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NEW EVIDENCE
In Supportive Care Oncology

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A CANADIAN PERSPECTIVE

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Overview

Between June 30 and July 2 of 2005, the historic city of Geneva, Switzerland played host to the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) 17th International Symposium on Supportive Care in Cancer.

The symposium brought together healthcare professionals from around the world and provided attendees with an exceptional forum for sharing ideas, participating in lectures, and interacting with colleagues. The symposium focused on methods to minimize cancer-induced side effects, and the symptoms and complications of cancer treatment.

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A Canadian perspective provided by Ronald Feld, BSc, MD, FRCPC, FACP

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Dr. Feld has coordinated clinical trials in lung and hepatocellular cancer therapy and in supportive care. His research studies have included a special interest in febrile neutropenia and fungal infections in cancer patients. He has published over 180 manuscripts in peer-reviewed journals as well as numerous book chapters and review articles. In addition to being a member of the Clinical Studies Resource Centre at the Ontario Cancer Institute, Dr. Feld is the Director of Oncology Continuing Medical Education at the University of Toronto. He participates on the editorial boards of a number of oncology and infectious diseases journals and serves as chairman for many international conferences including MASCC 2006.

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Neutropenia: Chemotherapy-induced Myelosuppression

Neutropenia hospitalization affects over 60,000 patients with cancer each year in the United States, at an average cost of US$13,372 per hospitalization and an associated inpatient mortality rate of 6.8%.[1] In fact, a study by Herold and Hieke shows that the management of neutropenia and fever/infection is the most expensive adverse event cost associated with conventional chemotherapy of relapsed low-grade non-Hodgkin's lymphoma. Toxicity costs are substantial for the most commonly used chemotherapy regimens, namely CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), COP/CVP (cyclophosphamide, vincristine, prednisone), and fludarabine therapies. In Canada in 2002, CHOP-associated adverse event costs were more than two-fold greater than drug acquisition costs and more expensive than adverse events associated with COP/CVP or fludarabine.[2]

Myelosuppression and its complications such as neutropenia frequently lead to dose reductions and treatment delays resulting in compromised clinical outcomes. The most serious manifestation of neutropenia, febrile neutropenia (FN), can lead to life-threatening infection, which, in the majority of cases, prompts immediate hospitalization for evaluation and therapy with empiric broad-spectrum antibiotics.

It is imperative, therefore, for clinicians to identify high-risk patients for neutropenic complications to guide the use of more intensive and targeted supportive care. As reported at the 2005 MASCC symposium in Geneva, Crawford et al. demonstrated varying rates of neutropenia and FN according to tumour type and treatment. Of the 2,302 patients treated, most neutropenic events occurred during the first cycle of chemotherapy. The findings revealed that the proportion of patients with neutropenia varied by tumour type: breast (59.3%), non-Hodgkin's lymphoma (52.6%), ovary (43.3%), lung (34.7%), and colorectal (14.6%). In terms of FN, patients with breast cancer were predominant (20.1%) followed by non-Hodgkin's lymphoma (16.0%), ovary (11.7%), lung (11.0%), and colorectal (6.5%). However, colorectal cancer patients constituted the major proportion of those with neutropenia episodes in the first cycle of chemotherapy.[3]

Based on the records of 40,163 adult cancer patients with FN hospitalized between 1995 and 2000, Kuderer et al. validated an original risk model for predicting mortality during hospitalization with FN to assist clinicians in identifying high-risk patients for more intensive supportive care. A risk of mortality of ≥ 10% was predicted in 22% of 16,379 adult cancer patients with FN admitted in 2001–2002, providing the following test performance characteristics: sensitivity 71%, specificity 83%, positive predictive value 29%, and negative predictive value 97%. A low-risk subgroup (23%) was also identified with a risk of inpatient mortality < 1%. The model demonstrated excellent fit ($P < 0.0001$) and high level of discrimination for inpatient mortality ($R2 = 0.81$; C-statistic = 0.85 [95% CL: 0.84, 0.86]; $P < 0.0001$).[4]

As the most life-threatening toxicity of chemotherapy, neutropenia compromises the clinical outcomes of cancer therapy and often leads to hospitalization with accompanying financial burden to the healthcare system and significant mortality. With evidence continuing to demonstrate which chemotherapy regimens and tumour types are most associated with greater rates of severe neutropenia, it is imperative that clinicians proactively identify high-risk patients that will most benefit from intensive targeted supportive care.

References: 1. Caggiano V, Weiss RV, Rickert TS, et al. Incidence, cost, and mortality of neutropenia hospitalization associated with chemotherapy. *Cancer*. 2005 May 1;103(9):1916–24. **2.** Herold M, Hieke K. Costs of toxicity during chemotherapy with CHOP, COP/CVP, and fludarabine. *Eur J Health Econ*. 2002;3(3):166–72. **3.** Crawford J, Dale D, Wolff D, et al. Risk of neutropenic events during the first cycle of systemic cancer chemotherapy: results from a prospective study. *Support Care Cancer*. 2005;13:425 Abstract # 06–049. **4.** Kuderer N, Crawford J, Dale D, et al. A validated risk model for mortality in hospitalized adult cancer patients with febrile neutropenia. *Support Care Cancer*. 2005;13:425–426 Abstract # 06–050.

Dr. Feld's perspective:

In a multinational, multicentre study of more than 700 patients with fever and neutropenia, researchers incorporated and improved upon the pre-existing Talcott scoring system to develop the MASCC scoring system for identifying low-risk febrile neutropenic cancer patients. It was determined that a MASCC risk-index score of ≥ 21 accurately identifies patients at low risk for complications and may be used to select patients for testing therapeutic strategies that may be more convenient or cost-effective.[1]

Naturally, the MASCC scoring system also nicely defines those patients at high risk (< 21) for neutropenic complications. However, the standard hospital-based IV empiric therapy results in an increased financial burden to the healthcare system. While there is evidence that fewer patients experience complications after oral therapy in an outpatient setting, it is important to note that outpatients at risk for neutropenia require careful, regular monitoring. Few centres in Canada have the infrastructure to offer the necessary support.

At our institution, we adhere closely to the ASCO (American Society of Clinical Oncology) guidelines when making treatment decisions. New ASCO guidelines are in development. With patients receiving chemotherapy for hematologic malignancies, we may use prophylactic growth factor treatment for those at high risk of developing neutropenia. Prophylactic treatment is less common for patients with solid tumours. It would be legitimate, however, to consider prophylactic therapeutic approaches if a chemotherapy regimen historically showed a high incidence of neutropenia. Patient-specific and disease-specific risk factors also impact the risk of FN and should be evaluated, as indicated in the new 2005 NCCN (National Comprehensive Cancer Network) guidelines.[2]

As stated in the NCCN guidelines, data from clinical trials and economic models suggest that colony-stimulating factor prophylaxis should be considered in high-risk patients with a 20% or higher probability of developing neutropenia or other neutropenic events that potentially compromise treatment efficacy.[2] We must keep in mind that this economic data is not Canada-specific. While an individual patient risk threshold for FN of ≥ 20% may respresent a clinically effective indicator, it may not be the most cost-effective marker in the Canadian healthcare system.

References: 1. Klastersky J, Paesmans M, Rubenstein EB, et al. The Multinational Association for Supportive Care in Cancer Risk Index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Onc.* 2000 August; 18(16): 3038–3051. **2.** National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Myeloid Growth Factors in Cancer Treatment. Version 2.2005

Managing Chemotherapy-induced Anemia: EORTC Guidelines

Anemia and chemotherapy-induced anemia are common in cancer patients and are associated with risk of transfusions and debilitating fatigue, contributing significantly to a reduced quality of life. Recognizing anemia in cancer patients may help to promote prevention and treatment and improve associated outcomes.

According to Matti S. Aapro, of IMO Clinique de Genolier (Switzerland) and Chair of the MASCC symposium, erythropoiesis-stimulating proteins (ESPs), when used within label, are safe and indicated for all anemic cancer patients, as evidenced by European Organisation for Research and Treatment of Cancer (EORTC).[1]

The EORTC task force conducted a systematic literature review (1996–2003) to produce evidence-based guidelines on the use of ESPs in anemic patients with cancer. Hartmut Link of Medizinische Klinik I (Westpfalz-Klinikum, Kaiserslautern, Germany) summarized the guidelines, which recommend the initiation of ESP therapy at a hemoglobin (Hb) concentration of 90–110 g/L for a target of 120–130 g/L.[1] However, Lyman et al. suggest the initiation of erythropoietic therapy at Hb levels of 100–120 g/L for an increased clinical benefit.[2] Developers of the guidelines also considered the use of less frequent administration schedules. Fewer injections and fewer clinic visits reduces the burden to patients.[3] In this regard, Dr. Link noted the approval of darbepoetin alfa Q3W by the EMEA (European Medicines Agency).[4] Darbepoetin alfa 500 µg Q3W was shown to be comparable (non-inferior)

to 2.25 µg/kg QW with respect to efficacy and safety. Overall, it was well tolerated with no differences in toxicities or thrombotic events observed between the groups.[3] Since chemotherapy is typically administered every three weeks, the administration of darbepoetin alfa Q3W enables the possibility of synchronizing ESP therapy with chemotherapy cycles and may simplify the treatment of chemotherapy-induced anemia.[5]

For optimal prevention and treatment as well as improved associated outcomes, it may be beneficial to establish a flexible dosing strategy with ESPs given the emerging trend toward dose-dense (DD) regimens in an attempt to improve disease-free survival. New evidence presented at the 2005 MASCC symposium demonstrated that DD therapy given every two weeks (Q2W) with adriamycin/cyclophosphamide (AC) followed by paclitaxel in a longitudinal study of symptom patterns in 192 women undergoing adjuvant chemotherapy for breast cancer — 32 women receiving DD and 160 receiving standard regimen with AC +/- paclitaxel — showed higher rates of Grade 1 and 2 anemia during DD chemotherapy despite usage of epoetin or darbepoetin alfa in the DD arm. In fact, by AC cycle 4, Hb was lower in women who received DD chemotherapy (11.42 vs. 11.83; P=0.002), and remained so at the first cycle of taxane for those who received this chemotherapy (10.67 vs. 11.48; P=0.005; N=76). There were higher rates of anemia observed in DD compared to standard chemotherapy for early-stage breast cancer, underscoring the need for earlier intervention with erythropoietic agents.[6]

Although there is no evidence to support the use of ESPs with the aim of improving response to treatment in anemic patients with cancer, the two major goals of improved quality of life and prevention of red blood cell transfusions are best accomplished through less frequent administration schedules — with fixed doses within reasonable limits of body weight.

References: 1. 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 Oct;40(15):2201–16. **2.** Lyman G, Rossi G, Glaspy J, et al. Does the treatment of mild anemia result in improved clinical outcomes? Examining the benefits of early erythropoietic intervention in patients with chemotherapy-induced anemia (CIA). *Support Care Cancer.* 2005;13:410 Abstract # 02–009 **3.** Canon J-L, Vansteenkiste J, Bodoky G, et al. Darbepoetin alfa administered once every 3 weeks (Q3W) is effective for treating anemia in patients receiving multicycle chemotherapy: results of a randomized, double-blind, active-controlled trial. *Support Care Cancer.* 2005;13:408 Abstract # 02-004. **4**. Ludwig H, van Belle S, Barrett-Lee P, et al. The European Cancer Anemia Survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anemia in cancer patients. *Eur J Cancer.* 2004;40:2293–2306. **5.** Boccia R, Silberstein P, Tchekmedyian S, et al. The effectiveness of darbepoetin alfa 300 mcg every 3 weeks for the treatment of chemotherapy-induced anemia in cancer patients. *Support Care Cancer.* 2005;13:407–08 Abstract # 02-003 **6.** Stricker C. Women receiving dose-dense adjuvant breast cancer chemotherapy experience higher rates of anemia. *Support Care Cancer.* 2005;13:410 Abstract # 02-010.

Dr. Feld's perspective:

The management of anemia in Canada does not directly parallel that of Europe. However, the EORTC evidence-based guidelines serve as an important resource that may assist in updating the Canadian guidelines.

While Canadian guidelines and practices vary slightly across the country, most provinces recommend the use of ESPs (epoetin alfa or darbepoetin alfa) for cancer- and chemotherapy-induced anemia when Hb levels decline below the level of 100 g/L. For those patients with less severe anemia (100–120 g/L), the decision to initiate ESP therapy or wait until the levels drop below 100 g/L should be considered case by case and depend on the severity of the patient's symptoms. Hb levels can be raised to a target concentration of 120 g/L. Ideally ESP dosage should be adjusted to maintain this level or restarted if levels fall close to 100 g/L. There is insufficient evidence to support raising the Hb levels above 120 g/L.

While darbepoetin alfa Q3W is not yet approved in Canada, the findings at the 2005 MASCC symposium with respect to efficacy and safety of Q3W dosing present interesting new evidence. The possibility of synchronizing ESP therapy with chemotherapy cycles and simplifying the treatment of chemotherapy-induced anemia would obviously benefit the patient.

Evidence shows that erythropoietic agents are effective in improving quality of life and reducing red blood cell transfusion requirements. Further study is necessary to investigate whether ESP therapy can improve treatment response in anemic patients with cancer.

Mucositis Management: Guidelines and Beyond

Mucositis is a frequent, often dose-limiting complication of systemic and high-dose chemotherapy, radiation for head and neck cancers, total body irradiation, hematopoietic stem cell transplantation (HSCT), and combined modality therapy. Development of oral mucositis is associated with significant increases in opioid and topical analgesics, gastrointestinal (GI) tubes, and weight loss, entailing additional hospitalization and increased cost.[1,2] Despite the improvements in the management of other chemotherapy-related toxicities, the incidence of mucositis is increasing. GI mucositis is associated with both bleeding and infection. Oral mucositis is one of the most debilitating side effects with significant increase in days with fever, risk of infection, additional days of total parenteral nutrition, use of intravenous narcotic analgesics, total hospital charges, and 100-day mortality in high-dose chemotherapy associated with HSCT. Increased frequency and intensity of oral mucositis are seen in HSCT recipients who receive total-body irradiation for conditioning as well as conditioning regimens that include melphalan and administration of 5-flurouracil (5-FU), with or without leucovorin. Radiotherapy to the head and neck or to the pelvis or abdomen is associated with an increased incidence of Grade 3 and Grade 4 oral mucositis in over 50% of patients — long after the conclusion of therapy. It is imperative therefore, to establish timely and appropriate prevention and treatment guidelines for complete response.

Clinical Practice Guidelines for Care of Patients with Oral Mucositis

The MASCC/ISOO mucositis expert panel suggests the use of oral care protocols that include patient education in an attempt to reduce the severity of mucositis from chemotherapy or radiotherapy (level of evidence, III; grade of recommendation, B). While palliation of mucositis and acute oral pain is an important component of patient care, other approaches include the use of systemic analgesics and other individual agents, palliative mixtures of agents (sometimes called magic or miracle mouthwash), coating agents, and topical anesthetics/analgesics. Pain management should include accepted approaches for the use of nonopioids, opioids, adjuvant medications, and assessment tools. Depending on the individual patient population, oral, transmucosal (oral and rectal), and transdermal routes, as well as various intravenous approaches (continuous infusion, bolus, and PCA) are recommended. A list of key guidelines for oral mucositis is summarized below (Table 1).

Table 1. Summary of Clinical Practice Guidelines for Care of Patients with Oral Mucositis[3,4,5]

Foundations of care
1. Oral care protocols including patient education in an attempt to reduce the severity of mucositis from chemotherapy or radiation therapy
2. Patient-controlled analgesia with morphine as the treatment of choice for oral mucositis pain in patients undergoing HSCT
Radiotherapy: prevention
3. Use of midline radiation blocks and three-dimensional radiation treatment to reduce mucosal injury
4. Benzydamine for prevention of radiation-induced mucositis in patients with head and neck cancer receiving moderate-dose radiotherapy
5. Chlorhexidine contraindicated for prevention of radiotherapy-induced oral mucositis in patients with solid tumors of the head and neck
Standard-dose chemotherapy: prevention
6. Oral cryotherapy (30 min) in patients on bolus 5-FU chemotherapy
7. Oral cryotherapy (20–30 min) in patients on bolus edatrexate chemotherapy
8. Acyclovir and its analogues contraindicated for mucositis prophylaxis
Standard-dose chemotherapy: treatment
9. Chlorhexidine contraindicated for established oral mucositis
High-dose chemotherapy with or without TBI plus HSCT: prevention
10. Pentoxifylline contraindicated for prevention of mucositis in patients undergoing HSCT
11. LLLT to reduce the incidence of oral mucositis and its associated pain in patients on high-dose chemotherapy or chemoradiotherapy before HSCT
12. Kepivance™ (palifermin) a recombinant human keratinocyte growth factor indicated to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support

HSCT: hematopoietic stem cell transplantation; 5-FU: 5-fluorouracil; TBI: total-body irradiation; LLLT: low-level laser therapy.

The 2005 MASCC updated guidelines, presented by Dorothy Keefe[4] of Royal Adelaide Hospital (Adelaide, Australia), recommend the use of Kepivance™ (palifermin) in patients with hematological malignancies receiving high-dose chemotherapy with or without total body irradiation in autologous stem cell transplantation. Kepivance™ does not interfere with the anti-tumour activity of 5-FU, Erbitux™ (cetuximab), or Avastin® (bevacizumab). In contrast, competing products such as amifostine, glutamine and antibiotics were ruled out.

References: 1. Elting LS, Cooksley C, Garden AS. Clinical outcomes of radiotherapy-induced oral mucositis among patients with head and neck cancers. *Support Care Cancer*. 2005;13:443 Abstract #15-096. **2.** Elting LS, Cooksley C, Garden AS. Economic burden of radiotherapy-induced oral mucositis among patients with head and neck cancers. *Support Care Cancer*. 2005;13:443 Abstract #15-097. **3.** Rubenstein BE, Peterson DE, Schubert M, et al. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. *Cancer*. 2004;100:S9:2026–2046. **4.** Keefe, D. The management of mucositis in 2005. Available at: http://www.touchbriefings.com/pdf/1432/Keefe.pdf. 5. Spielberger R, Stiff P, Bensinger W, et al. Palifermin for oral mucositis after intensive therapy for hematologic cancers. *NEJM*. 2004;351:2590–2598.

Dr. Feld's perspective:

With cancer treatment there are two major causes of oral mucositis: radiation and chemotherapy. When receiving radiation treatment, the risk of mucositis increases depending on where the radiation is directed and whether it affects the salivary glands. Complications due to chemotherapy are regimen dependent. A number of regimens do not cause mucositis, but there are some, particularly with solid tumours, that lead to severe mucositis.

Mucositis is a debilitating side effect of cancer and its treatments, especially in the area of nutrition. Food not only provides nutrition, but is also an essential part of real life and a quality of life indicator. When patients suffer from mucositis, they experience a great deal of discomfort and often can't eat. People get very upset when they can't eat. Furthermore, family members become frustrated because they cannot provide comfort, which for many is defined in part by food.

Unlike other cancer- and chemotherapy-induced symptoms, the visibility of mucositis allows for easy diagnosis. The importance of the grading and assessment systems becomes apparent when analyzing studies. Guidelines help researchers with the evaluation of treatments, for example, whether medication A is superior to B, or equivalent. In this respect, the 2005 MASCC mucositis guidelines update have put a science to how we diagnose and treat mucositis. Currently there are no Canadian guidelines for mucositis. In the absence of Canadian guidelines, the Pharmacy & Therapeutics (P&T) Committees will create their own.

It is noteworthy that, over the last three years, the MASCC study groups about mucositis have been well attended. They are always packed, indicating that, while there have not been many new developments in the area of mucositis, it is generating considerable attention. The approval of palifermin in Canada offers a welcome addition to supportive care in cancer. With the 18th Annual MASCC/ISOO International Symposium being held in Toronto in June 2006, we will be discussing this again in the near future.

About New Evidence

New Evidence in Supportive Care Oncology provides Canadian specialists in the area of oncology with timely, credible, and objective scientific data, focusing on supportive care issues from international oncology conferences. Unique to *New Evidence in Supportive Care Oncology* is the provision of a Canadian perspective on selected abstracts and presentations from renowned opinion leaders. *New Evidence in Supportive Care Oncology* is published quarterly. Our upcoming issues include: ICML 2005 and ASH 2005.

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