

# NEW EVIDENCE

A C A N A D I A N P E R S P E C T I V E

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OF NEW EVIDENCE IN ONCOLOGY

**ASCO** June 2–6, 2006  
Atlanta, Georgia

**42<sup>nd</sup> Annual Meeting  
American Society of Clinical Oncology**

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Aromatase Inhibitors Continue to Show Promise in Sequential Studies  
Focus on the Elderly

**MASCC** June 22–24, 2006  
Toronto, Canada

**Multinational Association of Supportive Care in Cancer  
18<sup>th</sup> International Symposium**

Toxicities Associated with Targeted Therapies  
Current and Future Developments of Mucositis Therapy  
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# ASCO

**42<sup>nd</sup> Annual Meeting**  
**American Society of Clinical Oncology**

## Overview

The 42nd annual meeting of the American Society of Clinical Oncology (ASCO), held from June 2 to 6, 2006, brought together over 35,000 health-care practitioners to learn about the major research and treatment advancements in clinical oncology research. The packed four-day program consisted of oral and poster presentations as well as education programs in the areas of breast, gastrointestinal, genitourinary, gynecologic, and lung cancers as well as supportive care.

Highlighted in this issue of *New Evidence in Oncology* are some of the cutting-edge data reported during ASCO 2006 regarding supportive care.

## A Canadian perspective provided by

**Natasha B. Leigh, BSc, MSc, MD**



Dr. Natasha Leigh is a medical oncologist at the Princess Margaret Hospital, and Assistant Professor in the Department of Medicine at the University of Toronto. She is involved in clinical studies of novel agents for the treatment of lung and breast cancer, and has been a member of the Lung Disease Site Group Executive in the National Cancer Institute of Canada Clinical Trials Group. Dr. Leigh has served on committees including the Royal College of Physicians and Surgeons of Canada Credentials Committee, the University of Toronto Undergraduate Medical Education Committee, and is currently a member of the University Health Network Research Ethics Board, National Cancer Institute of Canada Grant Review Panel (I), and Canadian Breast Cancer Foundation Grant Review Panel (Ontario Chapter).

## New Guidelines for the Prevention of Chemotherapy-Induced Neutropenia

Lesley McKarney

Neutropenia, which increases the risk of potentially fatal infections, is one of the more serious manifestations of chemotherapy-induced myelosuppression. Myelosuppression, historically, is managed with a dose delay or a dose reduction in the next scheduled cycle of chemotherapy, to allow hematopoietic activity to recover. However, such modifications to the chemotherapy regimen result in a lower relative dose intensity (the ratio of delivered dose intensity to planned dose intensity), which may compromise long-term survival.<sup>1</sup>

Numerous studies have suggested risk factors that may predict the development of chemotherapy-induced febrile neutropenia or its complications, which may be disease-, patient-, or treatment-related.<sup>1,2</sup> Thus far, risk models for neutropenic complications that have been developed have been based on retrospective analyses and have defined neutropenic complications in various ways.<sup>1</sup> A prospective registry has been set up by Dr. Gary Lyman and colleagues in order to further identify pretreatment and early treatment risk factors for subsequent neutropenia.<sup>3</sup> The primary goal of this registry, which has recorded the details of approximately 3,600 patients treated at 117 practice sites in the United States, is to develop and prospectively validate risk models for the occurrence of severe neutropenia (SN) and febrile neutropenia (FN). In addition, the registry will also provide further information on the risk and timing of neutropenic complications in patients treated with systemic chemotherapy. The first complete data analysis derived from this registry was presented at the ASCO annual meeting in June 2006. The data confirm that while the risk of SN and FN varies among cancer types and treatments, the risk is greatest in the first cycle, ranging from 5.5–30.2% and averaging 18.5% across tumour types. Clinical risk factors for first-cycle neutropenic complications included a history of recent surgery or chemotherapy ( $P=0.044$ ); certain comorbidities (e.g., low platelets [ $P=0.004$ ], diabetes [ $P=0.023$ ] and reduced glomerular filtration rate [ $P=0.013$ ]); concomitant medications (e.g., concurrent antibiotics [ $P=0.023$ ] or phenothiazines [ $P=0.006$ ]); type of cancer ( $P<0.0001$ ), particularly lung cancer and non-Hodgkin's lymphoma; and the intensity of chemotherapy (e.g., anthracycline-based regimens [ $P<0.0001$ ]).

The advent of myeloid growth factors provided an alternative to dose reduction or delay strategies to prevent chemotherapy-induced neutropenia (CIN). The benefit of the colony-stimulating factors for shortening the duration and severity of neutropenia in patients receiving cyclic myelosuppressive chemotherapy has become increasingly evident.<sup>1</sup> The CSFs most frequently studied have been granulocyte colony-stimulating factor (G-CSF, filgrastim) and granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim). More recently, a pegylated preparation of filgrastim (pegfilgrastim) has been introduced into clinical practice.<sup>4-6</sup> Furthermore, prophylactic CSF has been demonstrated to reduce the risk of FN, the number of documented infections, and the need for dose reduction or treatment delay, often enabling the delivery of full dose intensity.<sup>3,7,8</sup>

While clinical trials have demonstrated that CSFs are safe and well tolerated, they have not been designed to assess the impact of CSFs on survival.<sup>1</sup> When used inappropriately, CSFs can substantially add to the cost of care.<sup>1</sup> However, the cost of caring for patients with FN should also be balanced against the cost of administering CSFs. A retrospective cohort study presented at ASCO suggests that while the costs of FN have been reported to be substantial, these costs were underestimated because of a failure to account for follow-up care. Weycker and colleagues collected data from a U.S. health-care claims database on 746 adult cancer patients who received a course of chemotherapy between 2001 and 2003.<sup>9</sup> Patients who developed FN within a chemotherapy cycle were further identified based on hospitalization for neutropenia, fever and/or infection, and related health-care charges, both inpatient and outpatient, were tallied. In all, costs related to the development of FN were substantially higher, at U.S. \$40,928 (95% CI \$28,783–\$62,586) per case versus U.S. \$3,933 (\$2,890–\$5,119) for those patients who

did not develop FN. Moreover, follow-up care subsequent to initial hospitalization accounted for \$9,872 (or 27%) of the higher FN-related charges among cases.

The cost-effective use of CSF depends on the oncologist's ability to identify those patients who are most likely to benefit from it.<sup>1,2</sup> Clinical practice guidelines for the use of CSFs were developed by ASCO to assist decision-making regarding CSF use.<sup>10</sup> Based on the original randomized trials that led to the approval of filgrastim,<sup>11,12</sup> the ASCO guidelines committee recommended first-cycle use of CSFs only in patients receiving chemotherapy regimens associated with more than a 40% risk of febrile neutropenia.<sup>10</sup> This recommendation was based on studies that showed a >40% risk of FN in the control group and demonstrated almost a 50% reduction in risk in the group receiving filgrastim.<sup>13</sup> An economic analysis based on a limited assessment of the direct medical costs of hospitalization for febrile neutropenia at a single institution supported the initial recommendations.<sup>14</sup> However, when current hospitalization costs were studied both within single-institution and in multi-institution studies, this economic model provides threshold risk estimates closer to 20%.<sup>14</sup> In addition, at the time the original guidelines were drafted, the benefit of CSFs in low-risk patient populations was unknown. In recent years, randomized controlled trials have demonstrated the clinical benefit of CSFs in lower-risk populations. The new ASCO CSF guidelines, first presented at the annual meeting and then published in the *Journal of Clinical Oncology* in July, 2006, reflect current data.<sup>15</sup>

The most notable update in the new guidelines is the committee's recommendation of routine use of primary prophylactic CSF in the first and subsequent cycles in patients with a greater than 20% risk of FN.<sup>15</sup> The revised guidelines are now consistent with recent data from the Vogel trial<sup>8</sup> in which pegfilgrastim was shown to significantly reduce neutropenic complications in patients in whom the risk of FN was 10–20%. In that trial, a placebo-controlled study using CSF support with pegfilgrastim was performed in women receiving 100 mg/m<sup>2</sup> of docetaxel in the setting of breast cancer. Pegfilgrastim reduced the incidence of FN by 94%, FN-related hospitalizations by 93%, and IV anti-infective use by 80% when administered in the first and subsequent cycles.

In addition, the guidelines now state that patients  $\geq 65$  years of age with diffuse aggressive lymphoma who are undergoing CHOP or more aggressive chemotherapy regimens should also be given prophylactic CSF to reduce the risk of developing FN and infections.

The new ASCO guidelines are in line with those recently released by the National Comprehensive Cancer Network (NCCN).<sup>16</sup> The NCCN convened an expert panel in 2005 to review current clinical data, including the trial published by Vogel *et al.*,<sup>8</sup> in order to formulate its own set of guidelines for the use of CSFs to prevent CIN.<sup>2</sup> The NCCN guidelines also recommend prophylactic CSF use in patients at high-risk for FN (>20%); however, for patients at low risk (<10%), CSF use is discouraged. In the intermediate risk group of 10–20%, the decision to use CSF should be made on a case-by-case basis and should align with treatment goals and patient risk factors.

Interestingly, a cost-effectiveness model that evaluates the economic impact of G-CSF prophylaxis based on the model developed by Lyman and colleagues<sup>3</sup> suggests that G-CSF support in breast cancer patients receiving adjuvant chemotherapy could be cost-effective at an overall FN risk of 10%, far less than the 20% now recommended by the ASCO and NCCN guidelines.<sup>17</sup> The study, conducted by Dale and colleagues, analyzed data on 974 consecutive breast cancer patients receiving adjuvant chemotherapy, and compared the clinical and cost impact of G-CSF prophylaxis in high-risk patients with no G-CSF support, primary prophylaxis, and secondary prophylaxis. The observed decrease in risk of FN with prophylactic G-CSF use and the clinical risk factors identified in this study were similar to those found by Lyman *et al.*<sup>3</sup> The cost of primary prophylaxis was consistently lower than that of secondary prophylaxis. Primary prophylaxis was also more cost-effective than no prophylaxis at FN risk >18%, while the model outperformed both strategies at an FN risk >10%.

Ultimately, with the new data from randomized controlled trials and the decision to set the clinical threshold of benefit at an FN rate of 20%, the ASCO Update Committee made a point of recommending that CSFs “should be used when indicated for clinical reasons, not economic ones.”<sup>15</sup>

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## Aromatase Inhibitors Continue to Show Promise in Sequential Studies

Lesley McKarney

Over the past decade, there has been a new sense of excitement at international oncology research meetings, followed by ripples in the clinical world, as the new agents based on our understandings of molecular pathways controlling cancer formation are emerging in the clinic. Standards of care for the treatment of breast cancer have improved with the introduction of new, novel therapeutics (such as aromatase inhibitors [AIs], trastuzumab, and novel taxanes) that are more effective and less toxic than the conventional chemotherapy they replaced. What is clear is that these new agents challenge not only treatment paradigms but also the way in which toxicities are monitored.

About 22,000 women are diagnosed with breast cancer in Canada each year.<sup>1</sup> Of these, approximately 40% will be postmenopausal and have tumours that express estrogen receptors (ER) or progesterone receptors (PR). For these women, the AIs (anastrozole, letrozole, and exemestane) are challenging tamoxifen as the hormonal standard, and are now the leading agents for treating postmenopausal women with ER-positive metastatic breast cancer.<sup>2-4</sup> These drugs have proven particularly useful for patients in whom tamoxifen is contraindicated or who are intolerant of tamoxifen.<sup>2</sup>

New data from two previously reported clinical trials, the Intergroup Exemestane Study<sup>4</sup> and National Cancer Institute of Canada (NCIC) MA.17<sup>3</sup> announced at the ASCO 2006 meeting confirm that postmenopausal women who switch from tamoxifen to one of the AIs may experience significant benefits in preventing a recurrence of their breast cancer.

The Intergroup Exemestane Study (IES), which compared exemestane to continued tamoxifen, provided data on greatly improved disease-free survival for postmenopausal women with endocrine-responsive disease who switched to exemestane.<sup>5</sup> Exemestane was originally approved in Canada in 2000 for the treatment of postmenopausal women with advanced breast cancer whose tumours no longer responded to tamoxifen. In 2006, Health Canada extended its indication to include treatment of postmenopausal women with estrogen-receptor positive early breast cancer following two to three years of tamoxifen, for a combined total of five consecutive years of adjuvant therapy.

The IES was a randomized phase 3 double-blind trial that enrolled 4,742 postmenopausal women in 37 countries and 20 cooperative groups. Approximately half of these women were randomly assigned to receive exemestane

while the remainder continued on tamoxifen for the full five years. Participants had received an average of 2.4 years of tamoxifen therapy and were disease-free prior to being switched to exemestane. At the median follow-up of 4.8 years, overall survival improved in women who switched to exemestane, with a 15% reduction in deaths (222 deaths on exemestane versus 261 deaths on tamoxifen; HR 0.85, 95% CI 0.71–1.02; P=0.08). There was also a significant improvement of 24% in the primary outcome of disease-free survival (DFS) in the exemestane group (354 versus 454; HR 0.76, 95% CI 0.66–0.88; P=0.0001). This is a significant improvement on the initial difference of 4.7% DFS reported at 30.6 months.<sup>4</sup> Of the exemestane group, 17% had a reduction in the risk of distant recurrence and a 50% lower incidence of cancer in the other breast (Table 1).

Outcomes	Exemestane (n=2,352)	Tamoxifen (n=2,372)
Patients completing therapy (%)	71	79
Events contributing to DFS (n)		
Contralateral breast cancer	18	35
Distant recurrence	214	256
Local recurrence	49	68
Intercurrent deaths (cardiac, vascular, and other cancers)	73	95
<b>Total DFS (any first event)</b>	<b>354</b>	<b>454</b>

Exemestane therapy was well tolerated and had an acceptable safety profile. Women taking exemestane experienced side effects such as hot flashes, fatigue, joint pain, headache, insomnia, and increased sweating. However, women who stayed on tamoxifen had more thromboembolic events (P=0.006) while on treatment and more serious gynecologic events (P<0.001) during and after treatment than women who switched to exemestane. Women in the exemestane group, however, experienced more bone fractures in the follow-up period (P=0.003). The incidence of cardiac side effects (myocardial infarctions, angina, or cerebrovascular accidents) was similar between the two groups.

The landmark NCIC MA. 17 trial involved more than 5,100 postmenopausal women with early-stage breast cancer. All trial participants had taken tamoxifen for approximately five years and remained disease-free for three months after completing tamoxifen treatment. The participants were randomly assigned to receive letrozole or placebo. The first analysis, conducted at a median follow-up of 30 months, showed that letrozole reduced the risk of a breast cancer recurrence by 42%.<sup>3</sup> On the basis of these results, letrozole was approved in Canada in 2005 for use in the extended adjuvant treatment of hormone receptor-positive early breast cancer in postmenopausal women who have received approximately five years of prior standard adjuvant tamoxifen therapy.

The initial results prompted researchers to unblind the study in October 2003, allowing 1,655 of the 2,268 women on placebo to switch to letrozole. Recent data from this trial revealed that the women who switched to letrozole experienced a significant improvement in DFS (HR 0.31, 95% CI 0.18–0.55; P<0.0001) at 4.5 years follow-up compared to those who chose no further hormonal treatment.<sup>6</sup> In addition, women who switched to letrozole experienced a 47% reduction in the risk of death and a 72% reduction in distant metastases compared to those who chose no further treatment.

The authors of the MA. 17 trial report that the treatment switch was well tolerated with no significant difference in bone fractures or cardiovascular events, and suggest that even after a long delay from completing tamoxifen,



women with hormone dependent breast cancer should be prescribed letrozole. The analysis also suggested that extended adjuvant use of letrozole, even after years of no treatment, provides significant benefit to women who had received chemotherapy for node-positive disease, as women with node-positive disease who continued treatment with letrozole experienced a 61% reduction in the risk of recurrence compared to no treatment. However, it has been noted that the unblinding and crossover of placebo to active therapy in this trial makes it impossible to determine the real benefit of overall survival or the total burden in adverse side effects and their impact on quality of life.<sup>7</sup>

The data from these trials are welcome news for women who find tamoxifen difficult to tolerate in the long-term. But while the results from these trials are promising, they should be taken in context with results from other recent trials that examined the effects of AIs on bone density. Tamoxifen causes significantly more hot flashes and a higher incidence of vaginal discharge than placebo, and less common toxicities associated with this drug include cataracts, endometrial cancer, venous thrombosis, and pulmonary embolism.<sup>8</sup> In contrast, the AIs are generally associated with fewer hot flashes and less endometrial toxicity and venous thromboembolism than tamoxifen.<sup>2-4,8</sup> Estrogen is, in part, responsible for maintaining bone density. Tamoxifen acts as an estrogen in bone by reducing bone demineralization, and is therefore protective against bone fracture,<sup>9</sup> whereas the AIs are consistently associated with a higher risk of musculoskeletal effects such as arthralgia, myalgia, and bone fracture than tamoxifen.

So far, there are no compelling safety data to differentiate among the three approved AIs in Canada. In the LEAP trial, an open, randomized, multicentre phase 1 pharmacodynamic study, the effects of letrozole, exemestane, and anastrozole on serum markers of bone formation and resorption, lipid profiles, and adrenal function in 102 healthy postmenopausal women with normal bone mineral density at the spine and hip were compared.<sup>10</sup> All three AIs resulted in increased bone turnover and had similar effects on bone biochemical measurements. Moreover, published phase 3 studies have demonstrated that prolonged use of either letrozole or exemestane results in modest increases in bone loss and fractures in postmenopausal women undergoing adjuvant therapy.<sup>11,12</sup> Similarly, two sub-analyses of the main ATAC trial, described at ASCO, revealed significant bone loss and a higher incidence of bone fractures in women treated with anastrozole for five years, whereas women in the tamoxifen arm experienced a benefit in bone mineral density (BMD) and fracture risk.<sup>13,14</sup>

Another study revealed that low blood levels of vitamin D may worsen the bone loss associated with AIs.<sup>15</sup> A randomized, double-blind trial conducted by the Norwegian Breast Cancer Group enrolled 147 postmenopausal women with early breast cancer (median age 60 years) who were randomly assigned to receive either exemestane for two years or placebo, in order to evaluate potential detrimental effects of the AI on bone.<sup>11</sup> A sub-analysis of this study, which analyzed various biomarkers of bone metabolism (25-hydroxyvitamin D, parathormone, calcium, estrogens, androgens), demonstrated that the majority of study participants (88%) suffered from vitamin D deficiency at baseline, with comparable mean levels of vitamin D between groups (22.6 ng/ml in the placebo group and 21.6 ng/ml in the exemestane group). Patients in the exemestane group with low vitamin D at baseline (<30 ng/ml) experienced accelerated loss of BMD in the lumbar spine area (P=0.026). Moreover, loss of BMD in the femoral neck was significantly correlated with low baseline levels of calcium (P=0.014). The authors suggest that vitamin D deficiency could be the most important factor elevating bone loss among patients treated with AIs, and vitamin D supplementation may be warranted in breast cancer patients, both pre- and postmenopausal, during treatment with this class of drugs.

Considering the latest evidence, the AIs remain an acceptable alternative to tamoxifen in postmenopausal women with ER-positive breast cancer, and their optimal use in this setting will continue to evolve over the next few years. The oral administration of these drugs allows patients coveted freedoms, yet the potential for toxicity requires that supervision be maintained. No formal guidelines yet address bone density screening for women receiving these agents, and long-term follow-up is necessary to assess the safety of AIs in breast cancer survivors. The area of supportive care is therefore likely to change as the new practices evolve.

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### Dr. Leigh's perspective:

Given the mounting evidence in support of aromatase inhibitors (AIs), I think it is reasonable for postmenopausal women who have been on tamoxifen for two or three years to switch to an AI. We have evidence from several trials now that the inclusion of an AI as part of adjuvant breast cancer therapy improves disease-free survival, and there is now a clear trend towards better survival in the exemestane arm of the IES study. Aromatase inhibitors are significantly more costly, but a switch at some point from tamoxifen to these agents, or initial adjuvant therapy with an AI, is a reasonable approach. In Canada, both switching to or starting with an AI are becoming more common and certainly available funding is changing in support of these strategies. The issue of what strategy to choose remains complex. The question of whether there is an advantage to sequencing tamoxifen and an AI or just using an AI upfront as initial adjuvant therapy should be answered by the pending results of the Breast International Group 1-98 (BIG 1-98) study. This large European trial has four arms: (1) five years of an AI, (2) five years of tamoxifen, (3) two years of tamoxifen followed by three years of an AI, and (4) two years of an AI followed by three years of tamoxifen.

There are still some unanswered questions about the clinical impact of the long-term side effects of the AIs, such as concerns regarding the profound estrogen-deprivation effects of AIs, particularly osteoporosis. For example, some patients, despite therapy with bisphosphonates, have returned to tamoxifen after initial AI therapy to improve bone density. It is likely that the effects of AIs on bone density will become an increasingly common clinical problem in the adjuvant setting, particularly in younger patients undergoing prolonged estrogen deficiency and patients with pre-existing osteopenia. Therefore, regular monitoring of bone mineral density and bone protection strategies such as using bisphosphonates are likely to be required. In this regard, the data reported on vitamin D levels in breast cancer patients undergoing adjuvant therapy are potentially very important. The idea of supplementing with vitamin D to correct levels at the outset of therapy has merit, as most Canadian women have low levels of vitamin D at baseline. Dr. Mark Clemons at the Princess Margaret Hospital is conducting a study in women with metastatic breast cancer to bone, examining the impact of vitamin D supplementation on vitamin D levels and markers of bone turnover. This will hopefully be expanded to patients on aromatase inhibitors in the adjuvant setting in future. We also have to offset the potential for osteoporosis against the reduced risk of endometrial cancer and venous thromboembolism with AI use, compared to tamoxifen.

## Focus on the Elderly

Lesley McKarney

The elderly account for the fastest growing segment of the global population.<sup>1</sup> The elderly population itself is also growing older, with the “oldest old” population (80 years and older) being the fastest-growing segment.<sup>1</sup> Levels of illness and disability among this group far exceed those of other age groups. And while more than half of all cancers occur in the over-65 age group,<sup>1</sup> there has been a relative lack of concentration on this patient population in clinical trials reported thus far in Canada, and globally.<sup>2,3</sup> In Southwest Oncology Group (SWOG) trials, for example, only 25% of patients enrolled in trials were age 65 years and older,<sup>3</sup> while Yee *et al.* determined that the enrollment rate in Canadian trials was 22%.<sup>4</sup> Meanwhile, Kumar and colleagues at the H. Lee Moffitt Cancer Center and Research Institute reported at this year’s ASCO meeting that exclusive enrollment of older patients (≥65 years) in National Cancer Institute-sponsored trials was extremely low at 0.5%.<sup>5</sup> Moreover, a majority (57%) of the 413 consecutively completed randomized controlled trials they analyzed did not have any stratification by age, and only 10% of the studies had a stratification age at >65 (n=42).

However, researchers are gradually beginning to focus more attention on older patients. The Cancer and Leukemia Group B (CALGB) formed a Cancer in the Elderly Committee that is currently addressing issues specifically relevant to the treatment of cancer in the older patient.<sup>6</sup> Among the committee’s strategies is the development of clinical trials to assess treatment efficacy and pharmacokinetic/pharmacologic issues related to chemotherapy and hormone therapy in the older cancer patient. Such studies are warranted given the contradictory evidence surrounding toxicity profiles in the elderly. It is universally thought that older patients are less able to tolerate chemotherapy — particularly more aggressive platinum-based therapies for advanced non-small cell lung cancer (NSCLC) and adjuvant chemotherapy for breast cancer — compared to their younger counterparts because of the progressive reduction of organ function and metabolic reserve, and comorbidities related to age.<sup>7</sup> This cohort is frequently considered ineligible for more aggressive chemotherapy regimens, resulting in data from clinical trials that are not always applicable to all patients with a particular type of cancer.<sup>6</sup> The toxicity evidence that can be gleaned from clinical trials so far has been mixed. Increased toxicity and the need for stem cell support for myelosuppression in older patients has been shown in some trials, while both younger and older patients have compared well in other studies.<sup>8–10</sup>

One study presented at ASCO provided further evidence that chemotherapy should not be withheld from older patients on the basis of age alone.<sup>10</sup> A team of researchers from Canada led by Dr. Carmela Pepe examined a subset of data from the previously published NCIC CTG–BR.10 trial<sup>10</sup> to see whether survival and side effects were any different between older patients and younger patients treated for NSCLC with platinum-based adjuvant chemotherapy. The majority of patients diagnosed with NSCLC are over the age of 65, and about 30% are over 70 at the time of diagnosis.<sup>11</sup> In the NCIC CTG–BR.10 trial,<sup>10</sup> patients with NSCLC were randomly assigned to receive either tumour resection followed by four rounds of chemotherapy with vinorelbine and cisplatin, or surgery alone, then observed. The median age in this published trial was 60 years, and 155 of the 482 patients were over the age of 65. In their retrospective analysis of the data, the investigators looked at overall survival advantage for the surgery plus chemotherapy group as well as any differences between older and younger patients in terms of the number of doses they received, the intensity of the dose, or the side effects. Older patients who received chemotherapy were more likely to be alive five years after therapy than those patients who underwent surgery alone (66% versus 46%; hazard ratio [HR] 0.61, 95% confidence interval [CI] 0.38–0.98, P=0.04). They were also no more likely to be hospitalized during treatment than were younger patients (28% versus 29%, respectively). There was no significant difference in the incidence of toxicities, nor was there a need for additional supportive care among the older patients. However, this is offset by the fact that older patients received fewer and less intense doses than the younger patients in the chemotherapy group. Fewer patients over 65 completed treatment (for reasons not recorded in the original trial), and they were more inclined to refuse treatment compared to the young

(P=0.03). Of note, the survival of patients older than 75 years was significantly shorter than that of patients aged 66–74 (HR 1.95; 95% CI 1.11–3.41, P=0.02).

The results of this subset analysis are similar to studies in advanced lung cancer in which older patients benefited from chemotherapy just as much as younger patients, with an acceptable increase in toxicity for older patients.<sup>13</sup> However, prospective randomized trials using platinum-based chemotherapy, particularly those including more patients in the 75+ age group, are still needed.<sup>10</sup>

In contrast, another retrospective study reported at ASCO this year analyzed more than 6,000 women enrolled in adjuvant chemotherapy trials for node-positive breast cancer, and found that older patients had more problems with side-effects from intensive regimens.<sup>14</sup> Muss and colleagues analyzed Grade 3–5 toxicity data for 6,174 patients enrolled in three CALGB/CTSU randomized clinical trials, where patients received either cyclophosphamide, doxorubicin, and fluorouracil therapy in three dose schedules: adriamycin and doxorubicin with or without paclitaxel (AC ± T); or AC ± T in either a dose-dense regimen (every two weeks) or every three weeks. Patients were divided into three age groups for comparison, though the total number of elderly patients (65 years of age and older) was small at 7%. The incidence of major toxicities and chemotherapy-attributed causes of death is presented in Table 1.

**Table 1: Grade 3–4 toxicity and death by age in patients enrolled in CALGB/CTSU trials<sup>14</sup>**

Toxicity	Age <50	Age 51–64	Age 65 +
Patients (n)	3,676	2,480	486
WBC/Platelets Grade 4 (%)	16/3	17/4	17/4
Nausea/Vomiting Grade 3/4 (%)	8/2	6/1	5/2
Stomatitis Grade 3/4 (%)	4/1	4/1	4/1
Diarrhea Grade 3/4 (%)	1/<1	2/1	4/<1
Neurologic Grade 3/4 (%)	8/<1	8/1	8/<1
Death attributed to Chemotherapy (n/%)	7/0.19	8/0.32	7/1.4
Death AML/MDS (n/%)	1/0.03	5/0.20	5/1.0
Death Congestive Heart Failure (n/%)	5/0.14	3/0.12	1/0.21

Older women who met the strict eligibility criteria for these trials had a higher incidence of chemotherapy-related acute myelogenous leukemia and myelodysplastic syndrome (AML/MDS), but not nonhematologic toxicity. The rate of AML/MDS increased with age. Additionally, older patients were significantly more likely to have a white blood cell count (WBC) of <1.0 x 10<sup>9</sup>/L, any Grade 4 hematologic toxicity, or to have discontinued treatment due to side effects. The authors of the study recommend that even though current adjuvant regimens are effective in older women, oncologists should nonetheless caution patients concerning the increased risks of AML/MDS in such treatments.

At present, there is no reliable method available to predict who is at risk or is destined to develop the sometimes fatal treatment-related toxicities such as AML/MDS. If age by itself is not predictive of treatment failure, and chemotherapy is not necessarily less effective or less tolerable in older patients, physicians must resort to a more comprehensive tool of pretreatment assessment that indicates which patients are more likely to benefit from cytotoxic treatment.<sup>15,16</sup> This is particularly important given the pace at which the population of oldest old is growing and the increasing life expectancies.<sup>14</sup> Such a tool would allow physicians to characterize the “functional age” of older patients in order to tailor treatment, stratify outcomes by factors other than chronological age, and develop interventions to optimize cancer treatment.<sup>16</sup> Geriatrician and medical oncologist Arti Hurria and her colleagues from the Memorial Sloan-Kettering Cancer Center are developing a short geriatric assessment (GA) tool for physicians that they claim can aid in treatment decision-making and minimize the burden on clinic resources.<sup>17</sup> As presented at ASCO, the investigators

provided 175 patients of mean age 76 with a brief, comprehensive, self-administered GA tool before their meeting with the oncologist. The self-administered GA tool covers the essential domains of assessment predictive of survival in the geriatric population, such as functional status, comorbidity, psychological state, nutritional status, and social support. Such a multidimensional GA would help to detect problems that can possibly interfere with cancer treatment. The feasibility of the tool was assessed by the number of patients able to complete the assessment unassisted, the number of patients requiring the assistance of staff members versus non-staff members, overall patient satisfaction, and time to complete. It took the 168 patients who completed the GA tool anywhere from three minutes to 60 minutes to complete the assessment, with a median time to completion of 13 minutes. Most patients (75%) completed it independently, 20% received assistance from a friend or family member, and only 4% required assistance from a member of the health-care team. Overall patient satisfaction was high at around 90%. Based on the assessment scores, patients were either referred to a social worker (38%), nutritionist (43%), visiting nurse/home health aide (30%), internist (23%), rehabilitation (13%), ear, nose and throat physician (13%), ophthalmologist (7%), or psychiatrist (5%). The effectiveness of the interventions offered needs to be tested in prospective trials, but the eventual goal of the investigators is to determine if this geriatric assessment measure can identify factors independent of age that predict cancer treatment morbidity and mortality and result in rational interventions to optimize cancer care.

Very little data on cancer survival has been collected for patients older than 85 years. However, a recent single-institution retrospective evaluation suggests that this age group should not be overlooked for cancer treatment, as nonagenarians with few comorbidities and a good performance status can be successfully treated for their cancer.<sup>18</sup> The charts of 121 of 643 patients registered at the Moffitt Cancer Center who were age 90 or older during their treatment/evaluation were eligible for review based on the following inclusion criteria: 1) a diagnosis of cancer, 2) a clear treatment plan with at least two follow-up visits over a one-month time period, and 3) patients with only one evaluation would be eligible if a clear treatment plan was outlined and their death occurred within six months of their evaluation at this cancer centre. The patients were generally healthy at the commencement of treatment, with an ECOG score of one in more than 95% of the patients. Nearly half of the patients underwent surgery for their cancer, which was most commonly breast cancer (14%), malignant melanoma (11%), head and neck cancer (9%), melanoma (9%), or prostate cancer (8%), while 7% were administered chemotherapy. Following evaluation, 54% of the patients were alive at one year and 42% were alive at two years, suggesting that these patients do derive survival benefit of months to years after their therapies and should not be declined treatment.

Furthermore, Kumar and colleagues showed that the overall survival in two trials that exclusively enrolled older patients actually favoured newer treatments (HR 0.62; 95% CI 0.44–0.87), while trials with more than 40% of patients over 65 had favourable outcomes involving innovative treatments for survival (HR 0.85; 95% CI 0.77–0.94), and event-free survival (HR 0.76; 95% CI 0.64–0.92).<sup>5</sup>

The under-representation of older patients in clinical trials not only handicaps research into new therapies, it also creates uncertainty about the proper use of current treatments in older patients.<sup>2</sup> Studies designed specifically to assess the susceptibility of older patients to toxicity with current regimens, as well as those in development, are needed. Advances are being made at the level of geriatric assessment to more adequately select those patients who will benefit from cancer treatment and to avoid excluding patients based on concerns about frailty and age alone.

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### Dr. Leigh's perspective:

A Comprehensive Geriatric Assessment (CGA) can aid the assessment of comorbidities and function to better help select older patients for appropriate therapies. Currently most oncologists use performance status, as it is simpler than a lengthy assessment in clinic, even though it does not provide as much information. The study conducted by Arti Hurria and colleagues is very timely as it provides a potentially efficient and convenient alternative to the CGA. This abbreviated version took an average of less than 15 minutes to complete and 95% of patients were able to complete it on their own or with the help of a family member. The next step will be to integrate this into a practical tool that can be used in clinic, to help improve treatment selection for older patients.

Undertreatment of older patients with cancer remains a problem in Canada. Reasons for this include the perception that older patients are less able to tolerate treatment-related toxicities and that they do not derive the same benefit from treatment as younger patients, as well as patient preference. Because few older patients are included in clinical trials, randomized data are limited in this group. There are many potential barriers to clinical trial participation for older patients, including physician concern for potential comorbidities and impairment of function, restrictive entry criteria (e.g., no prior cancers, no impaired renal function, limited comorbidities allowed, concomitant medication restrictions), as well as patient inability to access cancer centres, transportation concerns, and performance status.<sup>1</sup>

However, more information is needed about this rapidly growing population of patients to help guide practice. Carmela Pepe and colleagues showed that adjuvant chemotherapy can be given safely to patients who are ≥65 years of age and, despite receiving less chemotherapy, elderly patients clearly derive a survival benefit from this treatment. Studies such as this will hopefully promote treatment decision making based on patient function rather than chronologic age. As seen in other trials, there are very few patients over 75 in this study. Future clinical trials focussed on this subset of older patients are necessary, as well as information on outcomes of a less highly selected general population of older patients.

The study by Crane and Extermann demonstrates that even the oldest old patients can have good outcomes following cancer treatment, as 42% of nonagenarians treated at H. Lee Moffitt were still alive two years post-treatment. This contradicts the belief that most physicians would have about life expectancy and performance in this age group, and although these patients were carefully selected, clearly there is a group of older cancer patients who can and should be treated.

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# MASCC

**Multinational Association of Supportive Care in Cancer  
18<sup>th</sup> International Symposium**

## Overview

Toronto played host to the 18th International Symposium of the Multinational Association of Supportive Care in Cancer (MASCC) from June 22 to 24, 2006. The highly successful meeting brought together health professionals for an exceptional forum on ways to minimize the effects of cancer, reduce symptoms and complications of treatment, and address psychosocial issues facing cancer patients and their families. Highlighted in this issue of *New Evidence in Oncology* are some of the cutting-edge data reported during MASCC 2006 regarding supportive care.

## A Canadian perspective provided by

**David G Warr, MD, FRCPC**

**Janice Wright, RN, MS, ACNP**



Dr. David Warr is a medical oncologist and pain consultant, as well as a member of the Breast Site Group at the Princess Margaret Hospital. He is an associate professor in the Department of Medicine at the University of Toronto. His clinical research interests are in supportive care, including the control of nausea and pain, and in the treatment of breast cancer with chemotherapy and hormonal therapy.



Janice Wright is an acute care nurse practitioner with the Allogenic Stem Cell Transplant team at the Princess Margaret Hospital. She has received the Sigma Theta Tau Lambda Pi award for outstanding contribution to nursing practice and the University of Toronto Bone Marrow Transplant award for clinical excellence. Janice's practice and research focus involves developing and evaluating innovations in cancer supportive care delivery, and applying technology to support symptom management and improve patient symptom experience.

## Toxicities Associated with Targeted Therapies

Colleen Young

In the last decade, research on new anticancer therapies has focused more and more on the development of targeted molecular therapies. Clinical trial results, primarily in patients with very advanced cancers refractory to conventional treatments, indicate that targeted molecular treatments can mediate tumour regression with acceptably low toxicity. However, toxicities related specifically to such treatments can occur. Supportive care research investigating targeted therapy-associated toxicities, and examining how they may differ from those due to standard chemotherapy drugs, is becoming increasingly important.

During the oral session "Toxicities Associated with Targeted Therapies," speakers Dr. Edith Perez from the Mayo Clinic in Jacksonville, Florida, Dr. Dorothy Keefe from the Royal Adelaide Hospital in Adelaide, Australia, and Dr. Mark Kris from the Memorial Sloan-Kettering Cancer Center in New York discussed a variety of toxicities related to specific targeted therapies.

In the first presentation, Dr. Perez discussed the incidence, clinical relevance, and management of trastuzumab cardiotoxicity. Data from the North Central Cancer Treatment Group Intergroup trial 9831 (NCCTG-N9831) combined with data from the National Surgical Adjuvant Breast and Bowel Project trial (NSABP B-31) demonstrated a 52% reduction in the risk of breast cancer recurrence as well as a 33% survival benefit with adjuvant trastuzumab therapy.<sup>1</sup> These results were supported by the findings of the HERA trial, which found a 46% reduction in recurrence by adding trastuzumab to chemotherapy.<sup>2</sup> While trastuzumab was well tolerated, there exists a low possibility of cardiac events. Cardiotoxicity is most prevalent when trastuzumab was combined with anthracycline chemotherapy. Data from the first interim analysis of the BCIRG 006 trial reported a statistically significant higher incidence of cardiac events in the AC-TH protocol in comparison to AC-T, but not in TCH in comparison to AC-T (AC-T: 0.86%, AC-TH: 2.62% [P=0.0024], TCH: 1.04% [P=0.82]).<sup>3</sup> The AC-TH arm showed a statistically significant higher incidence of asymptomatic left ventricular ejection fraction (LVEF) decline in comparison to the TCH arm. However, Dr. Perez stated that, while statistically there is no difference between the two treatment regimens, TCH is not equivalent or necessarily preferable to AC-TH. The difference in clinical cardiac toxicity was 1% between the AC-TH arm and the TCH arm, whereas the difference in disease-free survival was possibly as high as 12%. Further follow-up is required.

How patients should be monitored for cardiotoxicity continues to be debated. Dr. Perez suggests that patients be monitored as they were in the clinical trial: LVEF should be evaluated before starting therapy followed by a repeat assessment every three months for the first year of therapy. After that time, appropriate frequency of monitoring is unclear. Understanding the nature and specificity of trastuzumab's cardiotoxic effects is important in better defining clinical criteria for inclusion and exclusion of patients who can safely receive trastuzumab for the treatment of breast cancer, or possibly for other malignancies.

The second speaker, Dr. Keefe, admitted that establishing the extent of mucosal damage from targeted therapies is a challenge since mucosal injury has not traditionally been a primary outcome in clinical trials of these agents. Current understanding of mucosal toxicity of the more standard anticancer therapies may prove useful when considering the management of mucosal injury associated with targeted therapies. However, more research designed with mucosal injury as a primary endpoint will be necessary.

New therapies targeting the epidermal growth factor receptor (EGFR) have proven effective in the treatment of several types of cancer, most notably colorectal carcinoma. Monoclonal antibodies against the EGFR such as cetuximab and panitumumab, or EGFR tyrosine kinase inhibitors such as gefitinib and erlotinib, are generally well tolerated and do not induce the severe systemic toxicities common to cytotoxic drugs. However, patients treated with these EGFR inhibitors (EGFRI), frequently develop dermatological side effects, most commonly as an



acneiform eruption. Presenter Dr. Kris repeatedly cautioned that while these eruptions may resemble acne, they are not acne and should not be treated with anti-acne solutions, which will only dry out the skin. Patients may also develop xerosis, eczema, fissures, telangiectasia, hyperpigmentation, hair changes, and paronychia with pyogenic granuloma. These effects appear to be mechanism-based and linked to the inhibition of EGFR action, but the exact pathophysiology remains unclear. The dermatological side effects generally appear one to two weeks after starting EGFR treatment and tend to improve over time even while continuing the targeted therapy. Regardless, changes to the appearance of the skin threaten patient compliance and should therefore be managed effectively. Secondary infection of these skin lesions is common, often necessitating early treatment with minocycline or topical clindamycin. Patients should not be discouraged from using cosmetics. Dermatological side effects can be distressing for some patients and allowing them to use cosmetics to cover up the lesions may help them to tolerate the changes to their skin and encourage them to continue therapy.

Clinically accepted guidelines for staging or managing the side effects of EGFR therapy do not as yet exist. The interdisciplinary SERIES (Skin and Eye Reactions to Inhibitors of EGFR and kinaseS) Clinic was established with a mandate to focus on early diagnosis and treatment of dermatological and ophthalmological reactions to EGFR and other kinase inhibitors, in order to ensure patient compliance and help improve quality of life. In a poster presentation, management algorithms for rash and paronychia were introduced as developed by the SERIES Clinic.<sup>4</sup> Following patients for more than three months, the algorithms were found to be effective in the management of these symptoms and thus dose alterations of anticancer therapy were minimized. To address the toxicities induced by EGFRs, the clinic recommended several critical factors that should be considered: treatment tailored to the type and stage of the toxicity, the use of pre-therapy or early intervention, close and frequent counselling and follow-up, and the involvement of an interdisciplinary management team including dermatologists, ophthalmologists, and oncologists.

During the symposium, the paper by Dr. Lee Schwartzberg and colleagues presented data examining patient burden, resource utilization, and treatment outcomes for patients experiencing grade 3/4 chimeric or humanized monoclonal antibody-associated infusion reactions.<sup>5</sup> Treatment with chimeric and humanized monoclonal antibodies (MAbs) is associated with infusion reactions that may limit their usage. Despite the growing use and importance of MAb regimens, there is little information describing MAb-associated infusion reactions (MAb-IRs) and the management of MAb-IR has never been systematically assessed. The researchers analyzed data from eight U.S. outpatient oncology practices between February 2004 and December 2005 for 41 adult cancer patients (bevacizumab n=4, cetuximab n=8, rituximab n=29) who experienced a grade 3 (34, 83%), grade 4 (6, 15%), or grade 5 (1, 2%) MAb-IR. Twenty-five (61%) of these patients received premedication before experiencing their grade 3/4 MAb-IR. The majority of MAb-IRs, 27 (66%), occurred during the first cycle, and six (15%) occurred at or beyond cycle four. The most common MAb-IRs were rigors/chills (23, 56%), bronchospasms (7, 17%), and dyspnea (8, 20%). The consequences of MAb-IRs required increased utilization of resources, as shown in Table 1.

Management Strategy (n=50)	n (%)
Hospitalization	12 (28)
MAb dose delay	6 (12)
MAb dose reduction	2 (4)
MAb infusion rate reduction	11 (22)
Permanent MAb discontinuation	22 (44)

Over 74% of patients had their MAb dose reduced, delayed, or discontinued. Discontinuation was necessary in almost half of the patients. While ongoing analyses will evaluate direct costs of drugs, indirect provider costs, and costs to payers and patients, the data presented show that major MAb-IRs result in significant human resource burden for the provider.

As new targeted agents are investigated and ongoing research identifies additional potential therapeutic targets to further improve patient survival outcomes, additional study of the associated toxicities will be required. This is undoubtedly an area that will warrant continued attention in upcoming MASCC symposia.

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**Dr. Warr’s perspective:**

Of the targeted therapies discussed during the oral session at MASCC, it is only trastuzumab that I currently use in my practice. There will be more in the future. In particular, we will be involved in trials studying the efficacy and safety of lapatinib, an EGFR and Her2/neu dual tyrosine kinase inhibitor under development as a treatment for solid tumours such as breast and lung cancer.

Optimal cancer treatment is always a fine balance of risk versus benefit. When treating breast cancer with trastuzumab at our institution, we monitor for cardiotoxicity every three months during the first year as was done in the clinical trials. While I have had patients who could not receive trastuzumab therapy because of pre-existing heart problems, I have not yet had a patient who has had to stop treatment. The data Dr. Perez presented, indicating that cardiotoxicity did not appear to be significantly different whether trastuzumab was administered concurrently with paclitaxel or sequentially, was reassuring and supports the initial suggested benefit of concurrent treatment.

However, in addition to balancing safety and overall survival improvements, the cost implications and regional guideline parameters of a treatment regimen must also be considered. For example, the Ontario guidelines do not allow the concurrent administration of trastuzumab and paclitaxel when using a dose-dense regimen. Furthermore, there are differences between provincial guidelines. The guideline recommendations dictating the use of rituximab are a classic example of regional disparities. Age is not a factor defining access to rituximab according to British Columbia’s guidelines, whereas in Ontario access was initially restricted to patients 60 years or older. Media exposure of this difference in the provincial guidelines helped relax the Ontario restrictions.

The question “At what point does the survival benefit warrant funding and access to a drug?” is continually revisited by governing bodies. Survival benefits of several targeted therapies have been demonstrated; however, because these agents are quite expensive, the additional benefit must be weighed against costs. At ASCO 2005, Malcolm Moore presented evidence of improved survival in pancreatic cancer patients by adding erlotinib, a small molecule EGFR inhibitor, to conventional gemcitabine chemotherapy as a novel therapeutic approach. The results of the study showed only modest survival improvement with the EGFR inhibitor. Before this regimen can be funded in Canada, further study demonstrating increased survival benefit will be required. The economic decision criteria that dictate funding help ensure our health-care dollars are spent wisely. Not every drug that indicates any statistically significant improvement in survival in a large randomized trial can receive full funding.

## Current and Future Targets of Mucositis Therapy

Colleen Young

Mucositis is one of the more troublesome side effects of antineoplastic treatment, yet historically it has been largely ignored by the oncology community. To address this oversight, the MASCC Mucositis Study Group (MSG) was formed in 1998. The group's initial goal was to develop mucositis management guidelines, which it completed in 2004 and updated in 2005. At the 2006 MASCC symposium, as in recent years, the MSG and oral sessions about mucositis generated plenty of interest and were well attended. Discussions focused on the complexity of the pathogenesis of mucositis, the current and future targets of mucositis therapy, and the dissemination of the mucositis guidelines.

Influencing the developments in mucositis therapy is the evolving understanding of the biological basis for mucosal barrier injury (mucositis) induced by cancer therapy with radiation or chemotherapy. A patient's mucosal response to cancer therapy appears to be controlled by both global factors (i.e., gender, underlying systemic disease, and race) and tissue specific factors (i.e., epithelial type, intrinsic endocrine system, local microbial environment, and function). Interactions of these factors along with underlying genetic influences most likely determine the risk, course, and severity of treatment-related mucosal injury.<sup>1</sup> Of current interest is the research regarding changes in gene expression. In an oral session, Dr. Stephen Sonis from the Brigham's and Women's Hospital in Boston, Massachusetts described work being done on identifying the genetic response to cancer treatment and how this relates to mucosal injury. Patients receiving radiation or chemotherapy treatment express a specific group of genes that track with toxicity. While mucosal damage occurs locally, it was hypothesized that genetic changes that occur may be more widespread. By analyzing the peripheral blood two weeks after patients had started chemotherapy or radiation treatment, genetic changes were tracked in advance of any mucosal damage. It is hoped that the results of this research will lead to new developments in toxicity interventions that modify the gene expression identified in the peripheral blood.

Mucositis occurs in almost all patients treated with radiation for head and neck cancer. In a poster presented at MASCC, researchers Elting *et al.* compared the impact of the use of intensity-modulated radiation therapy (IMRT) versus standard radiotherapy with or without chemotherapy on the risk, outcomes, and cost of oral mucositis (OM) among patients receiving head and neck radiotherapy.<sup>2</sup> While the preliminary results appeared to indicate that risk and duration of severe OM were lower among IMRT recipients compared with standard RT recipients, the results of a larger sample showed no significant differences in risk, severity, or duration between the two groups. However, the authors also observed that radiation-induced OM is associated with serious clinical outcomes, including pain requiring opioid analgesia, weight loss, and radiation delay or dose reduction. Serious clinical outcomes and costs are similarly frequent among IMRT and standard RT recipients. Results of this study further demonstrate the need for improved interventions for prevention and treatment of oral mucositis in this high-risk population.

Although the majority of chemotherapy is delivered in an outpatient setting, relatively little is known about the symptom experience, including OM, of chemotherapy outpatients. One study presented at MASCC set out to examine the relationships of symptom clusters in the outpatient setting. In a descriptive, longitudinal secondary data analysis of outpatients from four U.S. chemotherapy centres (n=227), sore mouth (SM) was used as a proxy for OM, to compare the symptom experience in cancer patients between cycles two (C2) and three (C3) of outpatient chemotherapy.<sup>3</sup> The relationships among levels of self-reported SM severity and distress related to depression, anxiety, difficulty sleeping, and fatigue were also explored. Measured on a scale from one to 10, researchers reported the mean score of sore mouth severity to be similar in both cycles (3.19 in C2 and 3.14 in C3, P=0.70). SM severity correlated significantly with difficulty sleeping (P<0.006) and severity of fatigue (P<0.001). Similarly, SM distress was associated with the distress of trouble sleeping (P<0.016) and of fatigue (P<0.004). However, SM severity and distress scores appeared not to correlate with depression or anxiety. These findings add to the understanding of the complex experience of OM and other chemotherapy associated symptoms, suggesting

that there may be common pathobiologic mechanisms between SM and other symptoms. Studies such as this contribute to the emerging concept of symptom clusters in cancer and suggest that intervention alleviating one symptom may lessen other symptoms.

Preclinical and clinical trials into the newly discovered biological pathways of mucositis will provide new options for combating this debilitating side effect of cancer therapies. As more is understood about the pathobiology of alimentary tract (oral and gastrointestinal) mucositis, the role of growth factors and cytokines in this intricate process continues to gain attention. At this year's symposium, two posters examining the effects of growth factors were presented.

Palifermin, a recombinant form of human keratinocyte growth factor, has shown promising results in reducing the incidence and severity of OM in patients undergoing hematopoietic stem cell transplantation, and recommendation for its use was added to the mucositis guidelines during the 2005 update. In a study comparing 27 historical controls with 32 patients who received palifermin, researchers found a significant reduction in the incidence of severe OM (3% versus 48%, P=0.003), length of hospital stay (14 versus 18 days, P=0.026), and number of nutrition-impact symptoms experienced (4.9 versus 6.0, P=0.003) in the palifermin group compared to standard care.<sup>4</sup> There was no significant difference in nutritional status, presence of infection, dietary intake, use of TPN, time to engraftment, or analgesic dose and duration of administration between groups. Further study through a randomized clinical trial is needed to confirm these results and to examine quality of life issues and the economic impact of palifermin therapy.

Currently velifermin, the recombinant human fibroblast growth factor 20, is being studied in phase 2 clinical trials for its potential to reduce severe OM. In a phase 2 randomized, placebo-controlled trial assessing the safety, efficacy, and pharmacokinetics of velifermin as a single dose given post-transplant at three dose levels, the primary endpoint was the incidence of grade 3/4 OM.<sup>5</sup> A total of 212 patients with hematologic malignancies undergoing high-dose chemotherapy and autologous stem-cell transplant were randomly assigned to receive either placebo (n=51) or velifermin 30 mcg/kg (n=50), 100 mcg/kg (n=56), or 200 mcg/kg (n=55). The grade 3/4 OM incidence rates in the placebo or velifermin arms were 37%, 18%, 38%, and 36%, respectively. While the dose-dependent trend of reduction of severe OM was not statistically significant (P=0.549), velifermin at 30 mcg/kg when compared to placebo alone (P=0.031) may prove effective in reducing chemotherapy-induced severe OM. The reported safety profile supports the continued phase 2 study to define an optimal dose.

Those interested in the developments of mucositis research eagerly await the findings of the multinational prospective observational study being conducted by Sonis *et al.*<sup>6</sup> The trial will estimate the incidence, severity, and duration of mucosal injury, as well as the clinical and pharmaco-economic impact of mucosal injury in nine mucotoxic radiation and chemotherapy regimens among patients in solid tumour and hematologic disease settings. Study enrollment was initiated in November 2005 and is scheduled to be completed in September 2008. The first analyses and results will be available by the fourth quarter of 2006. These findings will be helpful in developing and implementing efficacious interventions to reduce the burden of illness of mucosal injury. A reduction in the burden of illness may result in a decrease in medical resource utilization and associated costs.

The task ahead for the MSG will be to focus on disseminating and implementing the MASCC/ISOO mucositis guidelines in clinical practice. First, it will be vital to review institutional protocols and compare them to the guidelines, ensuring that current treatment regimens are not unnecessary or detrimental. Although some prevention and management strategies for alimentary mucositis are advocated by the MASCC/ISOO guidelines, few options are available. This limited evidence points to the importance of further research in pathophysiology, epidemiology, and therapy for alimentary mucositis. Epidemiological and clinical research into risk factors and burden of care, and clinical studies of newer, more promising agents are imperative to improve the management of this common yet debilitating toxic side effect of cancer therapies.<sup>7</sup>

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### Janice Wright's perspective:

Mucositis remains under-reported, underdiagnosed, and undertreated. While our understanding of the complexity of this symptom is constantly improving, the challenge ahead lies in the implementation of evidence-based standards of care into clinical practice. Wide-scale dissemination resulting in multi-institutional acceptance and implementation of the MASCC guidelines is a major priority of the MSG. In order for this to be accomplished, suggestions made by the MSG included collaborating with industry and seeking pharmaceutical support to help with the task of disseminating the guidelines.

We have always thought that mucosal injury visible in the mouth represents a window to what is happening throughout the GI tract. That is why the adoption of the new term “alimentary mucositis,” encompassing oral and gastrointestinal mucositis, is of such importance. The term alimentary mucositis more effectively speaks to the improved understanding of the pathogenesis of mucositis and will eliminate the duplicity of terms, such as mucositis and stomatitis. It makes more sense to consider the entire GI tract when discussing mucositis because we now know that it is not merely an epithelial event. There are several phases in the development of mucositis. For example, during the final phase — the healing of mucositis — it may appear that ulceration has disappeared and new epithelial growth has repaired the damage, leaving a normal-looking mucosa; however, research has revealed that the mucosal environment has been altered significantly. The residual angiogenesis places the patient at risk for future mucositis.

Currently, at our institution, mucositis is primarily managed proactively with systemic oral hygiene and care. Patients are routinely sent for a pretreatment dental assessment, and we educate them on basic oral care that includes brushing, rinsing, flossing, and keeping the oral cavity moist. We ensure that patients are coached to continue this oral regimen, because if they stop, the benefits are lost within 24 hours. The PRO-SELF self-care intervention model,<sup>1</sup> presented by Marilyn Dodd during MASCC, is an example that we follow. Because no one element of oral care offers a particular advantage, it is necessary to ensure overall systemic oral care as well as making tailored accommodations for the individual. Thus, depending on the intensity of the chemotherapy, the length of time the patient receives treatment, and the number and intensity of other symptoms the patient may be experiencing, we offer varying amounts of nursing intervention in the form of symptom management. We consider the individual's ability and willingness to carry out self-care and take into account the possible symptom clusters. For example, ameliorating one or some of the symptoms associated with mucositis, such as pain or fatigue, may enable a patient to successfully follow good oral care. We also know that low neutrophil counts and mucositis go hand-in-hand. Once the neutrophil counts recover, mucositis resolves. In fact, ongoing and future research will focus on a combined modality approach to mucositis, using a number of different agents that will be able to target the multiple pro-inflammatory cytokine pathways, and can be introduced at various points during the phases of mucositis pathogenesis.

The impact of the growth factor palifermin in the autologous transplant patient population has been tremendous. While this group represents only about 4% of the overall cancer patient population experiencing mucositis, the fact that palifermin has proven efficacy in reducing the incidence of grade 3 and 4 mucositis gives us hope that it will be similarly effective in other patient populations. As the clinical indications for palifermin are expanded into more settings, and more data becomes available regarding the efficacy of new agents, such as velaferrin, we will see a shift in the management of mucositis and guidelines will be modified.

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## Patient Communication: What Doctors Say and Patients Hear

Colleen Young

The communication of distressing news is demanding for both doctor and patient.<sup>1-3</sup> While there may be little clinical evidence of the best way to deliver a prognosis or of the impact of prognostic information on patient outcomes, communication remains a major component of cancer management. In chronic and palliative care, communication is sometimes all that health-care professionals have to offer. Furthermore, patients expect doctors to possess effective communication skills.

What patients hear during a medical consultation is influenced by their emotional state, their language skills, their participation in discussion during the consultation, and the communication skills of the doctor. A study by Girgis *et al.* conducted in 1997 found that 30% of 143 Australian surgeons did not feel competent at increasing patients' ability to remember what they have been told or at encouraging patients to express anxieties about their condition.<sup>4</sup> A further 13.3% reported a lack of competence at breaking bad news to patients about their diagnosis and prognosis. It would appear from the results of a descriptive study by a nursing group in Turkey that things have not improved much in the past decade.<sup>5</sup> According to the data collected via a 25-item questionnaire from 64 nurses and 37 physicians (n=100), only 10% of the respondents had had any formal training in communicating bad news, 29% indicated that their ability to break bad news was only fair, and 35% thought it was poor. Participants in the survey found the most difficult tasks to be “discussing the end-of-life issues” (55%) and “telling the diagnosis” (50%). The most difficult parts of discussing bad news were reported as “being honest but not taking away hope” (62%) and “dealing with the patient's emotion” (52%). Most of the participants (86%) indicated that guidelines on breaking bad news interviews would be helpful, and 92% would like to receive education in patient communication.

At the MASCC 2006 oral session, “Communication with Cancer Patients,” speakers Dr. Robert Buckman from Princess Margaret Hospital in Toronto and Dr. Martin Tattersall from the University of Sydney in Australia offered practical suggestions and strategical approaches to help make communication tasks easier. Dr. Buckman outlined a six-step protocol called SPIKES that provides a strategy for delivering information to a patient and responding to the patient's reactions, as well as tailoring the delivery to the individual patient.<sup>6</sup> The six steps of SPIKES are: **1. Setting:** getting the setting right to reduce any obstacles to good communication; **2. Perception:** establishing what the patient already knows or suspects about his or her condition; **3. Invitation:** establishing what the patient wants to know, and/or setting the agenda; **4. Knowledge:** sharing information in an intelligible, accessible manner; **5. Emotion:** responding to, and acknowledging, the patient's reactions to the news; and **6. Strategy and Summary:** closing the interview, including a summary, opportunity for questions, and a contract for the next contact. Practising the SPIKES technique gives the physician the opportunity to gain confidence using a planned approach and to acquire effective communication skills.

It has been shown that the majority of patients want a realistic and individualized communication approach from the cancer specialist and detailed information when discussing prognosis. They want to be able to have the opportunity to ask questions.<sup>7</sup> Dr. Tattersall suggested that providing patients with a question prompt list would help prepare patients for a medical consultation. This simple and inexpensive intervention allows the patient to control the flow of information, legitimizes question-asking, promotes active involvement, and may suggest topics that the patient had not considered. When endorsed by the health-care professional, question prompt lists have been shown to enhance patient recall, reduce anxiety, and shorten consultation time. Dr. Tattersall also suggested that audio taping consultations can be useful in providing feedback to patients, especially those with a non-English speaking background. A record of the consultation gives the patient the opportunity to share this information with others, such as caregivers and family members. Additionally, audio taping can offer a potentially excellent audit tool for physician communication training.



Dr. Tattersall pointed out that the education of health-care professionals in patient relevant communication skills as well as communication between health-care professionals continue to be areas in need of improvement and investigation, in particular in the palliative setting. Two posters at MASCC presented the results of evaluative surveys addressing some of these needs.

Community pharmacists may be among the most accessible health professionals, and when provided with appropriate training, they have the potential to actively contribute to the management of palliative care patients. The results of an evaluation of an online problem- and evidence-based educational program in palliative cancer care for Australian community pharmacists were presented during MASCC.<sup>8</sup> Sixty pharmacists started, 34 completed, and seven partly completed the program. The website data showed that the flexibility in the design and delivery of the program was successful, as pharmacists could access it from anywhere, at a time convenient to them. They engaged extensively with the material and their peers by submitting responses to the notice board learning activities. The evaluation showed that pharmacists perceived their knowledge and confidence in palliative cancer care to have increased and that they were better able to communicate with palliative care patients. Additionally, participants indicated that the program provided them with knowledge and skills to better interact with their interdisciplinary colleagues.

Similarly, family practitioners play an important role in end-of-life care and often maintain continuity of care for their patients undergoing treatment at a cancer centre. In a Canadian survey of patients with locally advanced or metastatic disease receiving palliative radiotherapy, researchers set out to determine patient perception of their family doctor's involvement in their cancer care.<sup>9</sup> Of the 299 patients questioned, nearly all patients (98%) reported having a family physician and 71% of patients had been under the care of this doctor for at least five years. Despite long-standing relationships and high levels of satisfaction with overall care, less than half (45%) the patients surveyed perceived their family doctor as being involved in their cancer care. Most patients felt the medical oncologist was looking after all their cancer needs and only 23% wanted their family physician to be more involved. Encouraging continuity of care between patients and their family doctors during cancer treatment may facilitate transition of care back to the family practitioner once palliative therapy at the cancer centre has finished, and optimize pain and symptom management. Future study initiatives include examining the perception of family physicians and their role in the care of patients receiving palliative cancer therapy.

A 2005 systematic review of the literature revealed that, for both doctors and patients, prognosis remains a difficult topic to discuss.<sup>7</sup> Effective ways of imparting prognostic information that will ensure optimal patient understanding, psychological adjustment, and informed decision making have yet to be established.

Future research endeavours should involve the development of guidelines for clinicians on the best way of approaching prognostic discussions and the study of the impact of prognosis communication on patient outcomes.

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### Dr. Warr's perspective:

Many cancer centres in Canada have a multicultural, multilingual patient population, which presents obvious challenges to doctor-patient communication. Fortunately, effective communication skills can be learned and there are now a variety of strategies in place to help reinforce newly acquired skills and prevent physicians from slipping back to old habits. SPIKES is a particularly useful communication technique that is extremely easy to teach. Furthermore, structuring the steps of the protocol as an acronym makes it simple to memorize. Acronyms are commonly used in the medical community. They serve as tools to remind us of the symptoms of disease or differential diagnosis. Similarly, SPIKES can be used as a prompt for effective communication.

In addition to linguistic and cultural barriers, a doctor must also learn to interpret individual physical cues when in consultation with a patient. In order to draw doctors' attention to their own communication skills — both physical and verbal — I would add videotaping as a self-audit tool to Dr. Tattersall's suggestion of audio taping. I have been videotaped in training sessions. Although the situation is artificial and the tape can be painful to watch, it's very useful. Observations I made about myself have led to changes in my communication approach. For example, I am much more consistent in trying to verbalize empathy when a patient is in distress.

While there is little efficacy data available regarding the schooling of physicians in patient communication skills, I believe it is a priority and should be instituted early in a doctor's education. In addition to simply learning interviewing skills, physicians-in-training need to be taught how to facilitate tense situations. Cancer Care Ontario should be congratulated for its proactive effort to provide patient communication courses for health-care professionals. Several years ago, Cancer Care Ontario made a commitment to have as many oncology professionals as possible participate in a one-day course on health-care communication. The course developed in conjunction with the Institute for Health Care Communication emphasizes the "4 E's": Engage, Emphathize, Educate, and Enlist. Using small group teaching, videotaped case studies, and rehearsal, the session offers an interactive approach to learning that is very effective. The course has been successfully offered at several institutions across Ontario. Widespread participation in this type of training should be encouraged.

## Update on Chemotherapy-Induced Hematological Toxicities

Colleen Young

The hematological toxicities of chemotherapy — thrombocytopenia, anemia, and neutropenia — have a significant impact on cancer patients and are often the cause of chemotherapy dose delays or reductions, negatively affecting the general health and quality of life of the patient. Despite this, recent studies have suggested that the risk of chemotherapy-induced myelosuppression and its complications are considerably under-reported in randomized controlled trials.<sup>1</sup>

### New insights into the impact of chemotherapy-induced thrombocytopenia

Of the hematological toxicities, thrombocytopenia is the most underappreciated complication of chemotherapy. Chemotherapy-induced thrombocytopenia (CIT) presents a risk of bleeding, and the magnitude of risk closely correlates with the severity and duration of thrombocytopenia. As platelet counts fall below 20–50 x 10<sup>9</sup>/L, 10–20 x 10<sup>9</sup>/L, and <10 x 10<sup>9</sup>/L, the frequency of life-threatening bleeding rises steeply. Major bleeding is associated with increased mortality and significant human and health-care costs as well as with chemotherapy dose delays and/or reductions.<sup>2</sup>

A U.S. cohort study presented at MASCC 2006 reported the first comprehensive prospective data (n=2,842) defining the risk factors associated with CIT, defined as a platelet count of  $<75 \times 10^9$  cells/L<sup>3</sup>. Significant pretreatment risk factors for CIT include type of cancer and chemotherapy, prior chemotherapy or surgery, age, diabetes, low platelet count, low hematocrit or elevated alkaline phosphatase. Significant first-cycle risk factors are a drop in platelet or hemoglobin (Hb) level and severe or febrile neutropenia. The cut-off point of  $\geq 25\%$  risk of platelets  $<75 \times 10^9$ /L was used to divide patients into low- and high-risk groups (n=2,371, n=450) with average risks of platelets  $<75 \times 10^9$ /L of 8% and 73%, respectively. Once model validation is completed, it is hoped that this prediction model may provide a valuable tool for guiding chemotherapy and new supportive care measures, including thrombopoietin receptor agonists (TPO-R).

Furthermore, conclusions of a study involving 80 patients with CIT conducted in the U.S. and Europe suggest that further research evaluating CIT-related quality of life is warranted.<sup>4</sup> In this study, researchers evaluated patient perception of current management approaches and compared their view of CIT to other treatment-related toxicities, using quantitative exercises and qualitative interviews. The most common intervention for CIT was chemotherapy delay (54%) and fatigue was the symptom most often reported. All patients felt that CIT had a negative impact on their lives, suggesting that quality of life may be an important endpoint in clinical trials of novel thrombopoietic agents.

Recently, two TPO-R agonists, eltrombopag and AMG-531, have entered clinical trials and have shown promising efficacy and favourable safety profiles in the treatment of ITP (immune thrombocytopenic purpura, formerly idiopathic thrombocytopenic purpura). Eltrombopag is a small-molecule oral platelet growth factor mimetic. Results of a global, randomized, double-blind, placebo-controlled phase 2 trial studying the safety and efficacy of eltrombopag in adults with chronic idiopathic thrombocytopenic purpura (ITP) and platelets  $<30 \times 10^9$ /L were presented at MASCC.<sup>5</sup> Patients (n=104) were randomized into placebo (n=26), 30 mg (n=27), 50 mg (n=27) and 75 mg (n=24) eltrombopag arms. A dose-dependent increase in patients with platelets  $\geq 50 \times 10^9$ /L was observed at day 42 in all treatment groups with the odds-ratio of treatment response versus placebo showing significant improvement in the 50 and 75 mg arms (P<0.001). The safety profile was similar across all treatment groups and no dose-dependent safety concerns were identified. The most common side effect identified in the placebo arm was fatigue with an incidence of 19% versus 3% of all patients receiving eltrombopag. Phase 3 studies are ongoing. Given the pending emergence of these promising new agents, it will be important to define the optimal target platelet count of patients receiving chemotherapy, and to better understand the risk factors and impact of CIT.

### Comparison of erythropoietic management of anemia

For patients with chemotherapy-induced anemia (Hb  $<110$  g/L), evidence-based guidelines<sup>6-8</sup> recommend maintaining Hb levels between 110 and 130 g/L by treating with erythropoietic therapy. Two erythropoiesis-stimulating agents (ESAs) are available commercially in Canada, epoetin alfa (EA) and darbepoetin alfa (DA). Although it is well established that these ESA therapies improve anemia in patients undergoing cancer treatment, the question of which drug to use continues to be debated. In terms of safety, both drugs are similar and the varying endpoints of the available study data make direct efficacy comparison a challenge.

Underlining the similarities of the available ESA therapies, a systematic review of controlled trials plus prospective uncontrolled studies involving more than 300 patients reported no clinically or statistically important differences between the two agents in terms of transfusion requirements, quality of life scores, or risk of VTE or death, particularly when these products are used according to their labels.<sup>9</sup> Ross and colleagues therefore suggest that existing guidelines be updated to include recommendations for the use of DA for the treatment of chemotherapy-induced anemia. In order to confirm comparability or establish significant differentiation of the two available erythropoietic agents, further study is required to address predictors of response, optimal dosing regimens, use of iron supplementation, and clinical consideration that might impact cost or patient quality of life.

In Europe, once-every-three-weeks (q3w) dosing of darbepoetin alfa has been licensed for use since October 2004. The final analysis of a prospective registry examined the utilization patterns and clinical outcomes associated with q3w DA in routine clinical practice in Hungary to provide a real-world snapshot of this dosing application.<sup>10</sup> While physicians rated DA therapy good to excellent in reaching Hb target for RBC count in 82% of patients, the data from this analysis indicate that 53% patients received fewer than the average number of DA doses ( $\geq 3$ ), despite a low mean baseline Hb ( $\leq 100$  g/L). Researchers suggest that these data indicate suboptimal anemia management in Hungary.

The recent approvals of darbepoetin 500 mcg q3w dosing by Health Canada and the U.S. FDA have added this extended dosing regimen to the evolving dosing schedules of ESA therapies in North America. The dosing variations of EA and DA provide flexibility in anemia management, offering physicians choice when aligning ESA administration to their patients' individual needs.

### Guideline implementation of using G-CSF neutropenia management

Chemotherapy-induced neutropenia (CIN) poses a major risk factor for infection-related morbidity and mortality, and can be a dose-limiting toxicity. Patients developing severe neutropenia (SN) or febrile neutropenia (FN) while receiving myelosuppressive chemotherapy regularly require dose reductions and/or delays to their treatment. The incidence of SN or FN can be reduced by prophylactic treatment with granulocyte-colony stimulating factors (G-CSFs), such as filgrastim, lenograstim, or pegfilgrastim. While recently updated guidelines by ASCO<sup>11</sup> and NCCN<sup>12</sup> both recommend primary prophylaxis with a G-CSF when the risk of FN is  $\geq 20\%$ , or when older patients are undergoing more aggressive chemotherapy regimens, treatment varies widely in clinical practice, both in the timing of therapy and in the patients to whom it is offered. Several posters presented at MASCC 2006 examined the use of G-CSFs in a variety of settings.

In a retrospective study, data collected illustrate the patterns of use of both chemotherapy regimens (NHL and breast cancer) and G-CSFs in 11 U.S. community oncology practices (n=618) during 2001 to 2003.<sup>13</sup> More patients were treated with very myelosuppressive chemotherapy during 2002–03 (high=39%, intermediate=32%, low=28%) compared to 2001–02 (high=14%, intermediate=53%, low=33%). Patients were more likely to receive primary prophylaxis in 2002–03 versus 2001–02 in all the chemotherapy risk categories: high-risk 42% versus 7%, intermediate-risk 28% versus 2%, low-risk 9% versus 1%. While the data demonstrated an increased administration of G-CSFs, less than half of the patients at high-risk of FN, for whom primary prophylaxis is recommended, received a G-CSF in the first cycle of chemotherapy.

Studies support the importance of maintaining full chemotherapy doses on schedule.<sup>14,15</sup> However, the majority of older patients — 60% of cancers occur in people older than 65 — are treated with less than standard doses of chemotherapy.<sup>16</sup> In a large randomized, prospective trial (n=852), Balducci *et al.* set out to compare the proportion of older cancer patients experiencing FN when receiving first cycle pegfilgrastim versus current community practice, which may include growth factor support in later cycles.<sup>17</sup> In typical elderly cancer patients, they found growth factor support from the first cycle effectively reduced FN incidence by 60% in solid tumour patients (n=343, P=0.001) and by 59% in patients with NHL (n=73, P=0.004). Thus, the findings of this study support the new guidelines recommending the use of proactive growth factor support in older cancer patients to facilitate the administration of mild to moderately myelosuppressive chemotherapy.

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### Janice Wright's perspective:

A platelet count of  $<75 \times 10^9/L$  is a higher value than we use to define CIT in either our solid tumour or hematological malignancy patient groups. Because of the myelosuppressive therapy patients with hematological malignancies receive, pancytopenia involving severe thrombocytopenia is anticipated. We monitor patients closely and, in the transplant and hematological setting, we do not intervene unless the platelet count is below  $10 \times 10^9/L$  or the patient is experiencing bleeding complications. A higher platelet transfusion threshold may be indicated in some solid tumour patient groups. Currently, platelet transfusion is the therapy of choice should intervention be required. While health-care providers may be comfortable with such low platelet levels, it can be very distressing for the patient and their caregivers. That is why we have instituted an education program teaching people about the risks of CIT and precautions that patients should take. We also administer supportive care for patients with CIT by maintaining reasonable Hb levels. Higher Hb is considered to be associated with a decrease in risk for bleeding with CIT. Maintaining reasonable Hb levels may contribute to a reduction in platelet transfusion requirements. The studies involving TPO-R agonists are being watched with interest. A drug that improves CIT without the potential risks and side effects of platelet transfusion would be a welcome addition to the existing complement of supportive care agents.

When deciding which ESA therapy to use, or more specifically, which dosing regimen is best to administer to raise Hb levels, it is imperative to consider the needs of the patient. A patient's risk factors coupled with what the physician is trying to achieve determine optimal dosing. More frequent dosing is appropriate when the patient requires closer monitoring, thus allowing the clinician to easily control the rise—or decline, if necessary—of the Hb level. With Health Canada's recent approval for a q3w dosing regimen for DA, we can now offer a less frequent dosing for those patients who do not require constant monitoring. The benefit of convenience —fewer injections and fewer visits to the clinic — for patients receiving q3w is obvious. But I would like to stress that it is the individual needs of each patient that must come first. Flexible dosing, whether at qw, q2w, q3w or even longer intervals, allows us to focus on what is right for the patient.

At our institution, we are administering dose-dense chemotherapy regimens more and more. With increasing evidence supporting the importance of keeping treatment on schedule without dose reduction, we are also seeing an increased use of G-CSFs as a primary prophylactic rather than waiting for the first incidence of FN. Furthermore, our ability to differentiate those patients at risk has improved and we are better able to select those candidates best suited for primary prophylactic treatment.

Unfortunately in Canada, clinical practice and the provincial guidelines vary widely. What may be approved and funded in one province may not be available in another. As with any supportive care intervention, the patient's experience is our primary concern. By assessing chemotherapy-induced toxicities as clusters of symptoms rather than individual events, understanding how these toxicities correlate, and evaluating patient quality of life, I think that a reasonable costing model would find that these supportive care agents are in fact cost-effective, particularly in high-risk patients and the elderly.



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