

From the Perspective of an Oncology Nurse

A Time for Hope: Promising Advances in the Management of Anemia, Neutropenia, Thrombocytopenia, and Mucositis

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This is a time of great hope in cancer therapeutics and supportive care. Death rates attributed to cancer have declined for 2 consecutive years,¹ due in part to more effective therapies. Supportive care is an integral component of an effective cancer treatment plan that is individualized, minimizes potential toxicities, maximizes therapeutic outcomes, and maintains optimal quality of life for the patient. Anemia, neutropenia, thrombocytopenia, and mucositis are some of the most common toxicities associated with cancer and cancer treatment. They may result in dose reductions, dose delays, premature discontinuation of therapy, and increases in morbidity and mortality. Oncology nursing professionals are vital to the management of these problems.

Anemia

Anemia is a common problem for cancer patients. It may be associated with the underlying disease or result from bone marrow effects of chemotherapy or radiation therapy. Many cancer patients suffer from both. Clinical guidelines²⁻⁴ use similar definitions of anemia (hemoglobin level < 10 g/dL) and provide recommendations for the use of the erythropoiesis-stimulating agents (ESAs) epoetin alfa (Procrit) and darbepoetin alfa (Aranesp). Avoidance of transfusions, improvement in hemoglobin levels, and a reduction of fatigue are the most common primary endpoints for clinical trials evaluating these agents.

Prior studies have effectively documented the association of fatigue with anemia and the negative impact of fatigue on quality of life. The study by Henry et al (page 18) further validates this finding, noting that 79% of the 1,569 cancer patients sur-

veyed rated fatigue as the most common symptom of cancer treatment, and 54% considered it to be debilitating. Patients often discuss these symptoms more freely with the oncology nurse than their oncologist. Awareness of the potential association with fatigue or anemia and patient education for energy conservation, nutritional support, and strategies to improve sleep are important nursing interventions.

Perhaps the most important finding in the studies presented is the similar efficacy and safety profiles for both ESAs with variable dosing regimens (Chen et al; page 12). Both agents are given subcutaneously; epoetin alfa doses of 40,000 U weekly or 80,000 U every 2 weeks and variable doses of darbepoetin alfa (200 μ g every 1–2 weeks, 300 μ g every 2–3 weeks, 500 μ g every 3 weeks as initial therapy) demonstrated similar results and safety (Henry et al, page 16; Canon et al, page 26; Chen et al, page 12; Schwartzberg et al, page 22; and Berger et al, page 8). Customization of ESAs to the individual patient treatment plan and use of fixed dosing offer several options to the patient and provider, allowing convenient but still effective dosing.

Thromboembolic events remain a rare but serious potential adverse event with both ESAs and warrant pretreatment risk assessment and continuous surveillance. Target hemoglobin levels should not exceed 12 g/dL. Levels higher than 12 g/dL have been associated with significant adverse events, including thromboembolic events, heart failure, and death in patients with chronic kidney disease not receiving dialysis; shortened time to tumor progression in head and neck cancer patients receiving radiation therapy; and shortened survival in metastatic breast cancer patients receiving chemotherapy.⁵⁻⁷ A rise in hemoglobin level of >1 g/dL within a 2-week period warrants a dose reduction, and hemoglobin levels should be monitored every 2–4 weeks after initiation of therapy or a dose escalation. Blood pressure should be checked before administration and, if above normal, should be reported to allow treatment before continuing ESA therapy.

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Appropriate use of ESAs with the lowest dose that will gradually increase the hemoglobin and reduce the need for transfusions is recommended to avoid these adverse events. The oncology nurse should be aware of these guidelines, provide patients receiving ESAs with education regarding reportable signs and symptoms, encourage patients to maintain their laboratory appointments, and follow-up with a provider to discuss the results.

The use of epoetin alfa in patients with low-risk MDS has been well established; patients with low-transfusion requirements (< 2 U/month), refractory anemia, and low serum erythropoietin levels (< 500 mU/mL) have been shown to have the best response. Gabrilove et al (page 14), showed that darbepoetin alfa (500 μ g every 3 weeks) was effective in patients with low-risk MDS, with a 56% major erythroid response in those patients who had not received prior ESA therapy and 30% in those who had.

Based on response rates in chronic kidney disease and cancer patients receiving chemotherapy, ESAs have been explored in patients with anemia and cancer not receiving chemotherapy. A phase III, double-blind, randomized, placebo-controlled clinical study using darbepoetin alfa in patients with cancer who were anemic but not receiving chemotherapy did not reduce the need for red blood cell transfusions and showed an increase in mortality in the patients receiving darbepoetin alfa compared with those receiving placebo.^{8,9} In response to this data, the US Food and Drug Administration has released an advisory statement to reinforce the appropriate use of ESAs in only approved indications.

Neutropenia

Chemotherapy-induced neutropenia is the most common dose-limiting toxicity in cancer treatment. It is associated with an increased risk for febrile neutropenia, life-threatening infections requiring hospitalization, additional medications, increased costs, and decreased quality of life. Patients who experience febrile neutropenia may choose to discontinue therapy prematurely due to the anxiety associated with severe toxicities and hospitalization. Pretreatment risk evaluation and effective utilization of granulocyte colony-stimulating factors (CSFs) are clearly outlined in multiple guidelines.¹⁰⁻¹² These guidelines were modified in 2006; previous recommendations for primary prophylaxis were regimens with a 40% or greater risk of febrile neutropenia, and this level has now been reduced to 20%. In addition, patients receiving regimens that are of inter-

mediate (10%–20% risk of febrile neutropenia) or low risk (< 10%) but who have other known risk factors, including age > 65 years, poor nutritional status, poor performance status, combination therapies, extensive prior therapies, hepatic or renal dysfunction, or uncontrolled comorbidities should also be considered for primary prophylaxis.⁷

Several of the studies highlighted in this issue validate these recommendations. The abstracts presented by Maxwell et al (page 46) and Doyle et al (page 34) confirm the value of pretreatment risk assessment and primary prophylaxis and provide useful tools for integration of the guidelines and development of practice-specific implementation plans. With the use of effective risk assessment, Doyle and colleagues saw a significant reduction in the number of hospitalizations for febrile neutropenia from 9.7% to 2.1%, a reduction in hospital days, and improvement in appropriate utilization of primary prophylaxis with CSF, all of which reduce costs. The significant costs associated with febrile neutropenia are effectively described in the analysis by Weycker and colleagues (page 44). Patient education regarding infection prevention, reportable signs and symptoms to allow prompt interventions, and the ongoing evaluation of patients at risk may also reduce the severity of chemotherapy-induced neutropenia and febrile neutropenia. Self-administration capabilities also should be assessed to ensure the patient receives the intended dose. Administration in a clinical setting may be required for safety or reimbursement.

Much like the studies in chemotherapy-induced neutropenia, efficacy and safety in the use of the long-acting CSF pegfilgrastim (Neulasta) are the focus of several studies (Belani et al, page 30; Biron et al, page 32; Pettengell et al, page 40; Ozer et al, page 38; Noga et al, page 36; Saven et al, page 42). Each of these studies confirms the benefit of CSF therapy in reducing the incidence of grade 3/4 neutropenia, particularly in the first cycle of therapy. Similar efficacy and safety profiles for filgrastim (Neupogen) and pegfilgrastim are also described.

Unlike the ESAs, which can be safely administered on the same day of therapy, it is recommended that CSF agents be given 24 hours after chemotherapy administration. For the sake of convenience, many clinical practices allow same-day administration of pegfilgrastim. In a randomized, double-blind analysis of 75 patients with non-Hodgkin's lymphoma, Saven and colleagues (page 42) found the duration of severe neutropenia in

cycle 1 of R-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab [Rituxan]) to be 1 day longer in patients receiving same-day CSF than in patients receiving next-day CSF. The incidence of febrile neutropenia (grade 4) was most common in cycle 1 of therapy, seen in 86% of patients receiving same-day CSF versus 64% in the next-day group. No significant differences were demonstrated in severe adverse events, full dose on schedule, or hospitalization.

Belani and colleagues (page 30) also evaluated same-day versus next-day dosing of pegfilgrastim in 88 patients with non-small cell lung cancer receiving carboplatin and docetaxel (Taxotere), both myelosuppressive agents. The incidence of febrile neutropenia was reduced in both groups and no significant differences in serious adverse events were demonstrated. These trials emphasize the need for further studies with larger cohorts to confirm the safety of same-day dosing with pegfilgrastim, particularly in the first cycle of therapy where the risk of febrile neutropenia is greatest.

Thrombocytopenia

Thrombocytopenia is another common complication of cancer and its treatment. Standards for treatment of these complications rely primarily on platelet transfusions or changes in therapy to reduce the incidence. Oncology nurses can assist the patient by providing instruction for bleeding precautions; avoidance of medication or alcohol, which may precipitate bleeding; and immediate reporting of uncontrolled bleeding or bruising. Safety evaluations, particularly in the elderly patients, are important to avoid trauma or falls.

Several new agents show promise in the treatment of thrombocytopenia associated with idiopathic thrombocytopenic purpura (ITP). Most current treatments for ITP, including steroids, intravenous immunoglobulin, or splenectomy, focus on decreasing platelet destruction. Rituximab provides an exciting alternative as a safe and effective immunosuppressive therapy in ITP. Its use allowed avoidance of splenectomy in 40% of the 60 patients studied by Godeau and colleagues (page 72) and produced durable responses beyond 2.5 years in 14 of 31 patients studied by Patel and colleagues (page 82).

Three new thrombopoietic agents are being evaluated in clinical trials. In a series of studies, AMG 531, a thrombopoiesis-stimulating protein administered subcutaneously, was found to be ef-

fective in increasing platelet counts after a single injection without significant adverse events (Kumagai et al, page 76; Kuter et al, page 78). Similar to effective management of other cytopenias, effective treatment of thrombocytopenia with AMG 531 was associated with improved quality of life (George et al; page 70).

Two oral thrombopoietin receptor agonists, both taken once daily, have also been evaluated. The first, AKR-501, showed a > 50% increase over the baseline platelet count when given to healthy volunteers (Desjardins et al; page 68). The second, eltrombopag, has been shown to increase platelet counts in both healthy subjects and thrombocytopenic patients at doses of 50 and 75 mg and is currently entering phase III trials (Bussel et al; pages 66 and 84).

Thrombocytopenia as a result of underlying bone marrow abnormalities such as MDS has been well described by Kantarjian and colleagues (page 74). Myelosuppression, including thrombocytopenia, is common in active therapies for MDS and may limit effective treatment. Investigation into thrombopoietin therapy may offer additional clinical options for these patients.

Mucositis

Oral mucositis is a serious, painful, and costly toxicity common to patients receiving high-dose chemotherapy and radiotherapy to the head and neck, either in combination with chemotherapy or alone. Most interventions for treatment of mucositis have been focused on pain management, improved nutritional support (enteral and parenteral feedings), and prevention of secondary infections (oral rinses, antibiotics, and antifungals). Understanding the costs associated with these interventions is the focus of several of the highlighted studies.

Isitt and colleagues (page 54) evaluated 75 patients with head and neck cancer receiving chemoradiotherapy or radiotherapy alone. In this group, 76% of the patients developed mouth and throat pain, and 85% were prescribed opioids. Hospitalization was required in 37% of the patients, with 30% of those hospitalizations attributed to oral mucositis. The average length of stay was 4.9 days at an estimated cost of \$23,000. These studies confirm the need to develop effective strategies for prevention and treatment of oral mucositis in patients receiving chemotherapy and radiation therapy for head and neck cancer.

Oral mucositis is often severe in patients un-

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dergoing high-dose chemotherapy for stem cell transplantation. The recent development of cytoprotective agents provides hope for prevention of severe oral mucositis in these patients. Palifermin (Kepivance), a recombinant keratinocyte growth factor, was approved by the US Food and Drug Administration in 2005 based on a pivotal randomized phase III trial indicating a reduction in the duration and severity of oral mucositis in patients undergoing high-dose chemotherapy.¹³ Further validation of these data and refinement of the dosing guidelines are presented in the studies by Shea et al (page 60) and Nasilowska-Adamska et al (page 56). Recent modifications in the commonly used preparative regimens will require further analysis of the cost and benefits of routine use.

Additional agents for prevention of oral mucositis are also in clinical trials. Schuster and colleagues (page 58) have continued to evaluate velafermin, a fibroblast growth factor-20. A single intravenous dose of 0.03 mg/kg of velafermin resulted in the improvement in the incidence of grade 3/4 oral mucositis when compared with placebo. The safety profile was favorable, and continued evaluation at the 0.03-mg/kg dose is planned. ATL-104, a mouthwash that is swallowed and thought to stimulate the growth of epithelial cells, demonstrated a favorable toxicity profile in patients receiving high-dose chemotherapy before autologous peripheral blood stem cell transplant (Hunter et al; page 52). Additional studies are planned to further evaluate efficacy.

Cytoprotective agents alone are not likely to eliminate the need for effective oral hygiene regimens. Patients should be instructed in the use of a mucolytic rinse, such as bicarbonate solution, followed by a normal saline rinse throughout the day. Antibacterial, antifungal, antihistamine, and topical anesthetic agents may be used if indicated. However, chronic use of these agents may be associated with adverse secondary effects.

Summary

The studies highlighted in this issue of *The Journal of Supportive Oncology* provide important and exciting data for the management of anemia, neutropenia, thrombocytopenia, and mucositis. Many of these agents are based on an improved understanding of the physiologic processes and potential therapeutic targets for each of these problems. The challenge for the oncology professional is to integrate these findings with considerations of safety,

efficacy, cost, convenience, established guidelines, and the individual needs of the patient. Toxicities remain an important issue in cancer treatment, and nurses play a vital role in helping patients prevent, treat, and live with therapy-associated adverse events. Integrating recent advances in supportive-care strategies is as important to a favorable outcome as selecting the best available active therapy.

References

PubMed ID in brackets

1. American Cancer Society. Cancer Facts and Figures 2007. Available at: http://americancancersociety.org/docroot/STT/content/STT_1x_Cancer_Facts_Figures_2007.asp. Accessed January 28, 2007.
2. Crawford J, Demetri GD, Michaud LB, et al. Myeloid Growth Factors. NCCN Practice Guidelines 2007; v.1.2007. Available at: http://www.nccn.org/professionals/physician_gls/PDF/myeloid_growth.pdf. Accessed February 20, 2007.
3. Rizzo JD, Lichtin AE, Woolf SH, et al. Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. *J Clin Oncol* 2002;20:4083–4107. [12351606]
4. Bokemeyer C, Aapro MS, Courdi A, et al. EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer. *Eur J Cancer* 2004;40:2201–2216. [15454245]
5. Singh AK, Szczec L, Tang KL, et al; CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006;355:2085–2098. [17108343]
6. Henke M, Laszig R, Rube C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. *Lancet* 2003;362:1255–1260. [14575968]
7. Leyland-Jones B, Semiglazov V, Pawlicki M, et al. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. *J Clin Oncol* 2005;23:5960–5972. [16087945]
8. US Food and Drug Administration. FDA Public Health Advisory—Erythropoiesis-stimulating agents (ESAs): epoetin alfa (marketed as Procrit, Epogen) and darbepoetin alfa (marketed as Aranesp). Available at: <http://www.fda.gov/cder/drug/advisory/RHE2007.htm>. Accessed March 19, 2007.
9. Amgen's letter to healthcare professionals. Available at: http://www.amgen.com/pdfs/misc/healthcare_professionals_letter.pdf. Accessed March 19, 2007.
10. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Myeloid Growth Factors. V.1.2007. Available at: http://www.nccn.org/professionals/physician_gls/PDF/myeloid_growth.pdf. Accessed February 15, 2007.
11. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006;24:3187–3205. [16682719]
12. Aapro MS, Cameron DA, Pettengell R, et al; European Organisation for Research and Treatment of Cancer (EORTC) Granulocyte Colony-Stimulating Factor (G-CSF) Guidelines Working Party. EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. *Eur J Cancer* 2006;42:2433–2453. [16750358]
13. Spielbeger R, Stiff P, Bensinger W, et al. Palifermin for oral mucositis after intensive therapy for hematologic cancers. *N Engl J Med* 2004;351:2590–2598.