² daily (n=153) (12 patients were randomized but received no treatment or follow-up) administered intravenously 15 to 30 minutes before irradiation. Although nausea and vomiting (known to be side effects of amifostine administration) were far more prevalent in the amifostine + radiotherapy group, amifostine therapy was associated with a significant reduction in acute \geq grade 2 xerostomia (from 78% to 51%; $P < .0001$) and in chronic \geq grade 2 xerostomia (from 57% to 34%; $P = .002$) vs the radiation therapy-only group. Once again, amifostine did not compromise the antitumor effects of radiotherapy. In fact, overall survival was slightly higher in the radiotherapy-plus-amifostine group than in the radiotherapy-alone group (81% vs 73%), although the difference was not statistically significant.³²

When Antonadou et al administered amifostine (300 mg/m², IV infusion) to head and neck cancer patients (N=50) undergoing radiochemotherapy (2 Gy fractions 5 days weekly for a total of 60-74 Gy and carboplatin 90 mg/m² once per week before radiotherapy), they found that acute mucositis was almost nonexistent in the amifostine treatment

group (n=22; 9% grade 2 mucositis at Week 3 of treatment; 4.5% grade 4 mucositis at Week 5) compared with the control group (n=23; 100% grade 2 mucositis at Week 3; 52.4% grade 4 mucositis at Week 5). Late-phase toxicities were similarly diminished for the amifostine group: at the 3-month follow-up point, only 27% of the amifostine group had grade 2 xerostomia vs 74% of the combination therapy-only group; at 18 months subsequent to therapy cessation, the percentage of patients with grade 2 xerostomia in the amifostine group was 4.5% vs 30.4% in the control group. Again, far from interfering with treatment response, amifostine seemed to facilitate it: 90.9% of the amifostine group showed a complete response vs 78.3% in the control group. However, this difference did not reach statistical significance ($P = .414$).³⁵

To summarize: administration of amifostine in head and neck cancer patients receiving chemotherapy and/or radiation therapy reduces treatment-associated side effects and toxicities, particularly acute and chronic mucositis and xerostomia, and does so without impeding the cytotoxic efficacy of radiochemotherapy.

NON-SMALL-CELL LUNG CANCER: TREATMENTS, TOXICITIES, ROLE OF CYTOPROTECTION

In the United States, lung cancer is the leading cause of cancer-related mortality; an estimated 93,000 men and 80,000 women will die of lung cancer this year, and an estimated 172,500 new cases of lung cancer will be diagnosed. Although the 1-year survival rate for lung cancer has been increasing, largely as a result of improved surgical techniques and radiochemotherapy combinations, the overall 5-year survival rate for all stages of non-small-cell lung cancer is still only about 15% (Table 3). Only genital system cancer (most particularly cancer of the prostate) has a higher incidence than lung cancer. Signs and symptoms of lung cancer include persistent cough, bloody sputum, chest pain, and chronic recurrent bronchitis and pneumonia. Treatments include surgery, where feasible, and chemotherapy and radiotherapy alone or in combination. For non-small-cell lung cancer, optimal treatment includes chemotherapy, alone or in combination with radiotherapy.²⁹

CLINICAL TRIAL DATA: OUTCOMES AND TOXICITIES

As with head and neck cancer, chemotherapy administered concurrently with radiotherapy has been shown to improve survival rates and other outcome parameters in lung cancer patients when compared

with sequential radiochemotherapy or radiation alone. In a trial comparing the efficacy of hyperfractionated radiotherapy alone vs hyperfractionated radiotherapy in combination with chemotherapy, 169 patients with stage IIIA or stage IIIB non-small-cell lung cancer were randomized to 1 of 3 treatment arms: 1) hyperfractionated radiotherapy (HFX RT) dosed 1.2 Gy twice daily to a total dose of 64.8 Gy; n=61; 2) the same HFX RT dose plus chemotherapy (CHT) consisting of 100 mg of carboplatin (CBDCA) on Days 1 and 2 and 100 mg of etoposide (VP-16) on Days 1-3 of each week during the RT course; n=52; 3) the same HFX RT dose with CHT consisting of 200 mg of CBDCA on Days 1 and 2 and 100 mg of VP-16 on Days 1-5 of the first, third, and fifth weeks of the RT course (n=56). The median survival time was higher for both combination treatment arms vs radiotherapy alone and was significantly higher (18 months; $P=.0027$) for group 2. The 3-year survival rates were 6.6%, 23%, and 16%, respectively. The relapse-free survival rate in group 2 also was higher than that in group 1 ($P=.0024$). However, both combination-therapy arms experienced a higher incidence of acute and/or late high-grade toxicity compared with the radiation therapy-only group.³⁶

When Furuse et al compared sequential radiotherapy and chemotherapy with concurrent radiation and



NSCLC Stage-related Survival

Stage at Diagnosis (1995-2000)

5-year Survival

All Stages	15.2%
Local*	49.4%
Regional	16.1%
Distant	2.1%

* Only 16% of lung cancers are diagnosed at this early stage

American Cancer Society. *Cancer Facts & Figures 2005*; American Cancer Society: Detailed guide: lung cancer. How is lung cancer staged? 2004.

Table 3

chemotherapy in 320 patients with unresectable non-small-cell lung cancer, they found that patients in the concurrent arm (n=156; cisplatin 80 mg/m² on Days 1 and 29; vindesine 8 mg/m² on Days 1 and 28, and mitomycin 8 mg/m² on Days 1 and 29 plus radiotherapy beginning on Day 2 at a dose of 28 Gy (2 Gy per fraction and 5 fractions per week for a total of 14 fractions) had a significant increase in median survival time (16.5 months; $P=.03998$) compared with patients in the sequential treatment arm (n=158; 13.3 months) (5 patients were found to be ineligible, and 1 withdrew informed consent). Patients in the sequential treatment arm received the same chemotherapy regimen,

with radiotherapy commencing after completion of chemotherapy. Radiotherapy consisted of 56 Gy (2 Gy per fraction and 5 fractions per week for a total of 28 fractions). Side effects were significant in both treatment arms: out of a total of 156 patients in the concurrent group, 98 experienced some grade of esophagitis, as did 102 of 156 patients in the sequential group. Nausea/vomiting of grades 1-4 was experienced by 138 patients in both the concurrent and sequential treatment arms. The only significant difference in adverse events was myelosuppression, which was much higher in the concurrent treatment arm ($P=.0001$).³⁷

THE ROLE OF AMIFOSTINE IN NSCLC

The ability of amifostine to reduce treatment-associated toxicities has been assessed in a number of phase 2 and 3 trials involving radiochemotherapy for non-small-cell lung cancer. In a small (N=24) phase 2 trial of patients with stages II, IIA, and IIIB non-small-cell lung cancer, treatment consisted of induction chemotherapy (paclitaxel 225 mg/m² plus carboplatin (AUC concentration time of 6) on Days 1 and 21 with thoracic radiotherapy beginning on Days 42 to 63, to a total dose of 62.4 Gy. Once-weekly paclitaxel 60 mg/m² was delivered concurrently with the radiotherapy. In 12 of these patients, amifostine was added to the therapy: a twice-weekly regimen of 500 mg, with the first infusion immediately before the paclitaxel infusion and the second infusion administered prior to the thoracic radiotherapy. Incidence of grade 3 esophagitis was twice as high (18% vs 9%) in the group not treated with amifostine, while the mean survival time for all patients was 12.4 months.³⁸

In a phase 3 trial of amifostine added to a radiochemotherapy regimen, 62 lung cancer patients were randomized to treatment alone or to treatment plus amifostine (500-mg IV infusion 15-30 minutes prior to treatment on the first 2 days of each treatment week). Toxicities were significantly reduced in the amifostine arm: ≥ grade 3 odonphagia, 30% in the treatment-only arm vs 6% in the amifostine arm; ≥ grade 3 symptomatic pneumonitis, 20% in the treatment-only arm vs 0% in the amifostine arm; neutropenic fever occurred in 40% of the treatment-only arm vs 16% of the amifostine arm. Side effects associated with

amifostine infusion included hypotension, dysgeusia, and sneezing. Median and 2-year survival rates were slightly higher in the treatment-only arm (19.5 months vs 18 months, and 42% vs 39%, respectively), but locoregional control rates and 2-year metastasis-free survival were higher in the amifostine arm (40% vs 46%, and 36% vs 43.7%, respectively).³⁹

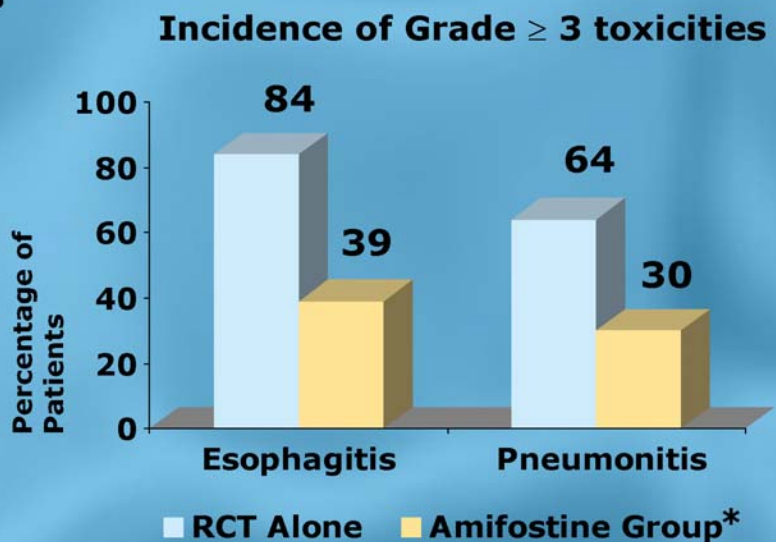
Similar results were reported in a phase 3 trial investigating the effects of amifostine on radiochemotherapy-induced toxicities in 73 patients with previously untreated, locally advanced non-small-cell lung cancer. All patients received either paclitaxel (60 mg/m²) or carboplatin (AUC of 2) once weekly during a 5- to 6-week course of conventional radiotherapy given as 2 Gy/5 days/week to a total dose of 55 to 60 Gy; in addition, 37 patients were randomized to receive a daily IV of amifostine (300 mg/m²). Amifostine significantly reduced the incidence of ≥ grade 3 esophagitis (38.9% in the amifostine arm vs 84.4% in the treatment-only arm, $P < .001$). Similar reductions were observed in the incidence of acute ≥ grade 3 pulmonary toxicity (19.4% in the amifostine arm vs 56.3% in the treatment-only arm, $P = .002$). Addition of amifostine did not appear to interfere with the antitumor efficacy of radiochemotherapy. Combined response rates (complete plus partial responses) were 82.2% in the treatment-only group and 88.8% in the amifostine group ($P = .498$). Twelve patients (33.3%) in the amifostine-plus-radiochemotherapy groups (n=36) were complete responders compared with 5 patients (15.6%) in the treatment-only group (n=32). Four patients in the treatment-only group either withdrew consent or were lost to follow-up.⁴⁰

Randomized Phase 2 Trial Outcomes

Overall response rates

- Amifostine + RCT = 89%
- RCT alone = 82%

*Based on 45 patients at 3 months



Antonadou D et al. *Int J Radiat Oncol Biol Phys.* 2003;57:402-408.

Figure 4

As with administration of amifostine in head and neck cancer, the addition of the cytoprotectant to radiochemotherapy in non-small-cell lung cancer significantly reduced treated-associated toxicities — particularly esophagitis and pneumonitis — compared

with treatment only, without compromising the efficacy of radiotherapy and chemotherapy use alone, sequentially, or concurrently in the treatment of lung cancer (Figure 4).

PELVIC CANCERS: TREATMENTS, TOXICITIES, ROLE OF CYTOPROTECTION

Pelvic cancers include cancer of the cervix, the urinary bladder, the uterine corpus, the ovaries, and the rectum, as well as other cancers. The estimated combined incidence of pelvic cancer in 2005 is approximately 177,000 new cases. The most common types of pelvic cancer are urinary bladder cancer, with an estimated 63,200 cases expected to be diagnosed this year; cancer of the uterine corpus (2005 incidence = 40,880 new cases); and cancer of the rectum (2005 incidence = 40,340 new cases). The virulence, or associated risk of mortality, varies greatly for pelvic cancers. While the estimated number of deaths from uterine corpus cancer is expected to reach 7310 this year, more than 16,000 patients with ovarian cancer (total incidence: 22,220 in 2005) are expected to die of the disease. Treatments for pelvic cancers include surgery, irradiation, chemotherapy, radiochemotherapy, and, for preinvasive cervical cancer lesions, electrocoagulation, cryotherapy, and laser ablation.²⁹

CLINICAL TRIAL DATA: OUTCOMES AND TOXICITIES

Concurrent radiochemotherapy has become the standard of care for locally advanced and/or unresectable pelvic cancers. A review of 12-year survival after treatment of cervical cancer with concurrent cisplatin-based chemotherapy and irradiation found a 30% overall survival advantage for

concurrent radiochemotherapy; nearly 50% of the patients evaluated (n=22) were alive at a median observation time of 12.1 years.⁴¹ A small trial of 39 patients with stage IB through stage IVA cervical carcinoma, in which weekly cisplatin (40 mg/m²) administered concurrently with radiation, reported that, at the median follow-up time of 20 months, 30 patients had demonstrated a complete response, 8 a partial response, and 1 with stable disease.⁴² In a trial evaluating chemotherapy (with cisplatin and docetaxel) administered concurrently with external radical radiotherapy in a range of urinary bladder carcinoma severity — clinical staging cT1, cT2, cT3, and cT4 — complete response rate assessed at 3 months posttherapy was 100% for cT1 patients, 63.6% for cT2 patients, 46.2% for cT3 patients, and 95% for cT4 patients. At the mean follow-up time of 32.2 months, 32 out of 42 patients were still alive, and 27 of these patients showed no evidence of disease.⁴³

As with the use of radiochemotherapy in head and neck and non-small-cell lung cancers, concurrent administration of these treatment modalities in pelvic cancer results in significant side effects and toxicities. In the 12-year survival analysis of cervical cancer patients treated with concurrent radiochemotherapy, all patients at the time of treatment showed acute hematologic toxicities, and some patients developed severe late-bowel toxicity. Even

12 years subsequent to therapy discontinuation, some patients continued to complain of vaginal changes ascribable to the lingering effects of radiation therapy.⁴¹

Among the patients with urinary bladder carcinomas treated with concurrent radiochemotherapy (n=42), there were 5 therapy discontinuations: 3 due to acute gastrointestinal toxicity and 2 resulting from patient noncompliance. Later treatment effects included a sigmoid stricture, a transient small-bowel obstruction, 4 cases of contracted bladder, and 1 death, which resulted from urethral obstruction and impaired renal function.⁴³

THE ROLE OF AMIFOSTINE IN PELVIC CANCERS

Clearly, the side effects and toxicities associated with current levels of combination radiochemotherapy in pelvic cancers can be formidable; moreover, it has been known that some patients would benefit if even higher doses of radiation and/or chemotherapy could be tolerated. In his discussion of a radiation dose-escalation trial involving both chemotherapy and the infusion of amifostine, Myerson observes that the ability to safely administer higher doses of radiation could potentially benefit certain groups of rectal cancer patients, including those whose lesions are likely to remain unresectable even after preoperative chemotherapy.⁸

Cytoprotectants, which could protect against toxicities associated with current levels of treatment and perhaps make even more aggressive regimens more tolerable, would certainly be beneficial in those patients and probably in others with advanced pelvic cancers as well.

The protective role of pretreatment with amifostine has been evaluated in a number of clinical trials involving patients with various forms of pelvic cancer. Kemp et al randomized 242 patients with advanced ovarian cancer to receive chemotherapy alone (n=120; 6 cycles of cyclophosphamide 1000 mg/m² and of cisplatin 100 mg/m² at 3-week intervals) or the same chemotherapy regimen plus pretreatment with IV amifostine 910 mg/m² (n=122). Compared with the group treated with chemotherapy alone, the chemotherapy + amifostine group demonstrated significantly reduced levels of hematologic toxicity (as instanced by grade 4 neutropenia requiring hospitalization or antibiotics (*P*=.005). Severity of neurologic toxicity (defined as peripheral neuropathy, reduced ability to perform daily functions, and ototoxicity) also was significantly reduced among chemotherapy patients who also were receiving amifostine. Amifostine pretreatment did not interfere with tumor response rates to chemotherapy, which were actually higher in the amifostine group (37%) than in the chemotherapy-only group (28%). Amifostine therapy appeared to make a major difference with respect to patient discontinuation of therapy: Twenty-four percent of patients in the chemotherapy-only arm discontinued vs just 9% in the amifostine-plus-chemotherapy group. There was no between-group difference in median survival time.⁴⁴

Similar cytoprotective results were reported in a trial that treated patients with locally advanced cervical cancer treated with concurrent radiotherapy plus cisplatin (n=10) vs patients on the same therapy regimen who were given amifostine 825 mg/m² (n=10) 15 minutes prior to cisplatin infusion. The incidence of grade 3 neutropenia in the amifostine group was half that of the radiochemotherapy-only group, and grade 2 neurological toxicity was 75% more likely in the radiochemotherapy-only group.⁴⁵

TEAM-BASED APPROACH TO CANCER THERAPY: AN EMPHASIS ON CYTOPROTECTION

The standard treatment regimens for a wide range of cancers have become increasingly aggressive, involving high doses of radiation and/or chemotherapy delivered within ever more contracted periods of time. These therapies are now routinely used in combination and even concurrently. Indeed, concurrent radiochemotherapy, often incorporating multiple chemotherapeutic agents and hyperfractionated and accelerated doses of radiation, has become the standard of care in a number of cancers, including head and neck, non-small-cell lung cancer, as well as in a range of pelvic cancers.

In previous decades, chemotherapy and radiation therapy were typically administered at different times, even on different days. Nursing teams from the different treatment modalities thus encountered the patient relatively independently; they did not have to be aware of the details of each other's treatment regimen. In addition, supportive care could also be concentrated on the probable side effects of each treatment independently.⁴⁶ Since concurrent radiochemotherapy involves both modalities of treatment, radiation and chemotherapy, which are often administered on the same day and perhaps in conjunction with the prior administration of a cytoprotectant, coordination between radiation oncology nurses and medical oncology nurses and other personnel is obviously of critical importance to

successful completion of the course of care (Figure 5). Medical oncology nurses need to be aware of the acute side effects and discomforts that may be associated with the administration of radiotherapy; similarly, radiation oncology nurses must understand and be able to respond to the acute toxicities and side effects associated with chemotherapy. Often, both the medical oncology nurse and the radiation oncology nurse will be seeing the same patient, on the same day, as the patient moves from one form of treatment to the other. And, since the concurrent administration of radiotherapy and chemotherapy increases both the likelihood and severity of treatment-associated toxicities and side effects, both medical oncology and radiation oncology nurses need to stand ready to intervene as necessary.⁴⁶

Both sets of nurses must also understand the logistics of the other's treatment modality, and that means being aware of the things that can go wrong, the things that can delay therapy; eg, waiting for blood work, waiting for the pharmacy to mix the chemotherapy, the extra time that might be required to ensure that the patient is properly hydrated, etc. Knowledge of the day-to-day obstacles and frustrations associated with the application of chemotherapy and the application of radiotherapy will help the medical oncology team and the radiotherapy team function more smoothly. Awareness



Uniting Medical and Radiation Oncology Nurses

- A multidisciplinary-team approach to caring for cancer patients and their families is a driving force behind the synergistic approach of these 2 areas of expert care
- Together, these groups provide patient and family support and education regarding a patient's clinical treatment
- In addition, medical and radiation oncology nurses work with other team members to meet patient needs

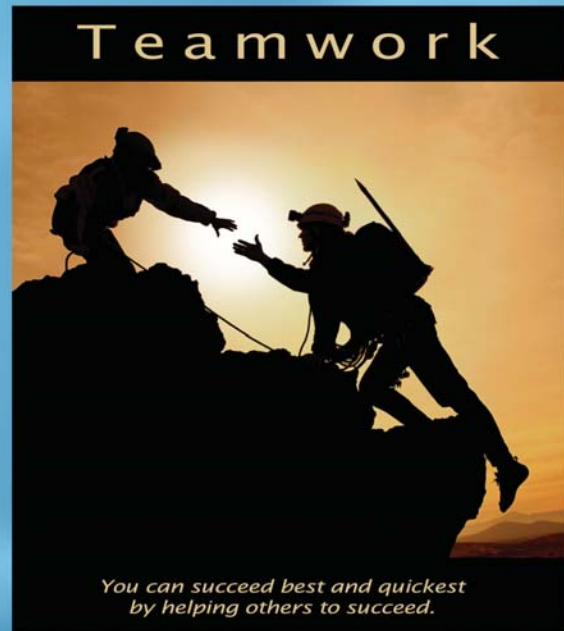


Figure 5

that combination therapy can have a synergistic effect on toxicities and side effects will alert both medical oncologists and radiation oncologists to be prepared to deal with these toxicities proactively. Preventing or ameliorating combination-treatment-associated toxicities can help to keep the patient on track with the therapy, without the necessity of treatment delays, or “breaks,” which can unfavorably affect prognosis.⁴⁶

This team-based approach to cancer care is often easier said than accomplished. An essential component of teamwork is the sharing of responsibilities, but that positive carries the negative danger of responsibility

being abandoned — one part of the team assuming the other part has taken on the task but never checking to see that the task has actually been completed. Alternatively, and equally to be avoided, is one team component taking upon itself all responsibility, thus reducing — or attempting to reduce — the rest of the team to the status of order-takers.

Equally to be avoided is the refusal to accept responsibility for side effects and toxicities associated with combination therapy. It may be that the side effects are of a kind or level of intensity such that neither the medical oncology nurses nor the radiation oncology nurses have seen before. The

temptation might be for each team to blame the other's treatment for these toxicities and side effects. That behavior is likely to confuse the patient, and might even cause the patient to lose confidence in one of the treatment modalities. The result might be a refusal on the patient's part to continue with combination therapy — even though it is the combination of chemotherapy and radiotherapy that is providing the added therapeutic benefit.⁴⁶

Both groups of nurses also need to be familiar with cytoprotective agents that may need to be administered to safeguard against both the acute and longer-term toxicities of radiotherapy and chemotherapy. Both nurse groups need to understand how to administer these cytoprotectants, and they need to be aware of the associated side effects — and what to do to mitigate those side effects. Proper patient management, including hydration, appropriate posture, use of antiemesis, and optimum dosing schedules may diminish or even prevent side effects associated with cytoprotection. Such knowledge and intervention can significantly improve the tolerability of both the cytoprotectant and, accordingly, the cancer therapy as well. Coordination of care, backed by the appropriate knowledge and skills, will increase the ease of use of both more-aggressive cancer therapy and the cytoprotectant. Teamwork and communication can also prevent treatment miscues, such as both the medical oncology nurse and the radiation oncology nurse administering an antiemetic to the patient who has received amifostine and who has been scheduled for both chemotherapy and radiotherapy. There is no additional benefit to the double-dose of antiemetic, just additional patient inconvenience. To facilitate the necessary cross-disciplinary communication, some

nurses advocate the use of an interdepartmental communications tool, a written checklist that shows each team member what has been done, and when.

PATIENT-CENTERED CARE

Compared with traditional models of cancer nursing, the care delivered by a coordinated, integrated nursing team can be of a higher quality, both more efficient and more effective. That is important because cancer patients are different from other patients, both because of the seriousness of their disease and the negative effects — the acute, chronic, potentially permanent, and even lethal toxicities associated with cancer treatments. It is a harsh irony of contemporary cancer therapy that the very treatments responsible for curing or mitigating one kind of cancer actually increase the risk for other kinds of cancer. Many cancer patients know this all too well. The possibility of long-term cancer risk is an additional reason, along with acute side effects, that patients might be leery of aggressive treatments. Thus, the coordinated team approach also must incorporate patient engagement and should attempt to manage not only patient treatment but patient expectations as well.

In the very stressful world of cancer diagnosis and care, it can become easy to forget that the patient, not the treatment paradigm, is the real center of focus. If a patient is not well informed, does not know the appropriate questions to ask, and does not have a good relationship with the treatment team, he or she can wind up feeling not in control of the disease or the cure, leading to increased anxiety and depression and reduced quality of life (Table 4).



Issues to Be Reinforced

- For survivors, cancer isn't forever. The loss of a sense of taste isn't forever. The loss of a voice isn't forever. The blurry vision isn't forever. We can take our lives back and turn them into anything we desire
- I never worried about dying—I worried, and many people do, about living
- Cancer is, many times, more difficult and traumatic on family members than it is on the patient. After all, the only things we have to do are lay down and take another dose of chemo, another surgery, or another session of radiation

Jeff Warren, Cancer Patient

Table 4

Although patients are becoming increasingly more self-educated, they still rely on the physicians and nursing teams as their main source of information. Appropriate communication with patients regarding treatment options, treatment toxicities, and options to reduce these toxicities is critical in helping the patients make informed decisions and to take control of their disease. Equally important is the manner in which this information is delivered. If it is delivered in

an impersonal, negative way, this will only increase the patient's already high level of anxiety. The use of positive, straightforward statements that do not gloss over the seriousness of the disease will go a long way in helping the patient feel positive about the treatment and the future. It is also important to keep a channel of communication open and make patients feel part of the treatment team, so they understand that they are not fighting this disease alone.

As cancer survivor Jeff Warren has said, “Cancer patients will rise to, or sink to, the expectations set for us. Cancer nurses need to understand that most cancer patients will have no framework for understanding either cancer or its treatment. Patients are dependent upon their caregivers — which very often means the oncology and radiology nurses — not only for treatment but for an understanding of

the treatment, both its positive and negative aspects. Make sure that you bring us into the equation” (Table 5). Finally, the team-based approach to cancer care, involving not only the medical oncology nurse and the radiation oncology nurse but also the patient, is so critically important because, quite simply, it improves the odds for success.



We Have a Choice to Make Each Day. . .

- A self-fulfilling prophecy
- When we’re doing our very best, whatever that means at a given moment, we are, by virtue of the fact we’re doing our best, pulling others along in the process
- The tendency for most people is to live each day as if it’s a dress rehearsal for some upcoming “big event,” when, in reality, each day is the big event
- If the only training we do for life is conducted in tailwinds, we’ll never be adequately prepared for life’s inevitable headwinds

Jeff Warren, Cancer Patient

Table 5

SYMPOSIUM AUDIENCE QUESTIONS TO FACULTY PANEL CONCERNING THE USE OF CYTOPROTECTIVE AGENTS

How long should the interval be between administration of amifostine and the start of the cancer therapy?

Amifostine has shown benefit for up to 4 hours after subcutaneous administration. However, maximum benefit will occur between 30 minutes and 1 hour. With IV administration, therapy should begin within 15 to 30 minutes post-administration.

How should one treat site reactions to subcutaneously administered amifostine?

For wheal and flare prevention (ie, red wheal; large, irregular pink skin blotch): use an oral antihistamine approximately 90 minutes prior to the administration of amifostine. Treat existing wheal and flare with hydrocortisone 1% cream.

What about systemic reactions?

Systemic reactions may manifest as a rash or wheal and flare located outside of the injection site and/or radiation treatment field. In other instances, mouth sores may be an early sign of a generalized cutaneous reaction. In these instances, amifostine may need to be withheld until a dermatologist can evaluate the patient.

Is it necessary to premedicate with an antihistamine prior to administration of amifostine?

That may be unnecessary. Use the antihistamine to treat if wheal and flare develops. If the patient is prone to local site reactions, pretreatment with an oral antihistamine may be recommended.

What if the patient presents with a fever?

First, determine the cause of the fever. The patient may be neutropenic, have an infection, or be on another medication that is causing the fever. Blood culture, urinalysis, sputum culture, etc, may help pinpoint the cause of the fever. If it appears that the fever is a result of amifostine, pretreatment with ibuprofen may be beneficial.

Is there a premedication regimen for use of amifostine in chemotherapy and/or radiotherapy?

Hydration is the key; patients on amifostine will need additional fluids. Particularly for patients on combination radiochemotherapy who are receiving amifostine, an antiemetic such as a 5HT₃-receptor blocker is recommended (if one 5HT₃-receptor blocker is ineffective, try another). Dexamethasone may also be used, alone or in combination with a 5HT₃-receptor blocker. For high-risk patients, compazine (another agent for the control of nausea and vomiting) might be added. With low-risk patients, adequate hydration may be sufficient to prevent nausea. Amifostine should not be given if the patient is dehydrated and has a low blood pressure reading. For patients whose hydration status may be doubtful, a useful precaution is the addition of metoclopramide (a remedy for gastroesophageal reflux) 10 mg, taken 3 or 4 times per day, or dronabinol (for nausea and vomiting) 2.5 mg bid. For delayed nausea and vomiting, which may often have an onset hours post-therapy, 1 mg of lorazepam, an anxiolytic, is effective, or use aprepitant 80 mg or 125 mg.

When administering amifostine subcutaneously, is it best to give it in 1 injection or 2?

If you are mixing amifostine with 2.9 cc of normal saline, then you will probably need to administer the dose via 2 injections. By using less saline (2.0, 2.5 cc), it is possible to administer amifostine via 1 injection, but the possibility of local site reactions is increased. Remember to rotate subcutaneous injection sites. Do not rub the site and do not use hot or cold packs or adhesive bandages after the injection.

At some clinics, both oncology personnel and patients have become leery of amifostine; there has been too much hypotension and nausea. What can be done?

It might be a hydration problem. Patients need to be well hydrated. It also may be a dose-delivery issue. The longer-duration infusion associated with the IV seems much more likely to cause hypotension and nausea than the subcutaneous injection. But be aware that 500 mg is the maximum dose that can be administered subcutaneously. Higher doses need to be administered IV.

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Post-Test



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- Cytoprotective agents are administered _____ radiation- and/or chemotherapy.**
 - Immediately after
 - 2 to 4 hours before
 - Immediately before
 - 4 to 6 hours after
- Which of the following is *not* presented as a cytoprotective agent?**
 - Mesna
 - Amifostine
 - Cisplatin
 - Dexrazoxane
- Hyperfractionation theoretically allows for a greater cumulative dose of radiation.**
 - True
 - False
- Chemotherapy is a _____ treatment, while radiotherapy is a _____ treatment.**
 - Local; systemic
 - Systemic; local
 - Hyperfractionated; fractionated
 - None of the above
- Combination therapies can be used _____ for tumor downstaging and _____ to help prevent recurrence.**
 - Postoperatively; preoperatively
 - Sequentially; concurrently
 - Preoperatively; postoperatively
 - None of the above
- Which of the following is *not* a common side effect associated with radiation treatment of advanced lung cancer?**
 - Acute/late-stage esophagitis
 - Acute pulmonary toxicity
 - Late-stage pneumonitis
 - Organ fibrosis
 - All are common side effects
- Amifostine is indicated for _____.**
 - Moderate-to-severe xerostomia associated with postoperative radiotherapy in head and neck cancer
 - Radiation-induced nephrotoxicities in lung and pelvic cancers
 - Cumulative renal toxicity associated with chronic administration of cisplatin
 - A & B above
 - A & C above
- While not FDA-approved, subcutaneous administration of amifostine seems to have major advantages over IV administration.**
 - True
 - False
- In a meta-analysis of 25 clinical trials that compared the addition of chemotherapy to local definitive treatment of head and neck squamous cell carcinoma, the addition of chemotherapy reduced mortality rates by ___% compared with local definitive treatment alone.**
 - 20
 - 11
 - 22
 - 80
- Based on material presented, which of the following is *not* considered one of the most common forms of pelvic cancer.**
 - Urinary bladder cancer
 - Cancer of the uterine corpus
 - Vaginal cancer
 - Cancer of the rectum
- In a study by Kemp et al of patients with advanced ovarian cancer, tumor response rates were _____ in the chemotherapy plus IV amifostine group than in the chemotherapy group only.**
 - Higher
 - Lower
 - About the same
- Patient engagement is an integral part of the team-based approach to cancer therapy management.**
 - True
 - False

Evaluation and Credit Form

Please answer the following questions:

Please answer all questions using a scale of 1 to 5, where: 1 = Strongly Disagree, 2 = Disagree, 3 = Neutral, 4 = Agree, 5 = Strongly Agree

1. Were the following learning objectives achieved?

a) Apply the team-based, patient-engaged approach to improve patient quality of life after chemo- and/or radiation therapy

1 2 3 4 5

Comment: _____

b) Integrate new clinical information on the use of cytoprotective agents and chemotherapeutic/radiotherapeutic toxicity management in multiple forms of cancer, including head/neck, lung, and pelvic

1 2 3 4 5

Comment: _____

c) Describe critical issues regarding dosing administration of cytoprotective agents and patient management

1 2 3 4 5

Comment: _____

2. Overall, do you feel that the activity was balanced and free of bias toward the commercial supporter?

Yes No

Please explain: _____

3. Do you think that you will change your practice as a result of this educational activity?

Yes No

Please explain: _____

4. Which other CNE activities would help you offer more effective or cost-efficient care for your patients?

Comment: _____

5. Would you like to receive e-mail notification of future activities from Medical Education Group LLC?

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Thank you for your comments. Your suggestions will be considered in the planning and development of future educational activities.

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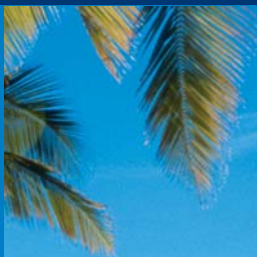
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