ABSTRACT

While substantial advances have been made in the chemotherapeutic treatment of cancer, a quiet revolution has similarly been taking place in the supportive care of patients with cancer. Too often, anemia, neutropenia, nausea and emesis, and mucositis arise after cancer chemotherapy, negatively affecting the quality of life and even morbidity in these patients. Research conducted over the past several years has led to successful evidence-based treatments in supportive care. Recombinant human erythropoietin and a novel erythropoiesis-stimulating protein are now available for the treatment of anemia in patients undergoing cancer treatment. Colony-stimulating factors (including granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor) that have been shown to decrease the incidence and duration of febrile neutropenia are also available. The corticosteroid dexamethasone and, more recently, 5-HT3 antagonists have proven effective in acute nausea, and an NK1 receptor antagonist is now used as an augmentative agent in both acute and delayed nausea. Oral pilocarpine and keratinocyte growth factor (KGF-1 and KGF-2) are showing promise in the treatment of mucositis. This review article discusses the clinical need for supportive care in cancer therapy in terms of risks and complications resulting from anemia, neutropenia, nausea and emesis, and mucositis; describes potential preventive measures; and discusses the advantages and disadvantages of available and emerging treatments for these various chemotherapy-related conditions. (Adv Stud Med. 2004;4(3B):S177-S187)

Over the past decade, numerous studies have made clear the debilitating effects of anemia, neutropenia, nausea and emesis, and oral mucositis on patients undergoing cancer treatment. The impact on health-related quality of life (HRQOL) is virtually indisputable. Some studies have indicated that the presence of these conditions can also undercut successful cancer therapy, reducing survival rates and/or locoregional control.1,2 The pervasiveness of these conditions has even, on occasion, caused the abandonment of once-promising chemotherapies. Awareness of treatment guidelines for anemia, neutropenia, nausea and emesis, and oral mucositis is especially important now because the incidence of cancer is poised to increase dramatically. Statisticians have estimated that by 2010, new cancer cases will approach 1.5 million per year and that in the ensuing 10 years, the growing and aging US population will drive the rate of new cancer cases to 2.5 million per year.3 Cancer is increasingly likely to become a chronic and controllable disease, making the need for effective supportive care for the sequela of cancer a medical imperative.

In response, the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) joined forces to create guidelines...
Risks and Complications of Anemia

Anemia, defined as either a deficiency in red blood cells or hemoglobin that leads to a reduction in the oxygen-carrying capacity of the blood, is common in patients with cancer. In reviewing studies on the occurrence of anemia in patients suffering from hematologic malignancies, Ludwig found that up to 63% suffer from anemia. Yount et al. note that the highest rates of anemia range from 50% to 70% in patients with lymphomas, lung cancer, gynecologic tumors, or genital or urinary tract tumors. Lower prevalence has been found in patients with colorectal or breast cancer. For patients receiving myelosuppressive chemotherapy, Cella et al. note that anemia can occur in up to 100% of patients.

Anemia, Cancer, and Therapeutic Outcomes

Recent studies have indicated that anemia may negatively affect therapeutic outcomes following radiotherapy, chemotherapy, or both. Shasha notes that more than 40 studies have identified pretreatment anemia as an adverse prognosticator in patients receiving radiotherapy or chemoradiation for solid tumors (Table). He notes that the most likely link between anemia and poor locoregional control is that anemia induces or exacerbates hypoxia. Similarly, in a literature review of managing cancer-related anemia, Littlewood noted that low hemoglobin concentration could impair survival by inducing hypoxia or impairing tumor oxygenation, thus increasing the tumor's malignant potential or reducing the effectiveness of chemotherapy, radiotherapy, or both. Littlewood also noted that the decrease in HRQOL caused by anemia can indirectly affect survival or cause a physician to decrease treatment levels.

Several other studies also have indicated that lower hemoglobin levels could be an independent prognostic factor for local control or survival of patients undergoing radiotherapy. These studies point to preclinical evidence suggesting that anemia might also have an adverse effect on survival in patients undergoing chemotherapy. Glaspian, in particular, notes that hypoxic tumor cells seem resistant to chemotherapy, though there is a need to pursue this idea in clinical correlative studies.

Anemia and Quality of Life

Even if treatment of anemia were found to have no implications for locoregional control or survival, the impact of anemia on HRQOL is clear and devastating. Fatigue is the primary symptom, but anemia can also cause cardiovascular complications, dizziness, headache, chest pain, depression, impaired cognitive function, anorexia, nausea, indigestion, sleeping disorders, menstrual problems, loss of libido, dyspnea, and respiratory distress. According to Yount et al., reduced HRQOL occurs because of the patient's reduced functional ability, including reductions in exercise tolerance, ability to work, social interaction, and pursuit of leisure activities.

Table. Postradiation Locoregional Control and Survival in Patients with Head and Neck Cancer, With and Without Anemia

<table>
<thead>
<tr>
<th>Tumor Type/Patient Subset</th>
<th>Tumor-Control Rate (%)</th>
<th>Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 years</td>
<td>5 years</td>
</tr>
<tr>
<td>Glottic squamous cell carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia*</td>
<td>66</td>
<td>NR</td>
</tr>
<tr>
<td>Normal Hb levels</td>
<td>95</td>
<td>NR</td>
</tr>
<tr>
<td>Head/neck squamous cell carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia†</td>
<td>34</td>
<td>32</td>
</tr>
<tr>
<td>Normal Hb levels</td>
<td>52</td>
<td>48</td>
</tr>
</tbody>
</table>

* Hb ≤13 g/dL; †Hb <14.5 g/dL in men and <13 g/dL in women. 
†p < .01 vs patients with anemia; ‡p < .001 vs patients with anemia.
NR = not reported; Hb = hemoglobin.
Reduced HRQOL occurs even in cases classified as mild anemia (hemoglobin levels ≤12 g/dL). Moreover, fatigue can continue to hound patients for months, even years, after treatment completion.

Cella et al noted that using such tools as the Functional Assessment of Cancer Therapy-Anemia (FACT-An) scale, the Linear Analog Scale, and the Functional Assessment of Cancer Therapy–Fatigue (FACT-F) scale, researchers discovered a number of HRQOL implications associated with anemia. One study found that one quarter of patients with hemoglobin levels of 12 g/dL or less reported that they were unable to work, compared with only 8% of patients with hemoglobin levels above 12 g/dL. In general, patients with higher hemoglobin levels have reported significantly less fatigue and other symptoms of anemia, better physical and functional well-being, and high general HRQOL (Figure 1). Nevertheless, many oncologists still undertreat mild to moderate anemia. Some estimate that more than 60% of US patients with cancer who are receiving chemotherapy and have hemoglobin values below 10 g/dL are not treated for anemia.

Unfortunately, as Littlewood notes, many clinicians were trained that anemia need not be treated in patients with malignant disease until it becomes severe. In addition, institutions are hesitant about treating mild anemia because of cost concerns and uncertainties about the treatment's real worth. Littlewood argues that the existing data suggest that treating malignant patients who have mild anemia (∼≤12 g/dL) might be the most cost-effective approach— as well as the most humane.

ANEMIA TREATMENT

To rule out reversible causes of anemia that are not associated with cancer or associated treatment, the NCCN guidelines recommend a complete workup before treatment, including a complete blood count, review of a peripheral blood smear, and possibly, bone marrow examination. Clinicians should also consider evaluation for renal disease, nutritional deficiencies, and evidence of hemolysis and gastrointestinal bleeding.

EVOLUTION IN TREATMENT

For many years, red blood cell transfusion was the only treatment available for patients with cancer and treatment-related anemia. It remains an option in cases of severe anemia that must be corrected immediately, but physicians have become understandably leery of this approach. Blood supplies are low, and legitimate fears of infection, such as HIV, hepatitis, severe acute respiratory syndrome, and West Nile virus, have caused physicians to avoid transfusions when possible. Equally important, the emergence of pharmacologic treatments has enabled clinicians to treat the more common, milder forms of anemia without the risks associated with transfusion. This ability is particularly important given the long-standing notion that these milder forms of anemia could be ignored.

In cases of iron deficiency, iron supplementation is necessary. If iron deficiency is not the cause of anemia, however, 2 agents—recombinant human erythropoietin (rHuEPO) and darbepoetin— are now available to physicians to treat anemia in patients undergoing cancer treatment. Although a few studies have raised concerns about rHuEPO and darbepoetin use is still relatively new (see below), much of the literature indicates both agents are safe and effective means of treating anemia in patients with cancer.

EPOETIN ALFA

Epoetin alfa was the first form of rHuEPO to achieve approval from the US Food and Drug...
Administration (FDA) for treating anemia in patients with cancer. Several studies have demonstrated that epoetin alfa improves hemoglobin levels in a majority of patients, with corresponding improvements in the HRQOL symptoms of anemia. Some in the research community disagree about proper dosage and hemoglobin levels—and a few studies have raised questions about possible negative effects—but there is little disagreement about the efficacy of the treatment. For example, Cella notes that epoetin effectively raises hemoglobin levels and decreases transfusion requirements in 50% to 60% of patients with cancer-related anemia. Studies of its use in conditions involving hematologic malignancies and breast cancer have all found advantages, such as decreased need for transfusions and dramatic improvements in HRQOL attributable to increased hemoglobin levels (Figure 2). The ASCO/ASH guidelines published in 2002—now in the process of being updated—recommend the use of epoetin as a treatment option for patients with chemotherapy-associated anemia and a hemoglobin concentration of 10 g/dL or less. For patients with declining hemoglobin levels between 10 and 12 g/dL, the guidelines recommend that the use of epoetin be determined by consideration of clinical circumstances.

The ASCO/ASH guidelines recommend a starting dose of 150 U/kg given subcutaneously 3 times weekly for a minimum of 4 weeks. Doses can be elevated at that point for those who do not respond; however, if no response is achieved after 6 to 8 weeks, there seems to be no advantage in continuing treatment. At hemoglobin levels of 12 g/dL, the dosage should be titrated to maintain that level or restarted when the level falls again to near 10 g/dL. ASCO/ASH also recognizes the inconvenience of a thrice-weekly regimen and notes that common clinical practice seems to support a weekly dosing regimen (40 000 U per week).

Epoetin alfa has 3 possible disadvantages. The recommendation of thrice-weekly subcutaneous injections is often inconvenient for patients, although it is common clinical practice to address that problem through a weekly dosing regimen. Some have found that response rates to epoetin alfa treatment are variable, and in select trials, a large proportion (40% to 50%) of patients did not respond or had a slow response rate. A few studies have also raised concerns about potential side effects of treatment with rHuEPO. In one study of patients with head and neck cancer and anemia, Henke et al found that despite a rise in hemoglobin levels, patients who received epoetin in a randomized, double-blind, placebo-controlled trial fared significantly worse in terms of disease progression or survival compared with their counterparts taking placebo. Littlewood also notes of anecdotal reports of venous thrombosis in patients whose hemoglobin rises rapidly and to greater than 15 g/dL. Littlewood also notes that pure red cell aplasia, secondary to the development of antiepoetin antibodies, was reported in 13 patients with chronic renal failure, but no such cases have been reported in patients with malignant disease so far. These studies raise important questions but do not discount the overwhelming evidence of the advantages of the treatment.

**Darbepeotin Alfa**

Darbepeotin alfa represents a new generation of erythropoiesis-stimulating proteins. Like rHuEPO, it...
stimulates erythropoiesis, but because it contains additional sialic acid, it has a 3-fold longer half-life and greater in vivo potency. Data suggest that darbepoetin alfa can improve hemoglobin levels and quality of life in patients with cancer who are not receiving chemotherapy or radiotherapy.

Results of recent trials have demonstrated that darbepoetin alfa effectively raises hemoglobin levels with less frequent dosing than epoetin alfa. Two separate studies found that a dose of 3.0 µg/kg of darbepoetin given subcutaneously every 2 weeks achieved a hematopoietic response in 71% of patients and demonstrated a tolerable level of adverse events. Glaspy et al have found similar results (Figure 3). They have also found that treatment with darbepoetin alfa appears to allow flexible dosing—weekly, biweekly, or every 3 weeks—and that preliminary data suggest front-loading/maintenance therapy would further improve dosing efficiency. This flexible dosing and efficiency would suggest advantages for patients and healthcare providers alike. The disadvantage of darbepoetin alfa is that it is a relatively new drug, and its use is not yet widespread. Still, extensive testing has not uncovered any significant drawbacks.

RISKS AND COMPLICATIONS OF NEUTROPENIA

Myelosuppressive chemotherapy commonly leads to neutropenia, which in turn can lead to infectious diseases that can cause death or prolong illness. The true incidence of neutropenia—especially that associated with fever—is difficult to glean from the published literature, and the data available are hard to interpret. Dale et al performed a systematic literature survey of large randomized early-stage breast cancer and non-Hodgkin's lymphoma chemotherapy trials reported between 1990 and 2000. The authors found that the reported rates of grades 3 and 4 leukopenias for the same and similar regimens varied widely (1% to 78% with cyclophosphamide, methotrexate and 5-fluorouracil; 5% to 86% with cyclophosphamide, doxorubicin, and 5-fluorouracil; 27% to 73% with cyclophosphamide, doxorubicin, vincristine, and prednisone) with no readily apparent cause.

It is, however, known that risks increase when the neutrophil count falls below 500/mm³ and become severe below 100/mm³. The risks of febrile neutropenia are especially acute in elderly patients, who will dominate the cancer census over approximately the next 20 years. This risk can contribute to reluctance to use chemotherapy in a patient who might otherwise be a good candidate for treatment.

According to the 2002 NCCN guidelines on fever and neutropenia, except for fever itself, the signs and symptoms of infection often do not appear in the neutropenic patient. NCCN defines febrile neutropenia as neutropenia accompanied by a temperature ranging from 38°C to 38.5°C in the absence of an obvious environmental cause. The NCCN guidelines state that “approximately 48% to 60% of patients who become febrile have an established or occult infection, and roughly up to 20% of patients with neutrophil counts of less than 100/mm³ will develop a bloodstream infection.” Although modern antibiotics and antiviral and antifungal medications have substantially cut the mortality rate directly attributable to these types of infections, significant consequences remain.

Perhaps most importantly, when fever or infection occurs, either cancer treatment must be delayed or dosages must be reduced. Ozer notes that chemotherapy...
apy-induced neutropenia is the primary cause for limiting doses of myelosuppressive chemotherapy. Lyman and Delgado have found that the greatest risk for hospitalization for febrile neutropenia occurred during the first 2 cycles of chemotherapy in patients with non-Hodgkin's lymphoma. These hospitalizations nearly always dictate discontinuation of treatment, and it is now widely accepted that delays in treatment or reductions in dosage may compromise therapeutic outcomes in patients receiving chemotherapy. Several studies have shown that actual relative dose intensity is a significant prognostic factor for survival in diffuse large-cell lymphoma. The delay or reduction in treatment is not the only consequence of febrile neutropenia. Antibiotics bring with them their own widely acknowledged set of risks. The financial cost of hospitalization due to febrile neutropenia and its complications also is considerable.

Many believe that dose-dense therapies, which have begun to show improved therapeutic results in certain forms of cancer, cannot be implemented without some means of maintaining neutrophil counts. This belief remains despite a study by Papaldo et al that found no significant advantage to using granulocyte colony-stimulating factor (G-CSF) in conjunction with a dose-dense chemotherapy regimen of epirubicin and cyclophosphamide.

PREVENTION AND TREATMENT OF NEUTROPENIA WITH COLONY-STIMULATING FACTORS

Given the dangers, costs, and prevalence of neutropenia, it is important to establish when preventive measures are appropriate and to understand the most up-to-date treatments. The most important development in preventing and treating febrile neutropenia has been the approval of colony-stimulating factors that have shown to decrease its incidence and duration.

G-CSF, commonly known as filgrastim, is a hematopoietic growth factor that stimulates neutrophil production. The pegylated version of filgrastim—pegfilgrastim—allows less frequent dosing. Granulocyte-macrophage colony-stimulating factor (GM-CSF), commonly known as sargramostim, is also a hematopoietic growth factor that some speculate is particularly powerful in stimulating the group of white blood cells that attack fungal infections, which have been on the rise over the past 2 decades. There has also been some experimentation with transfusing granulocytes in some leukemia patients. There is little evidence that such treatment is effective, but national trials are ongoing.

Generally, the research community is struggling to define when these growth factors should be used in conjunction with a chemotherapy regimen—especially as a preventive measure against neutropenia—but several studies have begun to define some parameters. Repetto et al noted that patients who have an expected incidence of febrile neutropenia of 40% or greater or who have a high risk of infectious complications should receive primary prophylaxis with hematopoietic growth factors. The authors further state that such patients should receive secondary prophylaxis to avoid recurrence of febrile neutropenia after an initial occurrence, and they note that the cutoff point is related to the cost/benefit tradeoff.

In addition, NCCN and ASCO have both recommended that patients older than 70 years who are receiving moderately myelotoxic chemotherapy should be treated prophylactically with hematopoietic growth factors. Repetto et al also recommended that G-CSF be used as a prophylactic measure to reduce chemotherapy-induced neutropenia, febrile neutropenia, and infections in elderly patients receiving myelotoxic chemotherapy. The group could not find sufficient evidence, however, to recommend GM-CSF; they noted an increased incidence of thrombocytopenia following treatment with GM-CSF. To understand the cost benefits, Bennett and Schumock studied 2 groups of older patients with acute myeloid leukemia; one group received G-CSF, and the other received GM-CSF. Despite limitations in the analysis, they found that the use of both growth factors was worth considering in this population. Lyman and Delgado note that randomized clinical trials have found that G-CSF given prophylactically effectively reduces the incidence of febrile neutropenia. Their study began to define parameters for identifying patients with non-Hodgkin's lymphoma who were at increased risk for febrile neutropenia and, therefore, were proper candidates for the use of prophylactic G-CSF.

Comparisons between the 2 therapies are limited. Stull evaluated studies done by the Eastern Oncology Group (GM-CSF) and the Southwest Oncology Group (G-CSF). Both treatments shortened the duration of severe neutropenia, with GM-CSF significantly decreasing the incidence of life-threatening or fatal infections. Moleski compared the adverse-event profile of the 2 drugs in the treatment of patients undergoing chemotherapy for breast, lung, lymphatic, or ovarian cancer. He found that with the use of GM-
CSF, there was a greater frequency of fevers of unknown origin and a greater number of nonfebrile adverse events, such as diarrhea and other gastrointestinal disorders. In contrast, in a limited study designed to understand the cost comparison between G-CSF and GM-CSF, Whalen et al found that GM-CSF generated cost savings without an increased incidence of adverse effects or negative outcomes.36

**PEGFILGRASTIM**

A disadvantage of G-CSF and GM-CSF is that these treatments require daily subcutaneous injections, typically 5 µg/kg. In response, a pegylated filgrastim (pegfilgrastim) has been developed that appears to produce similar results to filgrastim but requires only a once-per-chemotherapy-cycle dosing regimen (6-mg fixed dose), thus simplifying the process for patients and perhaps decreasing costs. Pegfilgrastim is typically administered 24 hours after chemotherapy, but there is a clear interest in beginning clinical trials to see if it can be administered on the same day, thus offering even more patient and cost benefits.

Several studies demonstrated that pegfilgrastim provides the same neutrophil support benefits as filgrastim. Holmes et al found that once-per-cycle pegfilgrastim (100 µg/kg) was comparable in both safety and efficacy to daily filgrastim in women with breast cancer. Crawford reviewed several studies and found that a single dose of pegfilgrastim administered 24 hours after a complete cycle of chemotherapy provided comparable neutrophil control to daily filgrastim in patients with breast cancer, non-Hodgkin's lymphoma, non-small cell lung cancer, and lymphoma. It also was effective in controlling the duration of neutropenia in the first and subsequent cycles of chemotherapy, when the highest incidence of neutropenia occurs (Figure 4).38

**ANTIBIOTICS, ANTIFUNGAL, AND ANTIBACTERIAL AGENTS**

When a patient becomes severely neutropenic, is neutropenic for a considerable length of time, or is febrile, treatment turns to preventing or counteracting infections. The NCCN guidelines call for immediately determining the potential sites and causes of infection, including a physical examination that assesses vascular access sites (often overlooked and the most common site for infection), the alimentary tract, skin, lungs, sinuses, and ears. The guidelines also remind clinicians to consider reactions to antibiotics and to perform laboratory/radiologic evaluation—a critical piece of a supportive care plan.

Although understandable caution exists regarding the use of prophylactic antibiotics, Vento and Cainelli have suggested that it might be appropriate in patients susceptible to candidal fungal infections.39 Certainly, as soon as an infection appears in a patient with febrile neutropenia, the typical response is to administer empiric antibiotics.40 In addition, NCCN notes that 2 new antibiotics—quinupristin/dalfopristin and linezolid—seem effective against gram-positive organisms and vancomycin-resistant pathogens. The latter are not covered well by broad-spectrum antibiotics, which is why the newer antibiotics are critical to stopping the spread of infection. In addition, given the danger of infection, many oncologists also include antifungal and antibacterial drugs as soon as there is any indication of infection.41

**RISKS AND COMPLICATIONS OF NAUSEA AND VOMITING**

The NCCN estimates that between 70% and 80% of patients receiving chemotherapy experience nausea, vomiting, or both. Nausea and vomiting are among the most common causes of patient morbidity, includ-
ing anorexia, weight loss, esophageal tears, stomach tears, and fatal hemorrhaging, and can cause discon-
tinuation of chemotherapy, a problem that significant-
ly influences patient outcomes. Equally important, nausea and vomiting dramatically affect quality of life. Nausea and vomiting tend to be classified into 2
main categories. Acute nausea and emesis occur within the first 24 hours of chemotherapy, often within min-
utes to several hours. Delayed nausea occurs between 24 and 72 hours after treatment. For the past 20 years, the severity of nausea and vomiting has typically been measured across 3 areas: frequency, duration, and level of distress. The use of scales, such as the Adapted Symptom Distress Scale and the Index of Nausea and Vomiting, have enabled clinicians to adapt treatments to patient needs.

PREVENTION AND TREATMENT OF NAUSEA AND VOMITING

Given the problems associated with nausea and vomiting—and the impact on quality of life—NCCN (among others) now recommends preventive treatment that begins before chemotherapy and should be contin-
ued along with any treatment that induces these symp-
toms. The antiemetic therapy should be administered at the lowest effective dose and should be matched to the level of emetic potential of the chemotherapy and to patient risk factors. Patients should also be screened for other causes of the condition.

ACUTE NAUSEA

There are now several treatments available for pre-
venting and treating acute nausea. Doses vary accord-
ing to the degree of emesis, and the NCCN recommends using the oral forms of these medications if tolerated. The corticosteroid dexamethasone is a long-standing antiemetic that has proven effective for acute nausea in some patients. More recently, the FDA approved the use of 5-HT3 antagonists, which have also proven effective in preventing acute nausea, with only mild side effects. Borjeson et al found that these antagonists, when used in combination with dexamethasone, are the most effective approach to diminish-
ing acute nausea and vomiting. The NK 1-receptor antagonist known as aprepitant is the latest addition to antiemetic medications. Tests have shown it to augment the effects of both dexamethasone and the 5-HT3 antagonists.

Nurse-pioneered interventions seem to have some positive effects on dealing with emesis. Borjeson et al found that an intensive nursing intervention program, which might include improved continuity of care, increased support, more patient education, as well as relaxation training, could improve patient well-being during therapy. Complementary techniques, including biofeedback, acupressure, and acupuncture, also seem to have positive effects, but research is ongoing.

DELAYED NAUSEA

Until about 2 years ago, it was widely assumed that nothing could be done to help patients with delayed nausea. The introduction of aprepitant has changed that, as the drug has proven effective on delayed, cis-
platin-induced emesis when used in combination with the 5-HT3 antagonists, a corticosteroid, or both. Aprepitant represents an important advance in the treatment of nausea. In addition, Passik et al recently completed a study that involved a chart review to understand if olanzapine affected delayed nausea. Although their data must be interpreted cautiously, they did find that the drug demonstrated some poten-
tial for treating delayed nausea.

RISKS AND COMPLICATIONS OF ORAL MUCOSITIS

Most patients undergoing chemotherapy are also like-
ly to develop oral mucositis. Because chemotherapy tar-
gets rapidly dividing cells, the oral mucosa and the mucosa of the entire digestive tract are affected. Localized radiation, especially to the head and neck region, can also result in significant mucositis and/or esophagitis.

The complications associated with mucositis are many, often with a negative effect on treatment course and patient quality of life. Discomfort and pain in the mouth and throat can be severe, dramatically decreasing food and fluid intake, leading to dehydration, malnutri-
tion, and a requirement for narcotic analgesia. Patients report sore throat, mouth ulcers, ulcerations and erosion in the esophagus, ulceration and erosion in the stomach, severe diarrhea with severe electrolyte loss, and hemorrhaging. The breakdown in the mucosal barrier may also compound the compromised antimicrobial defenses that afflict these patients, resulting in a greater risk of infec-
tion. These symptoms may also take a psychological toll; Dodd et al found that outpatients with oral mucositis suffered significantly higher degrees of depression, anger, fatigue, anxiety, and confusion.

Oral mucositis is also associated with discontinuation or reduction of cancer therapy, with a corresponding
downgrade in clinical outcome.47 Patients who experienced mucositis during their cancer treatment have rated it as the most debilitating side effect of therapy.48 Some promising chemotherapy regimens have been abandoned because of severe oral mucositis. Most prominently, a Southwest Oncology Group trial of bone marrow transplants for hematologic malignancies had the best cure rate in the 1990s, but the trial was abandoned because of a 70% incidence of grades 3 and 4 mucositis.

**Prevention and Treatment of Oral Mucositis**

Countless attempts to find treatments for oral mucositis have achieved only spotty success. After some initial enthusiasm about using G-CSF and GM-CSF, clinical trial results indicated these treatments were not effective for mucositis. The search for effective treatments continues, and a few treatments have shown some promise.

Awidi et al found that oral pilocarpine, which has been tested on patients undergoing radiation, high-dose chemotherapy, and graft-versus-host disease, was extremely effective in preventing mucositis and severe mucositis. The study was small but was a double-blind, placebo-controlled, crossover study. There was some evidence of palpitations and tachyarrhythmia as side effects, but these effects did not change the authors’ conclusion that the treatment was safe and effective.49

More recently, researchers have begun to test keratinocyte growth factor (KGF-1 and KGF-2). Administered intravenously before and during chemotherapy or radiotherapy, these factors stimulate proliferation, differentiation, repair, and survival of the early epithelial cells (both epidermal and mucosal), essentially creating a cytoprotective barrier against the effects of the chemotherapy.50,51 KGF-1 has moved ahead fastest, completing a phase 3 clinical trial involving patients receiving bone marrow transplants and phase 2 trials in those with colorectal and head and neck cancer. Benefits included significant reductions versus placebo in incidence and duration of severe mucositis and duration of parenteral opioid analgesic use. Patients were also able to swallow, eat, drink, talk, and sleep significantly better compared with those taking placebo.52 A recent study of KGF-2, however, showed that the agent did not achieve the primary endpoint of a 40% relative reduction in the incidence of Grade 2 to 4 mucositis. No other clinical trials of KGF-2 are under way or planned for any indication.53 There have been some concerns that these treatments might also stimulate tumor cells that harbor the KGF receptor. In vitro studies have not demonstrated stimulation of tumor cells, but investigations are ongoing. As of this writing, KGF-1 is available only through clinical trials.44

As for treatment once mucositis occurs, Malik et al found that there might be some benefit to using tetradecachloride oxide to manage pain.55 Others have tried various solutions that contain some combination of lidocaine, diphenhydramine, and/or aluminum hydroxide/magnesium hydroxide. Effectiveness of these agents was spotty, and patients still needed narcotics to control the pain.

**Conclusion**

The 4 conditions discussed in this article have a demonstrable effect on quality of life and, quite often, on the clinical outcomes of patients with cancer who are undergoing chemotherapy or radiotherapy. Too often, anemia, neutropenia, nausea and emesis, and oral mucositis go untreated or undertreated because clinicians are either unaware of the dangers posed or unaware of advances that have dramatically improved supportive care. These advances are not only therapeutically effective but also often cost effective. Trials continue with some of these treatments, and more advances are expected soon. Such advances demand that supportive care no longer be an ancillary piece of cancer treatment but a full partner with chemotherapy or radiotherapy regimens.

**References**


