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NEW EVIDENCE

Canadians Collaborating on Turkish Soil

I N S I D E T H I S I S S U E

ICCN: The Role of Supportive Care in Symptom Management
PMH: The Promise of Novel Systemic Therapy and Pathologic Predictors
Real Voices
Caring Voices, an Online Community for Breast Cancer Survivors

Highlights of Supportive Care at ESMO
Advances in the Treatment of Metastatic Colorectal Cancer
Lung Cancer Highlights
Welcome to the New Evidence in Oncology Fall issue for 2006. We are pleased to bring you coverage of four conferences in this special issue, reaching out to the whole Oncology multidisciplinary team.

New Evidence is committed to providing an educational, yet engaging publication for Canadians in Oncology. To achieve this goal, we have met with an Advisory Board of your peers in order to understand your educational needs. From this platform, we have redesigned our journal and introduced a number of exciting new features to improve its readability and make it more pertinent to your clinical practice. We are devoted to publishing high quality, timely, and authoritative articles on the latest clinical research in the field of oncology.

Your interest in New Evidence is deeply appreciated. We hope you enjoy reading and connecting into your Oncology community.

Our Mission: New Evidence in Oncology is a publication for Canadian healthcare professionals (physicians, pharmacists, nurses, etc.). Our concentrated effort provides busy oncology specialists with concise, timely, credible, and objective scientific data, focussing on prominent issues from international oncology conferences and select Canadian conferences. In every issue, key opinion leaders provide a distinctive Canadian perspective in response to the conference coverage. They comment on how the latest international developments may shape how oncology patients are treated and managed in Canada.
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Dr. Sehdev is a community-focused medical oncologist at one of Canada’s largest community hospitals. He completed his fellowship at the Princess Margaret in Toronto in 1991, and his clinical practice treats most types of cancer. However, he has a keen interest in breast cancer, lung cancer, and patient education. Dr. Sehdev has been involved in breast cancer clinical trials through NCIC and BCIRG groups and has recently chaired several medical advisory board meetings on the role of hormonal therapy in breast cancer. In particular, Dr. Sehdev has been part of one of the largest and longest running breast cancer trials ever, the ATAC trial.
The 31st European Society for Medical Oncology (ESMO) Congress was held in Istanbul, Turkey from September 29th to October 3rd, 2006. The meeting attracted approximately 10,000 oncologists, radiotherapists and other healthcare professionals from all over Europe and the world. New clinical trial data on combination therapies for breast and colorectal cancer as well as the recent progress in biologic and antiangiogenic therapy, the wider use of monoclonal antibodies, the role of oncogenes as therapeutic targets and the use of vaccines for cancer prevention, were just a few of the novel and exciting studies presented at the meeting.
Several studies presented at the 2006 meeting of the European Society for Medical Oncology (ESMO) could prove to have significant clinical impact in the area of supportive care. Of note were studies on the need for and timing of therapy for myelosuppression, including the new guidelines for prevention of neutropenia and anemia, and trials regarding prophylaxis for oral mucositis.

The EORTC Guidelines recommend the use of CSFs in both first and subsequent chemotherapy cycles where the risk of febrile neutropenia (FN) is 20% or more and in high-risk patients such as those over the age of 65 years.

New EORTC Guidelines for Hematological Support Officially Announced

While the guidelines have been circulating for some months in draft form, new guidelines from the European Organisation for Research and the Treatment of Cancer (EORTC) on the use of granulocyte-colony stimulating factor (G-CSF) to reduce the incidence of chemotherapy-induced febrile neutropenia (CIN) were officially announced at the recent ESMO meeting.1,2 The announcement made by Dr. Matti Aapro, on behalf of the EORTC G-CSF Task Force, comes on the heels of the American Society of Clinical Oncology’s (ASCO) 2006 update of recommendations of their evidence-based clinical practice guidelines for the use of hematopoietic growth factors for prevention of febrile neutropenia (Editor’s note: see the Volume 4, September 2006 issue of New Evidence for more details about the ASCO guidelines).3

The new EORTC guidelines were developed in response to a need for relevant and applicable guidelines that reflect current European practice, as there is considerable variation in clinical practice regarding how prophylactic treatment with G-CSF is used, both in the timing of therapy and in the patients to whom it is offered. The EORTC Guidelines recommend the use of CSFs in both first and subsequent chemotherapy cycles where the risk of febrile neutropenia (FN) is 20% or more, and in high-risk patients such as those over 65 years. The task force took into consideration Level 1 evidence which suggests that patient-related factors increase the risk of febrile neutropenia (FN); certain chemotherapy regimens increase risk of FN, especially in those over 65 years of age; and that G-CSFs such as pegfilgrastim, filgrastim, or lenograstim (not available in Canada) can be used to maintain the correct dose of chemotherapy and the relative dose intensity/density. The task force concluded that there is strong and consistent evidence that hematologic support with G-CSF can enable delivery of dose-dense/intense chemotherapy shown to have survival benefits, can reduce the incidence of FN, and can treat ongoing FN in patients who do not respond to antibiotic management.

Another of the EORTC’s main recommendations was that patient risk factors such as advanced disease, history of prior FN, poor performance and/or nutritional status, hemoglobin levels <120 g/L, or the presence of liver or cardiovascular disease should be taken into consideration on a patient-by-patient basis before using chemotherapy regimens associated with a 10–20% risk of FN. The guidelines also recommend that where the use of G-CSF is not crucial, clinicians should consider less myelosuppressive chemotherapy regimens or modify the dosing schedule.

In his presentation, Dr. Aapro suggested that while all three G-CSFs available in Europe have been proven effective for preventing FN, there is some evidence to suggest that pegfilgrastim is more efficacious than filgrastim in reducing the rate of FN (6% vs. 17%; P<0.001), though the results are preliminary and unpublished.4
The preliminary analysis of the results of a study conducted by the Spanish DELFOS Study group was presented by Dr. Antonio López-Pousa. The objective of this multi-centre non-interventional, prospective-cohort study was to determine a predictive model for first-cycle CIN in patients with solid tumours in order to facilitate the development of appropriate protocols in routine patient care and to improve clinical decision making. For the purpose of this model, CIN was defined as neutropenia grade ≥3 (with or without body temperature ≥38°C). This large study enrolled a total of 1,194 patients (56% female; mean age 58 years; 93.9% ECOG status ≤1) with solid tumours (breast, 38%; lung 18%; colorectal, 15%; other 30%), of whom 51% (n=508) were receiving adjuvant chemotherapy. To be eligible, patients must have had a histologically confirmed solid tumour, no prior chemotherapy, a performance status ECOG ≤2, and no concomitant diseases that could cause leucopenia, thrombocytopenia, or anemia. Using the hierarchical principle, risk factors related to CIN were modelled through logistic regression methods. Identified risk factors included: ECOG status 2 versus 0 (P=0.003; OR=3.12), baseline lymphocyte count (P=0.011; OR=0.67), baseline ANC (P=0.026; OR=0.90) and the interaction between gender (specifically male sex) and treatment intention (P=0.012). This interaction may reflect the weight of the breast cancer female population in the study sample, according to the investigators.

In a subgroup analysis of 435 patients with breast cancer (99% female; mean age 54 years; 100% ECOG ≤2), the authors found that, in addition to ECOG status (P<0.0005) and baseline lymphocyte and neutrophil counts, age ≥55 years (P=0.011) and treatment regimen (P=0.031) were strong predictors of first-cycle neutropenic risk, with anthracycline-based regimens being more toxic than taxane-based treatments (Table 1).

Extended Dosing and the Possible Benefit of Iron Supplementation in Anemia

If left untreated, severe anemia may cause a delay in cancer treatment and reduced quality of life, resulting in suboptimal chances of a cure or optimal long-term survival. In the last decade, ESAs have been integrated into the standard of care world wide for chemotherapy induced anemia (CIA) in patients with non-myeloid malignancies.

<table>
<thead>
<tr>
<th>Table 1: Predictive model of CIN</th>
<th>P-value</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender x Treatment Intention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male x Radical Adjuvant</td>
<td>0.413</td>
<td>1.576</td>
<td>0.298 – 1.140</td>
</tr>
<tr>
<td>Male x Radical Neoadjuvant</td>
<td>0.012</td>
<td>17.975</td>
<td>1.893 – 170.697</td>
</tr>
<tr>
<td>Male x Radical Curative</td>
<td>0.013</td>
<td>6.263</td>
<td>1.470 – 26.688</td>
</tr>
<tr>
<td>Baseline Lymphocytes</td>
<td>0.011</td>
<td>0.670</td>
<td>0.492 – 0.913</td>
</tr>
<tr>
<td>ECOG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG (1)</td>
<td>0.770</td>
<td>1.075</td>
<td>0.662 – 1.747</td>
</tr>
<tr>
<td>ECOG (2)</td>
<td>0.003</td>
<td>3.123</td>
<td>1.459 – 6.683</td>
</tr>
<tr>
<td>Baseline Neutrophils</td>
<td>0.026</td>
<td>0.901</td>
<td>0.823 – 0.987</td>
</tr>
</tbody>
</table>

(Model significance: Chi² = 0.0005)

Canadian Perspective by Dr. Sehdev

In the study by López-Pousa and colleagues, there were a few factors – curative versus palliative therapy, performance status, and baseline lymphocyte and neutrophil counts – that were determined to be important indicators of risk of febrile neutropenia. These findings are something we might use in practice to determine which patients are at very high risk of neutropenia, for whom we should potentially use filgrastim. For patients who have had a recent infection or postoperative abcess, or who have other significant comorbid illnesses (renal failure, diabetes), we could potentially use this assessment model to justify to government or private payers the need for a myeloid growth factor.
The two ESAs currently available in Canada, epoetin alfa (EA) and darbepoetin alfa (DA) differ in terms of their receptor-binding affinity and serum half-life, thus allowing for alternative dosing and scheduling strategies for DA. Clinical studies have demonstrated that EA and DA may be administered at extended intervals (weekly for EA and once every three weeks for DA) without loss of efficacy. Because the serum half-life of DA is almost three-fold longer than that of EA (25 h versus 9 h), resulting in an increased in vivo biological activity, dosing intervals can be successfully extended to three or four weeks. An extended dosing schedule, allowing possible synchronization to the chemotherapy cycle, may in fact simplify the treatment of cancer patients and minimize disruption to patients and their families. This has been confirmed by the recent approval in Europe, the US, and Canada for dosing of darbepoetin 500 mcg once every three weeks for the treatment of CIA in non-myeloid cancers. A randomized, controlled non-inferiority study, presented in poster format at ESMO by Dr. Lee Schwartzberg and colleagues, confirmed the ability of DA to be administered in an extended dosing schedule. The baseline characteristics of patients in the weekly and extended dosing arms were similar with regards to age, sex, primary tumour type, stage of cancer, and Hb values.

Darbepoetin alfa administered either weekly (150 mcg) or on an extended dose schedule (300 mcg once every two weeks or 500 mcg once every three weeks) effectively corrected hemoglobin levels in patients with primarily solid tumours and no iron deficiency at baseline (Figure 1). The rates of red blood cell transfusions and adverse events were also similar between groups. The results of the study suggest that the dosing interval for DA does not appear to affect the drug’s ability to raise Hb levels or reduce the need for blood transfusions.

It has been noted that patients with cancer may have an absolute or functional iron deficiency as a result of their disease or its treatment. Patients with CIA have low serum iron levels even though...
the bone marrow has adequate iron — this is termed functional iron deficiency (FID).10 In the presence of FID without adequate iron support, stimulation of erythropoiesis by ESA is impaired. Therapy to ameliorate chemotherapy induced anemia includes supplemental iron therapy, blood transfusions, and/or erythropoietic-stimulating agents (ESAs). Though the use of supplemental iron therapy is well established in anemic patients with chronic kidney disease, there is a lack of studies to support the use of iron supplementation in patients with cancer- or chemotherapy-related anemia who are treated with ESAs. Bastit and colleagues presented an interim analysis of a randomized, multicentre, open-label study that evaluated the safety and efficacy of intravenous (IV) iron versus oral iron/no iron in patients with CIA.11 Patients with non-myeloid malignancies were randomly assigned to receive DA 500 mcg every three weeks with IV iron 200 mg (single dose Q3W at the same time as DA or in two doses of 100 mg within three weeks) (n=102), or DA 500 mcg every three weeks with standard practice (oral iron/no iron) (n=94), for up to 13 weeks. The IV iron was administered as a sodium ferric gluconate complex in sucrose or iron sucrose for injection. Patients were stratified by tumour type (lung/gynaecological versus other tumours) and baseline Hb (<100 and ≥ 100 g/L).

For patients randomized to IV iron, a higher Hb response rate was observed (Figure 2). More importantly, trends to a lower risk of transfusion (Figure 3), a shortened time to target Hb, and a greater improvement in fatigue scores (≥3-point change) were achieved in the IV iron group, suggesting that IV iron supplementation may enhance the response to DA Q3W. The combination of DA Q3W and IV iron was well tolerated with no unexpected safety concerns based on the interim results.

Though the interim data have not reached statistical significance, the final conclusions of this study are awaited, and this and other confirmatory trials may prove important for understanding the role of concomitant iron supplementation and ESA use for improved erythropoietic management in patients with CIA.

Chlorhexidine Is as Effective as Cryotherapy for Oral Mucositis Prophylaxis

Oral mucositis, a common side effect of conventional chemotherapy or radiation therapy, remains a major source of illness despite the use of a variety of agents to prevent it. A recent meta-analysis of oral and prophylactic agents for the prevention of oral mucositis (OM) found that published trials were of varied design, low power, and poor quality, suggesting the need for well designed and conducted trials with sufficient numbers of participants.12

Until recently, there has been conflicting evidence for the use of chlorhexidine prophylaxis of OM. However, a Danish study presented at ESMO by Dr. Jens Sorensen showed that when compared to saline mouthwash, chlorhexidine and oral cooling (cryotherapy) were significantly better at reducing the severity and duration of OM.13 The randomized, double-blind, placebo-controlled trial enrolled 225 previously untreated patients undergoing chemotherapy for gastrointestinal cancers, the majority of whom had colorectal cancer and were over 40 years of age. The patients were receiving bolus 5-FU 425 mg/m² with leucovorin 20 mg/m² daily over five days. For this study, they were randomly assigned to one of the three prophylactic measures:

**Arm A:** chlorhexidine 0.1% 15 ml mouth rinse for one minute, once daily for three weeks

**Arm B:** placebo (normal saline with same taste additive as in A) with same dose and frequency as Arm A

**Arm C:** crushed ice 10 minutes before to 35 minutes after chemotherapy start

The trial arms were balanced with respect to diagnoses, stage, age, gender, smoking habits, and performance status. Patients self-reported the severity and duration of their OM. Compliance to treatment was similar in all arms; however, 48% of patients in the chlorhexidine group complained of taste disturbance while 21% in the cryotherapy group complained of headaches. Mucositis Grade 3/4 (impaired oral nutrition/need of artificial nutrition) occurred in 12%, 32%, and 10% in arms A, B, and C, respectively (Table 2). The severity of OM was significantly worse in the placebo (saline) group than in the chlorhexidine (P<0.01) and cryotherapy (P<0.005) groups.
The presentation by Jens Sorensen and colleagues was very useful, in my opinion, as I’ve not seen actual data on the value of these therapies in many years. While nurses may already be offering these interventions to patients, a lot of the evidence for their effectiveness was anecdotal. This was a relatively large trial and I don’t think we will see another of its kind done again. It was addressing a relatively old-fashioned question but it is definitely applicable to our practice, though it was based on a chemotherapy regimen that we don’t use very commonly in practice anymore.

Their data showed that both the oral cooling and the chlorhexidine were better than placebo. I am not so sure we ever took cryotherapy with popsicles very seriously in our practice. However, both chlorhexidine and oral cooling are practical measures that are easy to implement and they both seem effective, so it begs the question of whether it would be more helpful to do both simultaneously in some refractory patients, and whether such interventions would be well tolerated by patients.

We also note severe oral mucositis in patients who are receiving bone marrow or stem cell transplants, however, and the agent palifermin is increasingly being used in this environment. Patients receiving single-agent capecitabine as adjuvant therapy occasionally develop stomatitis, and I could see treatment with chlorhexidine becoming quite feasible for the prevention of oral mucositis in this population.

Patients treated with cryotherapy had a shorter median duration mucositis of one day (range 0–20) versus three days (0–17) for chlorhexidine and five days (0–20) for saline. Chlorhexidine was significantly better than saline in terms of reducing the severity (P<0.01) and duration (P=0.035) of OM. Similarly, severity (P<0.005) and duration (P=0.003) of OM were significantly improved with cryotherapy compared to saline prophylaxis, while there was no significant difference between cryotherapy and chlorhexidine in terms of frequency, severity, or duration. The authors conclude that cryotherapy and chlorhexidine are inexpensive and practical ways of reducing patient discomfort caused by chemotherapy induced oral mucositis.

**Vitamin B6 Is Not Effective for Hand-Foot Syndrome**

A number of chemotherapy agents, such as capecitabine, fluorouracil, and liposomal doxorubicin, can result in the uncomfortable side effect called hand-foot syndrome (HFS) or palmar-plantar erythrodysesthesia (PPE). Treatment can consist of reducing or stopping treatment with the drug that caused the syndrome. Pyridoxine (vitamin B6) has often been used empirically for the prevention and treatment of capecitabine-induced HFS. In 1990, a small phase 2 trial was published that suggested that treatment with pyridoxine reduced the symptoms of hand-foot syndrome in four of five patients treated. However, a recent study by Korean scientist Yoon-Koo Kang and colleagues has debunked any claims of efficacy of this compound in HFS.

The randomized double-blind, placebo-controlled study enrolled 382 chemotherapy naive patients with gastrointestinal tract cancers who were beginning treatment with capecitabine-containing chemotherapy. Patients were randomly assigned to receive either oral pyridoxine (200 mg/day) or placebo daily during chemotherapy, which was either capecitabine alone or in combination with cisplatin or docetaxel. Patients in the placebo group who developed Grade 2 or 3 HFS (according to NCI CTC version 2.0) during chemotherapy were randomly assigned to receive either pyridoxine or placebo for the next cycle in order to determine whether pyridoxine could prevent the recurrence of severe HFS.

Pyroxidine did not prevent the occurrence of HFS in treated patients, as 31% of patients in the placebo group (55/176) and 32% in the pyridoxine group (57/177) developed Grade 2 or 3

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**Table 2: Percentage of patients with oral mucositis, according to CTC Grade**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Chlorhexidine (n=73)</th>
<th>Saline (n=66)</th>
<th>Cryotherapy (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>43</td>
<td>23</td>
<td>43</td>
</tr>
<tr>
<td>1</td>
<td>26</td>
<td>27</td>
<td>27</td>
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<tr>
<td>2</td>
<td>15</td>
<td>15</td>
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<tr>
<td>3</td>
<td>11</td>
<td>32</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Not assessable</td>
<td>4</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>
HFS during chemotherapy irrespective of the cumulative dose of capecitabine received (116720.6 mg/m² vs. 116184.2 mg/m², P=0.83). The median number of chemotherapy cycles to Grade 2 or 3 HFS was three in both groups. Moreover, there was no difference in improvement of HFS symptoms between the pyrroxi-
dine group or among the 44 patients who had Grade 2 or 3 HFS and subsequently received pyroxi-
dine 200 mg/day (proportion of patients with improvement of HFS: 48% vs. 43%, respectively, P=0.94). Increased age and/or the development of mucositis after the first cycle of chemotherapy were independent prognostic factors for the development of HFS (OR: 1.57, 95% C.I.: 1.05–2.36, P=0.03; OR: 1.51, 95% C.I.: 1.00–2.36, P=0.00, respectively).


tively prevent (febrile) neutropenia and infection during neoadjuvant che-


Boiled Down

- The EORTC Guidelines recommend the use of CSFs in both first and subsequent chemotherapy cycles where the risk of febrile neutropenia (FN) is 20% or more, and in high-risk patients such as those over 65 years.

- In patients with solid tumours, ECOG status (P<0.0005), baseline neutrophil count (P=0.019), age ≥55 years (P=0.011) and treatment regimen (P=0.031) are strong predictors of first-cycle neutropenic risk.

- Preliminary data suggests that intravenous iron can boost the haemoglobin response and lower the transfusion rate in patients receiving an erythropoietic stimulating agent for anemia.

- Cryotherapy and chlorhexidine significantly reduced the severity and duration of oral mucositis.

- Pyridoxine does not prevent the occurrence of hand-foot syndrome in patients receiving chemotherapy.

Canadian Perspective by Dr. Sehdev

We have always had the anecdotal belief that using vitamin B6 could help prevent hand-foot syndrome. In our practice, we routinely give patients vitamin B6 100 mg twice a day believing that it may prevent or ameliorate symptoms of hand-foot syndrome. The Korean study found that B6 was of no value for the prevention of hand-foot syndrome. This simple and in-

expensive trial provides valuable evidence refuting the utility of pyridoxine, both for primary prevention and secondary use in PPE sufferers.
Advances in the Treatment of Metastatic Colorectal Cancer

Lesley McKarney

Colorectal cancer (CRC) continues to be a leading cause of cancer morbidity and mortality worldwide. Over the last 50 years, the treatment of metastatic colorectal cancer (mCRC) has consisted of 5-fluorouracil (5-FU) -based chemotherapy. In the past decade, treatment options for patients with colorectal cancer have increased with the advent of newer combination chemotherapy regimes (Figure 1). New molecular targets have provided novel opportunities in the treatment of mCRC (Table 1). One of the most advanced approaches to date is the use of targeted inhibitors of the epidermal growth factor receptor (EGFR).

At ESMO this year, there were numerous oral and poster sessions that provided the latest data on therapeutic strategies in the treatment of colorectal cancer, with particular interest and excitement surrounding the latest data for the monoclonal antibodies (MAbs) cetuximab, panitumumab, and bevacizumab. The overall conclusion of experts attending the meeting was that despite these clinical advances, new strategies are warranted in order to improve the efficacy as well as the safety of new therapies.

XELOX as Effective as FOLFOX as First-Line Therapy in mCRC

According to phase 3 results presented by Dr. Jim Cassidy during the Presidential Symposium at ESMO 2006, the chemotherapy combination XELOX (oral Xeloda® plus oxaliplatin) is as effective as FOLFOX (oxaliplatin, 5-FU, leucovorin) as first-line therapy.
The primary objective of the original two-arm study was to show non-inferiority of XELOX compared with FOLFOX. By February 2004, 634 patients had been enrolled. At this point in time, the investigators altered the protocol to a 2x2 and added bevacizumab to a random subset versus placebo, and enrolled a further 1,401 patients. At a median follow-up of 18.6 months, progression-free survival (PFS) was 8.0 months for XELOX and 8.5 months for FOLFOX.

Furthermore, the addition of bevacizumab to either treatment regimen provided a small but significant improvement in PFS among these patients compared to chemotherapy alone. When both regimens are considered together, those patients who were given bevacizumab had a PFS of 9.4 months versus 8.0 months with placebo (P=0.0023).

**Cetuximab and Panitumumab: Targeted Therapies for Metastatic Colorectal Cancer**

The epidermal growth factor receptor was one of the first proto-oncogenes recognized. It is a member of the erbB (or HER) family of genes. In the normal mammalian cell, EGFR is important in the control of cellular growth and differentiation. EGFR knockout in mice is essentially a lethal mutation. In the malignant cell, EGFR and its downstream effects have been shown to control cell cycle control, apoptosis, angiogenesis, invasion, and metastasis. EGFR is not just a proliferative signal but one of many components of the apparatus that a normal or malignant cell uses to decide whether to survive (or undergo apoptosis/cell death). Perturbation of EGFR leads to a strong survival signal whereas blockade of EGFR should decrease the impetus to survive in the face of cell damage induced by insults such as chemotherapy and radiation.

It has been demonstrated that EGFR expression is associated with many epithelial tumours, in particular 25–77% of colorectal cancers (all stages). In many of these tumours there is evidence from small series that EGFR or ligand over-expression is an adverse prognostic factor for tumour metastasis, recurrence, and overall survival. At least one study suggests there is no correlation between the level of EGFR expression and clinical response to EGFR targeting therapies in patients with CRC, so it is unlikely that it could be used to select patients for treatment with EGFR inhibitors.

Clinical trials have been conducted on selected tumours to assess the potential benefits of EGFR inhibitors alone or in combination with chemotherapy, radiotherapy, or other hormonal/targeted agents. There have been two strategies for the development of anti-EGFR agents: MABs to the extra-cellular domain of EGFR (cetuximab [chimeric], matuzumab [humanized], and panitumumab [human]) and small molecule, adenosine triphosphate-competitive inhibitors of the receptor’s tyrosine kinase (gefitinib and erlotinib).

**Canadian Perspective by Dr. Sehdev**

The Roche-funded trial comparing XELOX to FOLFOX is the largest trial ever done for colorectal cancer, involving more than 2,000 patients in British and Spanish clinics. This is also the first data for first-line metastatic disease showing the benefit of adding bevacizumab to FOLFOX. However, the clinical improvement in survival was not very impressive, even if it was significant. We know from preclinical studies that treatment with bevacizumab should be maintained after chemotherapy in order for disease control to be maintained. In the previous registration trial using bevacizumab in conjunction with IFL chemotherapy, most patients continued bevacizumab after chemotherapy discontinuation, until disease progression. In this study, however, most patients stopped using bevacizumab after chemotherapy ended. This could account for the smaller than expected result. Also, an imbalance in randomization was noted – the patients in the bevacizumab arm had an unanticipated shorter time to recurrence after their previous surgery or adjuvant treatment, possibly implying more aggressive disease, which may have biased results.

We may now comfortably substitute oral capecitabine for infusional 5-FU (i.e., XELOX in lieu of FOLFOX) in the advanced disease setting, and future trials will need to address the benefit of bevacizumab when continued as a maintenance treatment beyond chemotherapy and until progression.
Cetuximab
Cetuximab (Erbitux®) is a human-chimeric monoclonal antibody of the immunoglobulin G1 (IgG1) subtype. It binds the extra-cellular domain of EGFR to inhibit binding of its ligands such as EGF and TGF-alfa. In vitro, cetuximab has been associated with cell-cycle arrest (at G1 to S transition) and enhanced apoptosis. Synergy and additive cytotoxicity have been demonstrated with radiation and cytotoxics including platinum therapy, gemcitabine, taxanes, and camptothecins; therefore, it seemed logical to develop it as a combination therapy. Cetuximab has been evaluated both alone and in combination with radiotherapy and various cytotoxic chemotherapeutic agents in a series of phase 2/3 trials that studied primarily treated patients with either head and neck cancer or CRC. Cetuximab has been shown to re-sensitize tumours to chemotherapy in patients with colorectal cancer receiving irinotecan (the BOND trial). In EGFR-positive patients with irinotecan-refractory mCRC, cetuximab alone had minimal activity (10.8% response rate [RR]); however, when combined with irinotecan it had a 22% RR (P=0.007) and modestly increased progression-free and overall survival. It was this study that prompted the Food and Drug Administration (FDA) to approve it in February 2004 for use in the treatment of mCRC. Health Canada issued a Notice of Compliance for cetuximab in mCRC on September 9, 2005.

Panitumumab
Panitumumab (Vectibix™) is a recombinant fully human IgG2 MAb which binds specifically to the EGFR and competitively inhibits the binding of ligands to this receptor. Panitumumab differs from cetuximab in that it has a higher affinity for the receptor and it produces fewer hypersensitivity reactions. The compound was shown to be active in a phase 2 study in advanced colorectal cancer. In this study, 15 (10%) of 148 patients that had experienced failure with first-line chemotherapy achieved a clinical response to panitumumab. The safety and efficacy of the agent was further evaluated in a phase 3 randomized controlled trial of 463 patients who were EGFR-positive and had mCRC or metastatic rectal cancer. Patients were randomly assigned to receive panitumumab plus best supportive care or best supportive care alone (BSC) until disease progression. Panitumumab treatment resulted in a significant prolongation in PFS (96 days) compared to BSC alone (60 days). Based on the results, panitumumab became the second EGFR inhibitor approved by the FDA for the treatment of mCRC in September, 2006 (Table 1).

Safety of Anti-EGFR MAbs
Toxicity has been a major obstacle in the development of therapeutic antibodies for cancer. Cross-reactivity with normal tissues can cause significant side effects for unconjugated (naked) antibodies. In particular, skin toxicity is a problem facing the EGFR inhibitors in CRC (Table 2). An acneiform rash commonly occurs on the face and trunk in a majority of patients. In addition, hypersensitivity reactions have been reported for both agents, though they are more common with cetuximab. Severe infusion reactions occur in approximately 2–3% of patients treated with cetuximab, usually with the first infusion and requiring immediate discontinuation of treatment. In the pivotal trial of panitumumab, severe infusion reactions occurred in only 1% of patients.

<table>
<thead>
<tr>
<th>Table 1: Approved targeted drugs for advanced colorectal cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bevacizumab (Avastin®)</strong></td>
</tr>
<tr>
<td>Mechanism: Humanized monoclonal antibody against vascular endothelial growth factor (VEGF)</td>
</tr>
<tr>
<td>Indication: First-line treatment for metastatic colorectal cancer</td>
</tr>
<tr>
<td>Toxicities: Hypertension, intestinal perforation (rare)</td>
</tr>
<tr>
<td><strong>Cetuximab (Erbitux®)</strong></td>
</tr>
<tr>
<td>Mechanism: Chimeric monoclonal antibody against epidermal growth factor receptor (EGFR)</td>
</tr>
<tr>
<td>Indication: EGFR-positive, irinotecan-refractory metastatic colorectal carcinoma</td>
</tr>
<tr>
<td>Toxicities: Acneiform dermatitis, folliculitis, hypersensitivity reactions</td>
</tr>
<tr>
<td><em><em>Panitumumab</em> (Vectibix™)</em>*</td>
</tr>
<tr>
<td>Mechanism: Entirely human monoclonal antibody against epidermal growth factor receptor (EGFR)</td>
</tr>
<tr>
<td>Indication: EGFR-positive, after disease progression on, or following fluoropyrimidine-, oxaliplatin-, and irinotecan- containing chemotherapy regimens</td>
</tr>
<tr>
<td>Toxicities: acneiform dermatitis, hypomagnesemia, hypersensitivity reactions</td>
</tr>
</tbody>
</table>

*Awaiting Health Canada approval
As presented at ESMO, Hecht et al. reviewed the safety and tolerability data of ten clinical studies of panitumumab monotherapy for mCRC in enrolled patients after failure of oxaliplatin and/or irinotecan chemotherapy. They found that panitumumab was generally well tolerated, and while most patients (93%) had at least one adverse event considered related to panitumumab, only 22% reported an adverse event of Grade 3 or higher (Table 3). As expected, the most common adverse events were rash, fatigue, nausea, diarrhea and vomiting. Grade 3 or higher hypomagnesemia was reported in 5% of patients.

Interestingly, in the pivotal trial for cetuximab, there appeared to be a higher response rate among patients who experienced a skin rash. This finding has led to the suggestion that there may be a physiologic correlation between the onset of skin toxicity and adequate EGFR response. In a late-breaking abstracts session at ESMO, Dr. Eric van Cutsem presented the interim results of the EVEREST trial, a small (n=166) randomized, multicentre study that is evaluating this hypothesis using a “escalating dose-to-rash” strategy. Patients with EGFR-expressing mCRC failing prior irinotecan treatment were initially treated with cetuximab (initial dose 400 mg/m², then 250 mg/m²/week) plus irinotecan (2-weekly regimen 180 mg/m²). After 22 days of treatment, patients with mild to absent rash were randomized to one of two arms: continuation on standard dose (Arm A) or dose escalation (Arm B; dose increases of 50 mg/kg every week) until development of more severe rash, tumour response or dose = 500 mg/m². Patients who had already demonstrated a severe rash on the standard dose were excluded from the dose-escalation arm (Arm C). The results of skin and tumour biopsies taken before and after treatment suggest that patients who received the dose increases (Arm B) developed more severe rashes and demonstrated an increase in response rate that was similar to the response rate in the severe skin rash group (Arm C) (Table 4). Doses up to 500 mg were well tolerated. Van Cutsem cautioned against over-interpretation of the premature phase 2 data as the results have yet to reach statistical significance.

**How do they compare?**

In his discussion of the targeted therapy data presented at ESMO, Dr. Alberto Sobrero suggested that at the present time there is little difference in the rationale for using either anti-EGFR MAb therapy. In regimens tested thus far, both cetuximab and panitumumab result in slight increases in the time to progression and the response rate. In terms of monotherapy, response rates of about 10–15%, stable disease rates of about

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**Table 2: Skin toxicity data for EGFR antibodies in refractory mCRC**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Antibody</th>
<th>Patient population</th>
<th>n</th>
<th>Skin toxicity, % (Grade3/4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sastre et al. 2006&lt;sup&gt;10&lt;/sup&gt;</td>
<td>cetuximab</td>
<td>elderly</td>
<td>41</td>
<td>9.7</td>
</tr>
<tr>
<td>Cunningham et al. 2004&lt;sup&gt;2&lt;/sup&gt;</td>
<td>cetuximab</td>
<td>pretreated</td>
<td>111</td>
<td>12</td>
</tr>
<tr>
<td>Humblet et al. 2006&lt;sup&gt;3&lt;/sup&gt;</td>
<td>panitumumab</td>
<td>pretreated</td>
<td>176</td>
<td>13</td>
</tr>
<tr>
<td>Fischer von Weikersthal et al., 2006&lt;sup&gt;7&lt;/sup&gt;</td>
<td>cetuximab + XELOX</td>
<td>first-line</td>
<td>43</td>
<td>16</td>
</tr>
<tr>
<td>Hecht et al. 2006&lt;sup&gt;8&lt;/sup&gt;</td>
<td>panitumumab</td>
<td>pretreated</td>
<td>920</td>
<td>13</td>
</tr>
</tbody>
</table>

**Table 3: Treatment-related adverse events associated with panitumumab**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acneiform dermatitis</td>
<td>411 (52%)</td>
<td>39 (5%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Pruritis</td>
<td>389 (49%)</td>
<td>13 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Erythema</td>
<td>372 (47%)</td>
<td>32 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Rash</td>
<td>293 (37%)</td>
<td>22 (3%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Paronychia</td>
<td>147 (19%)</td>
<td>6 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>106 (13%)</td>
<td>3 (&lt;1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>105 (13%)</td>
<td>7 (1%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Note: toxicities were graded using NCI-CTC v.2.0 or CTCAE v.3.0 for selected skin toxicities.
### Table 4: Efficacy analysis after 18 weeks of cetuximab treatment

<table>
<thead>
<tr>
<th>Best overall response</th>
<th>Arm A (n=45)</th>
<th>Arm B (n=44)</th>
<th>Arm C* (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>6 (13%)</td>
<td>12 (27%)</td>
<td>9 (20%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>20 (44%)</td>
<td>18 (41%)</td>
<td>18 (41%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>12 (27%)</td>
<td>13 (30%)</td>
<td>9 (20%)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>7 (16%)</td>
<td>1 (2%)</td>
<td>8 (18%)</td>
</tr>
<tr>
<td>Response rate (95% CI)</td>
<td>13 (5%; 27%)</td>
<td>27 (15%; 43%)</td>
<td>20 (10%; 35%)</td>
</tr>
</tbody>
</table>

*Only patients who had experienced > Grade 1 skin reaction up to day 22 and who reached randomisation day

### Table 5: Latest trial results for EGFR antibodies in refractory mCRC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Antibody</th>
<th>Patient population</th>
<th>n</th>
<th>Overall RR (CR+PR)</th>
<th>Stable disease</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sastre et al. 2006*10</td>
<td>cetuximab</td>
<td>elderly (median age: 76)</td>
<td>41</td>
<td>15</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>Pessino et al. 200611</td>
<td>cetuximab</td>
<td>more than 2 sites</td>
<td>40</td>
<td>10</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>Cunningham et al. 20043</td>
<td>cetuximab</td>
<td>pretreated</td>
<td>111</td>
<td>11</td>
<td>35</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>cetuximab + irinotecan</td>
<td></td>
<td>218</td>
<td>23</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>Humblet et al. 2006**</td>
<td>panitumumab</td>
<td>pretreated</td>
<td>176</td>
<td>12</td>
<td>33</td>
<td>2</td>
</tr>
<tr>
<td>Fischer von Weikersthal et al., 2006**</td>
<td>cetuximab + XELIRI cetuximab + XELOX</td>
<td>first-line</td>
<td>43</td>
<td>42</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>41</td>
<td>65</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Peeters et al., 2006*</td>
<td>panitumumab</td>
<td>pretreated</td>
<td>231</td>
<td>8</td>
<td>28</td>
<td>2</td>
</tr>
</tbody>
</table>

*Data presented at ESMO  RR: response rate; CR: complete response; PR: partial response; PFS: progression-free survival

20–30%, and progression-free survival improvements of two to three months are consistent among studies of either agent (Table 5).

Panitumumab, Dr. Sobrero added, has the advantage in terms of affinity for the EGF receptor, but cetuximab has been tested in combination with chemotherapy and is more synergistic. There may be more convenience with panitumumab in terms of dosing: it can be dosed once every two weeks as opposed to weekly for cetuximab. Panitumumab is associated with slightly fewer Grade 3/4 toxicities (<1% compared to 2–4% for cetuximab). Nevertheless, there are more studies providing clinical efficacy data for cetuximab, whether in first-line or third-line studies, as monotherapy, or in combination with chemotherapy or other biological agents such as bevacizumab. The real difference between the two agents, Sobrero surmised, may be in the hypersensitivity reactions, which are more common with cetuximab and require pretreatment with histamines. Ongoing first-line, randomized combination trials will further define the toxicity profiles of these compounds, and decide their future.

### Boiled Down

- XELOX was non-inferior to FOLFOX in terms of PFS
- XELOX was more convenient than FOLFOX
- The addition of bevacizumab to either chemotherapy regimen significantly improved progression-free survival compared to chemotherapy alone
- Data for overall survival are not yet mature
- Cetuximab and panitumumab result in response rates of about 10–15%, stable disease rates of about 20–30%, and progression-free survival improvements of two to three months
- Panitumumab was shown to be safe and generally well tolerated; 22% of patients reported an adverse event of Grade 3 or higher
- Phase 2 data suggests a physiologic correlation between the onset and severity of skin toxicity and adequate EGFR response
Cetuximab is an expensive drug that has been approved in Canada but is not yet marketed. The take home message from the cetuximab study by Sastre et al. was that the response rates for first-line monotherapy were modest at around 15% and very similar to what has been observed in salvage therapy. Cetuximab clearly has significant activity, however, in combination with irinotecan in the third-line setting. The side effects and toxicity of panitumumab were manageable in the salvage setting. The suggestion by the commentator in this session was that perhaps cetuximab is favoured by a larger body of evidence due to the larger number of trials performed with this agent to date; however, panitumumab may have the edge in terms of side effects and toxicity. In our clinic, we have been quite excited about panitumumab because we have had good results with it in our patients (on a clinical trial) and the common skin toxicities such as the rash are quite manageable. As in the case of erlotinib, the ideal management of the rash is not yet well defined, yet simple topical therapies are rarely helpful; corticosteroids can occasionally be very effective (oral or topical) and most severe cases respond well to temporary withholding of therapy and re-challenge.

We would like to encourage all of our Canadian centres for cancer treatment to participate in ongoing clinical trials for these new agents, particularly for panitumumab, because these studies are already running in Canada. The overall response rates for both agents are modest and short-lived, so the evidence thus far for these biological agents suggests that they have a small degree of anticancer activity that is probably best explored in combination chemotherapy. They may also be of value in older people who can’t tolerate chemotherapy.
Non–small-cell lung cancer (NSCLC) accounts for 80% of all lung cancers. While newer treatment options have resulted in small improvements in survival for early- and advanced-stage NSCLC, clinical outcomes for this disease remain poor and the treatment is nonspecific, nonselective, and toxic. Current issues in lung cancer management thus include gaining a better understanding of lung cancer biology, better patient selection, and developing new, more effective and less toxic therapies. The latest clinical trial reports in genomic profiling were presented at ESMO 2006.

Utility of Predictive Markers for Chemotherapy Still Uncertain

Understanding the mechanisms of resistance or sensitivity to cisplatin chemotherapy and utilizing that knowledge to identify molecular markers that might be predictive of clinical outcome has been a major goal of lung cancer research. The mRNA expression of several genes in the nucleotide excision repair pathway has been implicated in cisplatin resistance. The excision repair cross-complementing (ERCC1) gene is involved in the NER pathway. It has been suggested that cancer patients with lower ERCC1 levels, resulting in lower DNA repair capacity, may have enhanced response and survival with cisplatin-based chemotherapy. This was supported by a molecular analysis of tumour samples from patients randomized on the IALT trial published in 2006 in the New England Journal of Medicine which demonstrated that of 761 patients with NSCLC who had undergone complete resection, those with ERCC1-negative tumours (56%) derived more survival benefit (P=0.009) from adjuvant cisplatin-based chemotherapy than those patients with ERCC1-positive tumours (44%). These data suggest that ERCC1 expression may be useful in selecting patients for cisplatin-based chemotherapy.

Somewhat conflicting data were presented by Rafael Rosell at ESMO 2006. The phase 3 randomized study was designed to further evaluate the predictive value of ERCC1 mRNA expression in advanced NSCLC. The investigators hypothesized that response to first-line chemotherapy could be improved by measuring pretreatment ERCC1 mRNA levels and customizing therapy accordingly. To assign the ERCC1 genotype, RNA was isolated from pretreatment biopsies from 444 patients with stage IV NSCLC who had been randomly assigned to either the control arm or the genotypic arm in a 1:2 ratio. The control arm received docetaxel/cisplatin, while in the genotypic arm, patients with low ERCC1 levels received docetaxel/cisplatin, and those with high levels received docetaxel/gemcitabine. A large number (17.6%) of patients withdrew from the study prior to chemotherapy because of difficulty in measuring ERCC1 mRNA. Of those patients who could be evaluated at the end of the study, the objective response rates were observed in 107 (51%) patients in the genotype arm and 53 (39%) patients in the control arm (P=0.019).
arm and 53 (39%) patients in the control arm (P=0.019). There was no difference in progression-free survival (HR 0.9, P>0.05), or overall survival (HR 0.9, P>0.05). The large number of patients who withdrew from the study post-randomization raises concerns about the potential for bias in this study.

The x-ray repair cross-complementing group 3 (XRCC3) gene is suspected of playing a role in cancer susceptibility. XRCC3 participates in DNA double-strand break/recombination repair through homologous recombination to maintain chromosome stability. Carlos Camps and colleagues from the Spanish Lung Cancer Group conducted a retrospective pooled analysis of three trials to assess the possible association of XRCC3 241 Met/Met with greater sensitivity to cisplatin-gemcitabine chemotherapy.5 The XRCC3 genotype was analyzed in 932 patients with stage IV NSCLC. Of the 932, 216 were treated with gemcitabine/cisplatin, 624 with docetaxel/cisplatin, and 92 with docetaxel/gemcitabine. Patient characteristics across the three regimens were balanced, with the exceptions that those on the cisplatin-docetaxel regimen were younger, while those receiving the cisplatin-gemcitabine regimen were more likely to have adenocarcinoma. The XRCC3 241 Met/Met variant was found in 126 patients (13.5%) at the same frequency in all age groups. The presence of the XRCC3 241 Met/Met variant was neither prognostic for survival nor predictive of improved survival for the combination of cisplatin-gemcitabine. The investigators found no significant differences in overall survival between the three chemotherapy regimens in carriers of XRCC3 241 Met/Met: median overall survival was 13 months for the gemcitabine/cisplatin arm, nine months for docetaxel/cisplatin, and 12 months for docetaxel/gemcitabine (P=0.29). It was noted that patients 57 years of age or younger with XRCC3 241 Met/Met had a longer survival time when treated with gemcitabine/cisplatin (P=0.004), which translated into a 60% difference in survival at two years. However, this post hoc analysis requires further investigation. Overall, the present study suggests that XRCC3 variants are not predictive of response to chemotherapy.

Molecular Markers for Targeted Therapies Show Promise

Receptor tyrosine kinase inhibitors of the epidermal growth factor receptor (EGFR) have demonstrated activity in the therapy of NSCLC.1 While over 80% of patients with NSCLC are found to over-express EGFR, substantially fewer patients have objective tumour shrinkage from therapies inhibiting the EGFR. Recent studies have led to the discovery of clinical and biological characteristics that may be associated with the enhanced benefit of targeted therapies.6–8 For example, never-smoker status or a positive EGFR FISH test has been consistently predictive of greater benefit from targeted therapies. Retrospective analyses have determined that activating mutations within the kinase domain of the EGFR are present in approximately 10% of NSCLC, with an increased frequency in adenocarcinomas arising in nonsmokers, women, and individuals of Asian ethnicity.5 The evidence so far...
is mixed as to whether these mutations correlate with greater response to the EGFR tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib.\(^6,7,9\)

Three presentations at ESMO 2006 reported on trials that further assessed the significance of specific mutations in the EGFR gene and other biological characteristics on clinical outcome with EGFR TKI therapy.\(^10\)–\(^12\) The message from all these trials was the same—patients selected for treatment on the basis of mutations in EGFR exons 19 and 21 have a high likelihood of response to EGFR TKIs. This raises the possibility of the development of rapid and reliable diagnostic tests that could guide patient selection for this therapy.

The West Japan Thoracic Oncology Group Trial (WJ-TOG0403) prospectively assessed whether mutations in EGFR exons 18, 19, and 21 affect the response rate of patients NSCLC who have been treated with gefitinib.\(^10\) Tatsuhiko Kashii and colleagues recruited 118 patients from 15 study centres in Japan and screened them for the presence of EGFR mutations. There were no restrictions on prior treatment. Thirty-two patients (27%) were EGFR mutation-positive and 79 were mutation-negative, while the mutation analysis failed in six patients. Twenty-eight patients with mutations of the EGFR were enrolled in this study; 14 patients had deletions in exons 19 and 21 and have a high likelihood of response to EGFR TKIs. This raises the possibility of the development of rapid and reliable diagnostic tests that could guide patient selection for this therapy.

The RR associated with exon 19 mutations was 86%, and 64% with exon 21, suggesting that EGFR mutations are strongly related to the response to gefitinib in Japanese patients.

Tatsuhiko Kashii and colleagues recruited 118 patients from 15 study centres in Japan and screened them for the presence of EGFR mutations. There were no restrictions on prior treatment. Thirty-two patients (27%) were EGFR mutation-positive and 79 were mutation-negative, while the mutation analysis failed in six patients. Twenty-eight patients with mutations of the EGFR were enrolled in this study; 14 patients had deletions in exons 19, and 14 had missense mutations in exon 21. Of the 28, the median age was 68 years, 27 patients had adenocarcinoma, 18 were female, 20 had never smoked, and 24 had an ECOG status of 0 or 1. Among the 26 evaluable patients, the overall response rate (RR) to gefitinib in patients who had not had prior chemotherapy was 73%; for patients with one or two prior chemotherapies, the RR was 71%. The disease control rate (CR+PR+SD), which also includes patients whose cancer did not progress, was 100%. The RR associated with exon 19 mutations was 86%, and 64% with exon 21, suggesting that EGFR mutations are strongly related to the response to gefitinib in Japanese patients. The mutation, Kashii postulated, likely increases the sensitivity of the tumour to EGFR TKIs by repositioning critical residues surrounding the ATP-binding cleft of the tyrosine kinase domain of the receptor. A randomized phase III study of gefitinib versus cisplatin plus docetaxel in lung cancer patients with a specific EGFR mutation (WJTOG3405) is currently ongoing in Japan.

Gefitinib is only effective in a small proportion of patients with NSCLC. The ONCOBELL trial is the first prospective phase II study designed to assess clinical activity and biological effects of gefitinib in patients with NSCLC selected on the basis of molecular or clinical characteristics predictive of response to EGFR TKI therapy.\(^11\) Eligible patients had tumours which overexpressed EGFR or p-AKT on FISH analysis, or were never smokers. EGFR mutations were present in 25 patients (21 in exon 19 or 21, and 4 in exon 20). Among the 42 enrolled, 36 had never smoked and of these, 19 were EGFR-positive. Patients were given gefitinib 250 mg once daily until progression, 16 of them as first-line therapy.

A high correlation was noted between mutational status and EGFR expression on FISH analysis. The recorded response rates are shown in Table 1. In never-smokers, the RR was 47% while the RR in EGFR FISH-positive patients (n=25) was 68% (Table 1). However, patients who were both never-smokers and EGFR-positive had the highest response rate (71%). Prior therapy and brain metastases had no effect on response to therapy. Toxicity was manageable and consisted of skin rash (71.4%, grade 1/2=69.1%, grade 3=2.3%) and diarrhea (57.1%, grade 1/2=54.8%, grade 3=2.3%).

<table>
<thead>
<tr>
<th>Category</th>
<th>Objective Response Rate (CR + PR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>47% (1 CR, 19 PR)</td>
</tr>
<tr>
<td>EGFR-positive</td>
<td>68%</td>
</tr>
<tr>
<td>p-AKT-positive</td>
<td>50%</td>
</tr>
<tr>
<td>EGFR + p-AKT-positive</td>
<td>58%</td>
</tr>
<tr>
<td>Never smokers + EGFR-positive</td>
<td>71%</td>
</tr>
<tr>
<td>Time to progression (TTP)</td>
<td>6.4 months</td>
</tr>
<tr>
<td>TTP, EGFR-positive</td>
<td>7.6 months</td>
</tr>
<tr>
<td>TTP, EGFR-negative</td>
<td>2.7 months</td>
</tr>
</tbody>
</table>

Table 1: Clinical outcomes in gefitinib-treated patients in the ONCOBELL trial

The RR associated with exon 19 mutations was 86%, and 64% with exon 21, suggesting that EGFR mutations are strongly related to the response to gefitinib in Japanese patients.
This study confirmed previous retrospective studies that demonstrated a higher response to gefitinib in patients who are EGFR-positive by FISH, particularly those with exons 19 and 21 mutations.

Erlotinib has proven efficacy and a favourable toxicity profile in previously treated advanced NSCLC. A study by Massuti and colleagues showed that the presence of an EGFR mutation confers a strong predictive factor for erlotinib response, and that there is possibly a trend for better efficacy of erlotinib in patients with exon 19 deletions. The SLCG study was a subgroup of 65 patients with NSCLC from the TARGET trial who had stage IV NSCLC, who had not received prior therapy and who carried EGFR mutations (38 patients with exon 19 and 27 patients with exon 21 mutations). The overall response rate to erlotinib treatment was 90% (53/59): 91% for exon 19 (31/34) and 88% for exon 21 (22/25). At a median follow-up of nine months, 71% of patients were alive without progression. The median TTP for the entire study group was 12 months; however, patients with exon 21 mutations had a shorter time to progression (nine months). Overall survival has not yet been reached but the median survival for patients with exon 21 mutations was 10 months (P=0.0003). The investigators also noted that EGFR mutations were more frequent in women than in men (P=0.001), in never-smokers than in ex-smokers or current smokers (P<0.001). However, neither smoking history nor sex was correlated with outcome. The investigators suggest that the predictive ability of EGFR mutations requires further study in order to develop a method for identifying a subgroup of patients with advanced NSCLC who could most benefit from first-line monotherapy with erlotinib.

The 14th International Conference for Cancer Nursing (ICCN), Reaching New Heights Together conference was held in Toronto from September 27th to October 1st, 2006. Co-hosts were the Canadian Association of Nurses in Oncology (CANO) and the International Society of Nurses in Cancer Care (ISNCC). The theme of the conference this year reflected on how nurses need each other to move forward. The conference addressed topics such as evidence-based symptom management, expansion of the role of nurses in cancer care, nurse and patient education and development of communication skills in nurses. This issue of *New Evidence in Oncology* highlights some of the themes that emerged in symptom management and supportive care at the conference.
Evidence-Based Symptom Management and The Role of Supportive Care in Symptom Management

Meenakshi Kashyap

Patients with cancer experience a range of symptoms, many of them simultaneously, as a result of their disease or as a result of treatments for their disease. The proper management of these symptoms is vital, since unrelieved symptoms can compromise patient outcomes.

In collaboration with other healthcare professionals, nurses are concerned with understanding and responding to diverse patient experiences of cancer; for example, distress, fear, fatigue, nausea, mucositis, pain, or neutropenia. The scope of nursing practice and its location in the system means that nurses are integral to identifying an individual’s supportive care needs and engaging an appropriate team response to address these needs. This article highlights some of the presentations relating to Evidence-Based Symptom Management and supportive care at the recent ICCN meeting.

Evidence-Based Symptom Management

During the plenary session on Evidence-Based Symptom Management, Dr. Deborah McGuire (University of Maryland School of Nursing, USA) briefly reviewed the 2005 update of the MASCC mucositis guidelines. The process involved the creation of interdisciplinary groups that focussed on specific topics and then conducted a coordinated literature search with the help of medical librarians. They rated levels of evidence in research articles and patient outcomes and these ratings were used to formulate guidelines based on evidence and group consensus. All work groups published their papers in the June 2006 issue of Supportive Care in Cancer. A summary paper was also prepared for the journal Cancer. The components of the guidelines are within the scope of nursing practice, are easy to implement and evaluate, and are applicable in many settings. Dr. McGuire discussed the application of these guidelines and suggested that they be collaborative to ensure that pretreatment dental care for any dental issues, initiation of systematic oral care protocol using a soft toothbrush with regular replacement of the toothbrush to prevent infection, flossing, rinsing, use of topical anesthetics, intravenous morphine if needed, and regular oral assessments all follow a course of mucositis.

Ms. Rebecca Clark-Snow (University of Kansas Cancer Center, USA) spoke about the use of anti-emetics guidelines. Control of emesis allows chemotherapy treatment to be administered and antiemetics continue to be crucial in the treatment of patients with most malignancies. Newer agents have significantly improved control of both acute and delayed emesis. The Perugia International Cancer Conference VII, held in 2004, was a consensus meeting on anti-emetic therapy. The official process was subscribed to by nine international oncology groups that included MASCC internationally, ASCO, ONS, NCCN in the US, CCO in Canada, ESMO and EONS in Europe, SASMO in Africa, and COSA in Australia. Each group worked on its area of concentration prior to the meeting. Changing an existing guideline required compelling evidence based on well-conducted trials, generally with a comparator felt to be consistent with guidelines and representing best practice. In addition, anti-emetic treatment guidelines were assigned for the four emetic risk groups: high, moderate, low, and minimal (Tables 1–4).
### Table 1: Emetic Risk Groups for Single IV Agents and Single Oral Agents

<table>
<thead>
<tr>
<th>Committee I (2/5): Emetic Risk Groups — Single Oral Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Minimal</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Committee I (5/5): Emetic Risk Groups – Single Oral Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Minimal</td>
</tr>
</tbody>
</table>

High: Risk is >90%; Moderate: Risk in 30%–90% of patients; Low: Risk in 10%–30% of patients; Minimal: Fewer than 10% at risk

### Table 2: Levels of Emetic Risk with Radiation Therapy (RT)

<table>
<thead>
<tr>
<th>Committee IX (1/5): Levels of Emetic Risk with Radiation Therapy (RT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Level</td>
</tr>
<tr>
<td>High</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Minimal</td>
</tr>
</tbody>
</table>

High: Risk is >90%; Moderate: Risk in 30%–90% of patients; Low: Risk in 10%–30% of patients; Minimal: Fewer than 10% at risk

### Table 3: Recommended Doses of Serotonin Receptor (5-HT₃) Antagonists for Acute Emesis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Route</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron</td>
<td>IV</td>
<td>8 mg or 0.15 mg/Kg</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>16 mg*</td>
</tr>
<tr>
<td>Granisetron</td>
<td>IV</td>
<td>1 mg or 0.01 mg/Kg</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>2 mg (or 1 mg**)</td>
</tr>
<tr>
<td>Dolasetron</td>
<td>IV</td>
<td>100 mg or 1.8 mg/Kg</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>100 mg</td>
</tr>
<tr>
<td>Tropisetron</td>
<td>IV</td>
<td>5 mg</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>5 mg</td>
</tr>
<tr>
<td>Palonosetron</td>
<td>IV</td>
<td>0.25 mg</td>
</tr>
</tbody>
</table>

* Randomized studies have tested the 8 mg twice daily schedule
** The 1 mg dose preferred by some panelists: small randomized study in MEC, Phase II study in HEC

### Table 4: Recommended Dexamethasone and Aprepitant Dosing

<table>
<thead>
<tr>
<th>Dexmethasone</th>
<th>Dose and Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
<td>Acute Emesis</td>
</tr>
<tr>
<td></td>
<td>Delayed Emesis</td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>Acute Emesis</td>
</tr>
<tr>
<td></td>
<td>Delayed Emesis</td>
</tr>
<tr>
<td>Low Risk</td>
<td>Acute Emesis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aprepitant</th>
<th>Dose and Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Emesis</td>
<td>125 mg orally, once</td>
</tr>
<tr>
<td>Delayed Emesis</td>
<td>80 mg orally, once for 2 days</td>
</tr>
</tbody>
</table>
Oral and gastrointestinal mucositis are common symptoms related to chemotherapy. As stated by Dr. McGuire, the guidelines outlined by Brennan et al. for the assessment and management of mucositis are very important, and need to be kept in mind during mucositis symptom management. Nausea and emesis are other symptoms that are commonly observed in patients undergoing cancer treatment. Defining nausea can be subjective, and it is therefore difficult to develop guidelines for its management. Control of emesis is imperative since it can affect patients’ ability to receive cancer therapy, and hence, patient outcomes. Newer drugs in the 1990s changed the way emesis is managed in patients with cancer. The level of evidence for the various anti-emetics available varies, and Dr. Grunberg’s work in this area is therefore very important.

Chemotherapy-induced anemia is also commonly seen in patients undergoing cancer treatment. Treating underlying anemia can significantly improve quality of life. Blood transfusion is one way of treating underlying anemia but this is a drastic and expensive measure. Moreover, there are people who would refuse a blood transfusion for religious and other reasons, such as fear of contracting blood-borne infections. It is more advisable to find other ways to manage anemia. Cancer Care Ontario guidelines recommend erythropoietin to be a safe and effective treatment option if given with the intent of reducing the incidence of symptomatic treatment-related anemia and the need for red blood cell transfusion, and as a reasonable treatment option in patients in whom a slow decline in hemoglobin is associated with increased fatigue and perceived a reduction in quality of life. More information on managing fatigue and other symptoms can be obtained from the Oncology Nursing Society (ONS) and Cancer Care Ontario. Ms. Donovan’s chemotherapy side-effect management interactive toolkit for nurses will also be very useful in evaluating and managing these symptoms.

The PRO-SELF pain control study compared the effectiveness of the PRO-SELF pain control program (PSPC) to standardized care in decreasing pain intensity scores in patients with cancer. Patients in the standard care arm (PSPS) were assessed by a research nurse in person, and were called three times by phone between the home visits. The PRO-SELF group patients by contrast were assessed by specially trained intervention nurses, educated in self-care, taught how to use a pillbox, and given written instructions on how to communicate with their physician about unrelieved pain and the need for changes in their analgesic prescriptions. The study found a significant decrease in pain intensity scores in the PSPC group (P<0.0001), and a significant increase in opioid intake to 50 mg/d by the PSPS group.

Ms. Gill Donovan (Director of Patient Services, Tenovus, UK) provided a brief overview of the management of chemotherapy side effects. The Cancer Resource and Education (CARE) team, a group of oncology nurses, utilizing an unrestricted educational grant from Sanofi-Aventis, has developed a chemotherapy side-effect management toolkit for nurses. This toolkit is available on a CD-ROM, is interactive, and contains a telephone protocol form, initial nursing assessment proforma, a core presentation slide kit, patient case studies, evaluation forms, a review article, a test-your-knowledge section, side effect algorithms that provide symptom-by-symptom management strategies—encompassing assessment of patient status, treatment recommendations, and advice to patients (Figure 1)—and references.
Several posters in the area of supportive care presented tools that nurses could use to manage treatment-related side effects. One such poster was by Ms. Kelley Moore and Dr. Barry Fortner (Supportive Oncology Services, Memphis, USA). The authors described the utility of a chemotherapy induced neutropenia (CIN) risk-assessment tool that was developed by the Assessment Information Management (AIM) Higher initiative for use in the clinical oncology setting. The tool was designed to assess the most common patient risk factors and actions taken in response to the findings in the risk assessment. Eighty-seven percent of the nurses who participated in the study said that the CIN risk-assessment tool was easy to use and that it helped them determine which patients were at risk for CIN in 67% of the cases. Because not all risk information is consistently present in the patient chart pretreatment, a majority of the nurses that participated in this study felt this tool could provide a framework for nurses to ask additional questions during the patient interview, and thus assist them in prompting interventions to prevent or lessen the severity of CIN and its complications in those patients at risk of CIN.

The poster by Ms. Cathy Maxwell and Ms. Alisha Stein (Advanced Medical Specialties, Miami, USA) discussed the implementation of the National Comprehensive Cancer Network (NCCN) practice guidelines for managing neutropenia through the development of algorithms by Florida Cancer Consultants and by developing standing orders at Advanced Medical Specialties. The authors provided simplified guidelines for common lengthy policies and procedures which help improve practice efficiency by reducing the human resource burden of managing chemotherapy induced neutropenia and its complications (Figures 2 and 3). The guidelines also provide useful data for collecting and analyzing patient outcomes and facilitate making decisions through practical, effective, and clearly defined methods and tools.

The importance of the role nurses play in symptom management was highlighted in the session, “Supportive Care: Symptom Management.” This session...
addressed the various ways in which nurses could play an active role in managing patient symptoms. Dr. Ann Berger (University of Nebraska, USA) discussed fatigue and factors associated with fatigue prior to beginning adjuvant breast cancer treatment. An earlier study by Dr. Berger’s group and Ancoli-Israel et al. had reported mild fatigue and disturbed sleep prior to treatment in women with cancer. Dr. Berger’s recent study was a randomized clinical trial with patients being treated for stage I–IIIA breast cancer (n=131) randomly assigned to receive an individualized sleep promotion plan and healthy eating information. Patients were monitored by wrist actigraphy for a continuous 48 hours. Her study revealed that sleep quality and anxiety were the two variables that influenced fatigue significantly. A stepwise regression analysis determined the Pittsburgh Sleep Quality Index and Hospital Anxiety and Depression Scale anxiety to be significantly associated with higher Piper Integrated Fatigue model scores (F=21.29, P<0.001). Higher baseline fatigue was associated with poorer subjective sleep quality and higher levels of anxiety. The key message from the study was that sleep intervention aimed at reducing pre-chemotherapy anxiety and improving sleep needs to begin prior to treatment.

Dr. Marlies Peters (Radbound University, The Netherlands) discussed the importance of assessing fatigue in cancer survivors. The Expert Centre for Chronic Fatigue (ECCF) of the Radbound University Nijmegen Medical Centre has developed a treatment for fatigue in patients with cancer based on the principles of cognitive behavioural therapy (CBT), which is carried out by psychologists. Ninety-nine percent of patients during treatment and 30–40% of cancer survivors still suffer from fatigue. However, as Dr. Peters explained, there are precipitating, perpetuating, and predisposing factors associated with cancer and fatigue. The precipitating factors are the disease itself, and treatment for the disease. Predisposing factors are the onset of fatigue before development of cancer. Perpetuating factors of fatigue include insufficient coping mechanisms to deal with the experience of cancer; fear of disease recurrence; irrational cognitions of fatigue; irregular sleep/wake rhythms; reduced physical activity levels; and insufficient social support and social interactions.

Two groups of patients undergoing cancer treatment were randomly assigned to either the CBT group (n=50) or a group that was waitlisted for six months, and then offered CBT (n=48) where predisposing and perpetuating factors for fatigue were assessed. Data was gathered from 38 patients in the CBT group and 44 patients from

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**Figure 3: Process for implementation guidelines**

- **Initial set-up**
  - Select Topic
  - Identify MD liaison & project team members
  - Develop practice guidelines, algorithms, standing orders, protocols
  - Obtain baseline data from chart review

- **Implementation**
  - Obtain review and approval
  - Educate staff
  - Implement (consider “pilot”)

- **Follow-up**
  - Audit practice’s use
  - Update as needed
the waitlisted group. A scale of 35 and over on the Checklist Individual Strength (CIS) fatigue severity scale was used to assess fatigue. Seventy-six percent of patients in the CBT group said they were not fatigued while only 21% of the waitlisted group said that they were not fatigued, suggesting that CBT has an important role to play in symptom management.

In summary, a recurring theme in this year’s ICCN conference was the need for educating patients about their symptoms, encouraging them to participate in self care, developing individualized symptom management plans, and most importantly, developing tools and algorithms that healthcare professionals can use for symptom management.

References:

Boiled Down

- Proper management of cancer-related and treatment-related symptoms is vital since unrelieved symptoms can compromise patient outcomes.
- The new MASCC guidelines for the prevention and management of chemotherapy-induced oral mucositis suggest a multidisciplinary collaborative effort is necessary to ensure adequate preventative measures for oral mucositis are implemented.
- New evidence-based anti-emetic treatment guidelines are available.
- Salt and soda, chlorhexidine, and “magic” mouthwash were equally effective at reducing the overall incidence of mucositis in a study of patients who were provided with information on mucositis, self-care exercises, and supportive interactive nursing care.
- The PRO-SELF educational program has been shown to effectively reduce pain intensity scores as well as opioid intake in patients with cancer.
- Nurses feel that a neutropenia risk assessment tool provides a useful framework in which to ask additional questions during the patient interview, and thus assists them in prompting interventions to prevent or lessen the severity of CIN and its complications in those patients at risk of CIN.
- Cognitive behaviour therapy (CBT) resulted in substantial improvements in fatigue in patients who received it during treatment compared with those in whom CBT was delayed.
Fatigue as a result of cancer treatment has been known for many years. In the early 1990s, the attitude among healthcare professionals was that fatigue was an unavoidable part of the cancer treatment process. In recent years, however, management of fatigue has become an important component of symptom management in supportive care. Dr. Ann Berger and Dr. Marlies Peters both addressed this issue in their presentations. Questions such as “What are the usual activities in your daily life?” are very important for elucidating answers that will help us design appropriate interventions for fatigue management.

A noteworthy point that was raised in this meeting was the need to inform patients of all the choices in symptom management treatment. There is a legal requirement in Canada to inform patients of all treatment resources whether they are funded by the provincial government or not. Nurses need to be aware of which drugs are funded so they can direct the patient to the person who can give them the information they need. In our hospital at Oshawa, a Symptom Management Coordinator provides this service. Patients themselves can play an active role in symptom management, and this is where the PRO-SELF model for symptom management that Dr. Dodd helped develop is useful. It is being widely used in hospitals across the US and it can easily be adopted in Canada. The tool might need to be modified according to the hospital’s needs, however.

In my opinion, algorithms to determine the risk of developing neutropenia as described by the CARE team and in several poster presentations, would be a very useful tool for nurses. Having direction provides a security blanket for the healthcare professional, helps in maintaining consistency in symptom management and in turn contributes to patients’ well-being. We are developing similar tools here in Canada. Ms. Tracy Nagy at the Princess Margaret Hospital in Toronto has developed a documentation tool and algorithm that provides a framework that supports more autonomous, consistent, and efficient practice at the bedside.

In our centre in Oshawa, we provide individualized symptom management for patients with cancer. The study by Dr. Peters was therefore of great interest. There is a relationship between anxiety, the irregularity and dysregulation of sleep patterns, and fatigue. The modules in Dr. Peters’ presentation build on each other and link up very nicely to Dr. Berger’s presentation. Patients need to be educated about managing their energy levels to prevent fatigue. An interesting observation from my doctoral work was the relationship between social support and fatigue. I was studying the quality of life issues in patients undergoing treatment for lung cancer and I found that it was related to the level of support they were receiving. Patients that perceived a need for more support felt more helpless and that feeling of helplessness led to a poorer quality of life. The quality of support that is given to patients is therefore of utmost importance. As Dr. Peters stated, patients need to be encouraged to be more self-sufficient and their family members need to be more involved. Providing patients with a telephone number that they can call with their questions and concerns is important in helping them feel psychologically secure, even if they won’t necessarily use it.

Although for many cancers increased rates of cure have occurred in the past two decades, for the population at large, the diagnosis of cancer is still inextricably linked with death. Moreover, living longer with cancer is one of the outcomes brought about by an increased ability to provide non-curative but disease-modifying treatments that have increased both the length of the disease trajectory and its chronic nature.

Palliative care is a person-centred approach that is concerned with physical, psychosocial, and spiritual care in progressive disease. It focuses on the remaining quality of life for patients who are terminally ill, and on providing support to their families during this difficult time. Palliative service providers must be up-to-date not only with the symptom control and psychosocial issues, but also with disease-modifying treatments, their benefits and morbidities. Some of the challenges faced by providers of end-of-life (EOL) cancer care were addressed at the “Palliative care: education for the role” session at the recent ICCN congress.

Good Communication Is Key
Communication is an important part of the palliative care process, and mechanisms that support this should be fostered. Dr. Susie Wilkinson from the Royal Free Hospital Medical, London, UK, discussed the results of a randomized clinical trial designed to evaluate a communication skills training program for cancer/palliative care nurses. The measures used to evaluate the effectiveness of such a training program were assessment of improvement in the nurses’ communication skills and the difference to patient care after the nurses had completed the course. Following recruitment and submission of two taped nurse/patient interviews, nurses (n=172) were randomly assigned to join either the intervention (a three-day course) or control (no intervention) groups. A third taped nurse/patient interview was submitted 12 weeks post-intervention or 12 weeks post-first submission (control). Results for the second tape indicate a significant difference in communication skills of the nurses who had taken the course (P=0.001), while there was virtually no change in the communication skills of the control group. Secondary outcomes of the trial were increased confidence in the nurses who had taken the course and greater patient satisfaction. The feedback from the nurses based on a questionnaire designed by Dr. Lesley Fallowfield indicated that 90% of the nurses “really liked” the course, and that role-playing was an important component in the training. The course improved their communication skills and decreased nurses’ stress, and from the patients’ perspectives, facilitated more effective health care. Undoubtedly, the key to enhancing the care of
Training Program Improves Delivery of Care

Ms. Linda Barrett, program manager at the Centre for Palliative Care Research and Education at the Royal Brisbane and Women’s Hospital in Australia spoke about the Program of Experience in the Palliative Approach (PEPA), an initiative of the Australian Government’s Department of Health and Aging. The objective of the program was to evaluate EOL issues and care delivery methods. The program involved clinical placement for nurses for up to ten days with a palliative care specialist. The usefulness of PEPA training was evaluated in 410 RNs and other healthcare workers including pharmacists. Twenty-six participants and 13 employers surveyed were asked if there was an improvement in confidence and knowledge of the participants and if they could identify issues in palliative care and address them adequately. The outcomes of the study suggest that the level of uncertainty in health-care workers in caring for the dying was decreased after placements. Nurses were able to implement new practices in their workplaces, interventions with patients were being effected earlier, there was more team work, and nurses felt more confident in advocating for their patients. A decrease in calls after hours by patients in places where PEPA has been implemented was also observed.

Role of Advanced Practice Nursing in Palliative Care

Dr. Doris Howell, a scientist at the Ontario Cancer Institute, Toronto and RBC Financial Group Chair in Oncology Nursing Research spoke about the advanced practice nursing (APN) learning needs and roles in EOL practices. Dr. Howell presented the result of a small study carried out in Kingston, Ontario. Four themes were identified in her study: Theme 1 was uncertainty in defining palliative care roles; theme 2 was the emotional toll on nurses who were expanding their role in palliative care for critically ill patients; theme 3 was the sense of disempowerment felt by nurses; and theme 4 was the need for enhancing their communication and counselling skills. She concluded by saying that nurses in all roles wanted to extend their capacity to deliver palliative care. Some of the challenges faced by APNs were the lack of recognition of their role in providing palliative care, and the lack of formal education and skills training needed to fulfill their role. She felt that a course such as the one Dr. Wilkinson and her team designed would help address these issues.

Ms. Lynn Kachuik from the Ottawa Hospital in Ontario, Canada, discussed the development and implementation of an APN role to enhance the quality and consistency of palliative care service delivery for patients and families across the local health integrated network in the Champlain region of Ontario. The planners developed a palliative coordinator role in the community in accordance with the Canadian Hospice Palliative Care Association Model. The coordinator provides clinical and administrative leadership to regional palliative care service delivery teams, fosters collaboration amongst those teams within and between care settings, identifies and facilitates the implementation of palliative care standards and best practices, and addresses inter-organizational/agency issues that affect the delivery of hospice palliative care for patients. Ms. Kachuik concluded by saying that adoption of the Australian PEPA model in Canada would be beneficial. She further stated that the regional APN/coordination role would help facilitate a palliative approach across the community setting, so that specialist palliative care resources can be used to provide the basic level of care at the bedside both at EOL and at an earlier trajectory of the disease.

Canadian Perspective by Dr. Lemonde

The PEPA model presented by Ms. Barrett was in a sense similar to Dr. Wilkinson’s training program since it focused on training healthcare professionals to be better communicators. Ontario has a similar program to PEPA called the Registered Nurses’ Association of Ontario (RNAO) fellowship that allows nurses to develop expertise in a particular field. The Advanced Clinical/Practice Fellowship (ACPF) offered by RNAO is a nurse mentoring experience aimed at developing and promoting nursing knowledge and expertise, and improving client care and outcomes in Ontario. At the University of Ontario, Oshawa, however, we are teaching communication skills at the undergraduate level. The students use self-assessment tools to improve communication skills and practise their skills on practice cases. This teaching tool is available on a CD. So in that sense, we are already training our nurses to be better communicators.
Highly Sensitive Tool Allows Identification of Psychological and Emotional Needs of Patients

An important step in the provision of supportive care services is the identification of the needs of the patient and of the patient’s family’s. A needs assessment helps identify patient perceptions of needs for optimal health and quality-of-life outcomes. Ms. Catherine Pigott (Peter MacCallum Cancer Centre, Australia) described the development and testing of a patient self-completed questionnaire, which was then followed up by a nurse who conducts a focused interview and plans appropriate interventions. The Peter Mac Supportive Needs Screening Tool (Peter Mac SNST) was designed after a literature review of the available tools in this area. It was determined that a self-completed tool has advantages over a clinician-completed tool in that it is inexpensive to produce, requires minimal time and energy input from staff, and yields quantifiable responses. A multidisciplinary team including nurses and medical staff was asked to choose the most appropriate questions from a list of over 300 questions. The tool is divided into the following domains: communication, physical health, emotional health, activities of daily living, support and coping, and information. A sample of 200 patients was required for the testing and the study was divided into two arms to identify bias. The three screening tools used in addition to the Peter Mac SNST tool were the Supportive Care Needs Survey, the Brief Symptom Inventory (BSI), and project-specific questions from the Sanson-Fisher tool. The first arm completed three screening tools first and then the Peter Mac SNST tool. The second arm completed the Peter Mac SNST tool first and then the three tools. There was a moderate-to-strong positive correlation between all the tools (P<0.001) in the psychological domains. The tool helped patients discuss what was important to them with their clinicians. Nurses found that the tool helped them focus their interviews with patients, while allied health workers found that referrals were made earlier. In conclusion, she stated that the Peter Mac SNST tool was found to be a highly sensitive tool that allowed healthcare professionals to identify patients with high psychological and emotional needs associated with depression and anxiety, who were in need of support. In short, the results indicate that the screening tool is able to identify needs that require further assessment and intervention by the multidisciplinary team.

Measuring Workload

Ms. Georgie Cusack from the National Institutes of Health, USA spoke about measuring patient intensity in the ambulatory oncology setting. The team at NIH developed an intensity system tool to measure staffing needs based on the Plan, Do, Check, Act (PDCA) Model. There are three major influences on nurses’ workload in the outpatient setting, namely patient census (the number of patients needing care), patient care demands (the factors that dictate the skill level of nurse taking care of the patient), and role of the nurse (the direct and indirect activities, clerical and administrative duties the nurse may be involved in). In the design of such a tool, she further explained, it is important to assess patient volume, the physical design of the institution, and also support services on the premises. The tool was tested for one month in the radiation unit and in the day hospital at NIH and has now been redesigned to further improve its usefulness. It is also being used in all the day hospitals of NIH instead of just the ambulatory care day hospitals.

The results indicate that the screening tool is able to identify needs that require further assessment and intervention by the multidisciplinary team.

Canadian Perspective by Dr. Lemonde

The benefit of a supportive-care screening tool such as the one developed by Ms. Pigott and her colleagues is in allowing for patients to be referred to the appropriate healthcare professional earlier than they usually would have been. It is important for healthcare workers to ensure that the patient’s supportive care needs are being identified to ensure that they live a balanced life. For example, if a patient has no family nearby for support, this tool would help identify the kind of support the patient needs and the patient could be referred to a social worker. This is a kind of individualized assessment of patients’ supportive care needs even after the treatment has ended. In Canada, currently we have no such routine systematic screening and referral process and it would be interesting to test the validity and reliability of the Peter Mac SNST tool in other clinical settings.
Breast cancer and the description of options to be helpful, while 92% of the women agreed that the information on risks and benefits of preventive measures was adequate. There was a significant decrease in decisional conflict and increase in knowledge and changed perception (P<0.05). In conclusion, participant satisfaction and the acceptability of the questionnaire was high, cancer-related distress decreased, although not significantly, the overall decisional conflict level decreased, the perception of risk and risk reduction estimates changed, and overall knowledge was increased.


Decision Aid for Patients with Breast Cancer

Patients must be assisted to make decisions regarding ongoing treatment. In the session on genetics, Dr. Kelly Metcalfe from the University of Toronto presented the development of a decision aid for breast cancer prevention in BRCA1 and BRCA2 mutation carriers.9 Women with a BRCA1/BRCA2 mutation have up to an 80% lifetime risk of developing breast cancer. Several options exist to reduce this risk—all have varying levels of risk reduction, but all options have physical and psychosocial risks and benefits. Dr. Metcalfe, with the help of Dr. Annette O’Conner, developed and tested a decision aid (DA) for breast cancer prevention in women with a BRCA1/2 mutation. Preliminary results from a study involving 21 women, of which 19 completed the pre-test questionnaire and 13 completed the post-test questionnaire, indicated that 100% of the women felt the DA was easy to follow, 70% found the length of the DA to be “just right,” 92% found it to be visually appealing, 100% found the review on hereditary breast cancer and the description of options to be helpful, while 92% of the women agreed that the information on risks and benefits of preventive measures was adequate. There was a significant decrease in decisional conflict and increase in knowledge and changed perception (P<0.05). In conclusion, participant satisfaction and the acceptability of the questionnaire was high, cancer-related distress decreased, although not significantly, the overall decisional conflict level decreased, the perception of risk and risk reduction estimates changed, and overall knowledge was increased.


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On October 17, 2006, Dr. Pamela Catton, Medical Director of the Princess Margaret Hospital Survivorship Program, successfully launched Caring Voices (www.caringvoices.ca), a web-based initiative complementing the services of PMH Survivorship Program. Caring Voices helps connect breast cancer survivors and gives them an opportunity to be partnered with another survivor for private peer-to-peer chats and to take part in online discussions with all participating registered users. Additionally, visitors to the site have access to topical education resources and scheduled forums moderated by a healthcare professional.

Caring Voices also supports research in patient education. The first research project will examine the feasibility of online education as a supplement to clinic visits in self management of lymphedema. Funding for the study has been provided by the Canadian Breast Cancer Research Alliance. Principal researcher David Wiljer, Director of Knowledge Management and Innovation Oncology Education at PMH, opened the study in October 2006 and it is projected to close January 2008.

Caring Voices is funded by The Quilt, a breast cancer support project (www.thequilt.com), and the Survivorship Program (www.survivorship.ca). Klick Communications Incorporated donated time and expertise for the technical development of the site.
The 6th annual Princess Margaret Hospital Conference, “New Developments in Cancer Management”, was held on October 4–6, 2006 in Toronto, Canada. The distinguished faculty included members of the Princess Margaret Hospital community, one of the largest multidisciplinary cancer centres in North America and a pioneer in basic research and development of new cancer treatments. In addition, the program featured international experts in various fields of oncology.

Year after year, this conference enjoys great success, offering quality scientific programs and speakers. Attendees are updated on standard cancer therapies, new experimental programs, and advances in supportive care. Discussions focus on how new information may apply to the treatment of cancer patients in the delegates own institutions or practice settings. This issue of New Evidence in Oncology highlights advancements in systemic treatment of locally advanced breast cancer and oncology nursing initiatives.
Assessing Treatment Response in Locally Advanced Breast Cancer: The Promise of Novel Systemic Therapy and Pathologic Predictors

Colleen Young

Locally advanced breast cancer (LABC) cases account for approximately 10–15% of all new primary breast cancer diagnoses in North America. According to the TNM staging system, LABC (stage III) is described as large breast tumours (>5 cm in diameter) associated with either skin or chest-wall involvement or with fixed (matted) axillary lymph nodes, or with disease spread to the ipsilateral internal mammary or supraclavicular nodes. Inflammatory breast cancer is also classified as a type of LABC.

The recommended treatment of LABC is combined modality therapy, usually consisting of neoadjuvant systemic therapy followed by surgery and then radiotherapy. Those patients with hormone receptor-positive tumours will subsequently receive endocrine therapy and those with HER-2/neu overexpression, adjuvant trastuzumab. Despite combined modality treatment and the improved systemic management of LABC, the long-term survival rate remains relatively poor at about 50%.

In part, the answers may lie in the promise of novel systemic therapy regimens. Therapies targeting self-sufficiency in growth signals are counted among the most successful to date. Notably, the addition of trastuzumab to neoadjuvant chemotherapy has shown a pCR rate of 65.2%. However, it is still unclear whether combining trastuzumab with chemotherapy improves patient prognosis versus standard postoperative adjuvant trastuzumab. Furthermore, it is hoped that the continued progress in the use of endocrine therapies will also improve patient selection for neoadjuvant endocrine therapy as oppose to neoadjuvant chemotherapy.

According to Dr. Clemons, early assessment of response is of key importance. It has been shown, for example, in a large European trial, that if the tumour is not shrinking after two cycles of chemotherapy,
then the chance of obtaining a pCR after six cycles of treatment is very small.6 Also, for LABC patients with residual disease despite treatment with an anthracycline- and taxane-based regimen, additional chemotherapy is not always the preferred option. When considering further chemotherapy for residual disease, an oncologist must ask whether it is a case of “treating the physician and not the patient.” “Clearly, if a patient has residual disease despite the use of the ‘best’ neoadjuvant chemotherapy, then the tumour is demonstrating chemo-resistance and the use of other agents such as capecitabine or even vinorelbine is futile,” maintains Dr. Clemons. Areas of interest requiring further study include exploring the evolving role of biological therapies and radiotherapy, alone and in combination with chemotherapy. There is also a need to gain a better understanding about chemo-resistance and response factors, and to develop better response assessment tools.

Dr. Susan Done, researcher at the University Health Network, Toronto, elaborated on the pathologic predictors of neo-adjuvant response. In her presentation, Dr. Done identified markers currently being researched and pointed out that results of the numerous studies vary widely and data is, as yet, frequently conflicting — likely a reflection of the small patient numbers analyzed.

A number of trials have sought to identify markers present in initial diagnostic biopsies as predictors of response to preoperative chemotherapy for breast cancer. While the role of traditional histology is frequently restricted by the small sample size and the nature of the initial biopsy, high nuclear grade on a fine needle aspiration or Tru-cut biopsy has been found to predict for pCR.7 Hormone receptor status and overexpression of Her-2 are well established in predicting response to hormonal and trastuzumab therapy, respectively. However, their prognostic role in the neoadjuvant setting is controversial, with some studies showing utility and others not.

Topoisomerase II, an enzyme located close to Her-2 on chromosome 17, and Ki-67, a proliferation marker, have both been reported to predict response to anthracycline-based neoadjuvant chemotherapy.8,9 Other markers have been examined in small patient numbers, but further study is needed before their potential can be evaluated. These include HIF1α and CAIX (hypoxia-related markers), Bcl-2, EGFR, and p53. Several trials observed that the levels of some markers change over the course of treatment. Researchers hypothesize that changes in response to treatment may be predictive of response and may allow treatment regimens to be adjusted as necessary — an exciting possibility that calls for additional research. The application of gene expression profiles to breast cancer treatment represents another area of heightened interest. Early study results
show few or no differences distinguishing responders from non-responders; however, it may be possible to reflect response through changes noted during the treatment period.

As new molecular therapies are developed, pathology researchers will continue to seek pathologic predictors of treatment response. Large studies with pathologic endpoints are required to definitively identify markers that can be effectively and routinely used in the clinical setting.

Improvements in the management of LABC will also depend on ongoing research to identify the targets that will provide therapeutic or predictive benefit, to develop new targeted therapies and improve the understanding of how they should be delivered, and to define optimal therapies for subgroups of patients, possibly through gene profiling.


Boiled Down

- LABC cases account for approximately 10–15% of all new primary breast cancer diagnoses in North America.
- Despite combined modality treatment and the improved systemic management of LABC, the long-term survival rate remains relatively poor at about 50%.
- Current standard neoadjuvant chemotherapy shows disappointing pCR rates — approximately 30% at best.
- Promise for improvement may lie in novel systemic therapy regimens.
- Further study is required into
  - the evolving role of biological therapies and radiotherapy, alone and in combination with chemotherapy,
  - understanding chemo-resistance and response factors,
  - developing better response assessment tools, and
  - identification of tumour markers that can be effectively and routinely used in the clinical setting.
Canadian Perspective by Dr. Clemons:

Canada has contributed significantly to the advancement of breast cancer treatment and is in a prime position to continue as a global leader in breast cancer research. The oncology community in Canada is relatively small and cohesive. Indeed, we share the same goal — to improve the quality of care for all patients with breast cancer.

Canadian treatment guidelines are very good. Treatment protocols for metastatic breast patients are increasingly being implemented in the adjuvant setting rapidly, something that previously would have taken many years. This swift acceptance of treatments with demonstrated efficacy in the metastatic setting to the adjuvant and neoadjuvant setting will allow patients to benefit from new treatments sooner. With continued forward thinking and research excellence, Canada will remain an important player on the world stage. This is clearly illustrated by the following sample of Canadian-led trials currently open in breast cancer research.

<table>
<thead>
<tr>
<th>Study Title</th>
<th>Canadian Chair</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA20</td>
<td>A Phase III Study of Regional Radiation Therapy in Early Breast Cancer</td>
</tr>
<tr>
<td>MA22</td>
<td>A Phase I/II Study of Increasing Doses of Epirubicin and Docetaxel Plus Pegfilgrastim for Locally Advanced or Inflammatory Breast Cancer</td>
</tr>
<tr>
<td>MA27</td>
<td>A Randomized Phase III Trial of Exemestane Versus Anastrozole in Postmenopausal Women with Receptor-Positive Primary Breast Cancer</td>
</tr>
<tr>
<td>MAC1</td>
<td>A Randomized Trial of Adjuvant Chemotherapy with Standard Regimens, Cyclophosphamide, Methotrexate and Fluorouracil (CMF) or Doxorubicin and Cyclophosphamide - (AC), Versus Cepacitabine in Women 65 Years or Older with Node-Positive or Node-Negative Breast Cancer</td>
</tr>
<tr>
<td>MAC2</td>
<td>A Randomized, Placebo-Controlled, Double-Blind Trial Evaluating the Effect of Exemestane in Clinical Stage T1-3 N0-1 Mo Postmenopausal Breast Cancer Patients Completing at Least Five Years of Tamoxifen Therapy (NSABP: B-33)</td>
</tr>
<tr>
<td>MAC4</td>
<td>A Phase III Trial Evaluating the Role of Ovarian Function Suppression and the Role of Exemestane as Adjuvant Therapies for Premenopausal Women with Endocrine-Responsive Breast Cancer</td>
</tr>
<tr>
<td>MAC5</td>
<td>A Phase III Trial Evaluating the Role of Exemestane Plus GnRH Analogue as Adjuvant Therapy for Premenopausal Women with Endocrine-Responsive Breast Cancer</td>
</tr>
<tr>
<td>MAC7</td>
<td>Phase III Randomized Trial of Anastrozole Versus Anastrozole and Fulvestrant as First-Line Therapy for Postmenopausal Women with Metastatic Breast Cancer</td>
</tr>
<tr>
<td>MAC8</td>
<td>A Randomized Clinical Trial of Adjuvant Chemotherapy for Radically Resected Loco-Regional Relapse of Breast Cancer</td>
</tr>
<tr>
<td>MAC9</td>
<td>Randomized Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer</td>
</tr>
<tr>
<td>MAC11</td>
<td>A Phase III Trial of Continuous Schedule AC + G vs Q2 Week Schedule AC, Followed by Paclitaxel Given Either Every 2 Weeks or Weekly for 12 Weeks as Post-operative Adjuvant Therapy in Node-Positive or High-Risk Node-Negative Breast Cancer</td>
</tr>
<tr>
<td>MAC12</td>
<td>Phase III Randomized Study of Adjuvant Combination Chemotherapy and Hormonal Therapy Versus Adjuvant Hormonal Therapy Alone in Women with Previously Resected Axillary Node-Negative Breast Cancer with Various Levels of Risk for Recurrence (TAILORx Trial)</td>
</tr>
<tr>
<td>MAP3</td>
<td>The Influence of Five Years of Exemestane on Bone Mineral Density in Postmenopausal Women at Increased Risk of Developing Breast Cancer—A Companion Study to MAP3</td>
</tr>
<tr>
<td>NCT00150917</td>
<td>RCT of a Group Intervention for Women with a Family History of Breast Cancer</td>
</tr>
<tr>
<td>NCT00247650</td>
<td>Comparison Study of Letrozole Alone or Letrozole with Zoledronic Acid in Early Breast Cancer, Neoadjuvant Therapy</td>
</tr>
<tr>
<td>NCT00115713</td>
<td>Effects of Aerobic Exercise Versus Weight Training in Breast Cancer Survivors During Chemotherapy</td>
</tr>
</tbody>
</table>
Oncology Nursing:
Taking a Leading Role for Change

Colleen Young

Since 2003, oral sessions dedicated to oncology nursing issues have been an integral part of the PMH annual conference. Once again, this year’s nursing sessions were very well attended and despite the last minute addition of extra chairs, late-comers found standing room only. A recurrent theme throughout all the nursing-related presentations was nurse leadership. The first of two oral sessions opened with a discussion about advanced care planning, establishing best practice standards, and driving change.

**Advanced care planning is a long-term initiative that requires early initiation, often by a healthcare professional, followed by sustained dialogue at various points throughout a patient’s continuum of care.**

Advance care planning helps patients formulate and communicate their preferences regarding future care during critical illness. An advance directive is a legal document that allows people to exercise their rights to accept or refuse medical care and to give instructions about future medical care should they be unable to participate in medical decisions due to serious illness or incapacity. Advance care planning is a long-term initiative that requires early initiation, often by a healthcare professional, followed by sustained dialogue at various points throughout a patient’s continuum of care. Ongoing discussions introduced in phases during treatment enable patients and families to have enough information, support, and confidence to guide their decision making.

With appropriate advance care planning, healthcare professionals are able provide the right care at the right time, thus improving quality of life and quality of care for the patient, and decreasing distress for the patient, their family members and the healthcare professionals.

In her presentation, acute care nurse practitioner Janice Wright from PMH, Toronto, outlined the current landscape of advanced care planning and discussed the role of the oncology nurse as a best practice leader. Examining her own institution, Wright found inconsistencies in the way healthcare professionals ask patients about advanced directives and discovered that there exists no systematic way of communicating or documenting an advanced directive. There are also discrepancies throughout the organization regarding provider knowledge of the policies and legalities.

In order to effectively implement best practices, the entire interdisciplinary team needs to embrace the importance of advance care planning. Although advanced care planning should involve all members of the healthcare team, the oncology nursing community advocates their taking a leadership position in helping to direct best
practice guidelines. “To be most effective, nurses need support, documentation standards, and responsibility,” says Wright.

The challenges in employing a best practice approach are many. In particular, clear definitions are required for who should direct the advance care planning, and when, where and how it should be employed. Not all healthcare professionals are comfortable with early rather than late discussion with patients. Furthermore, some providers feel that a policy or best practice standard is unnecessary, hence gaining consensus may prove difficult.

In order to effectively provide modern medical care, improvements need to be made in end-of-life and palliative care. Medical research has led to many advances at the physiological and technological levels. This same rigour of scientific study and research ethics must be applied to the advance care planning process to ameliorate the current lack of best practices and documentation standards.1

There is a growing movement towards establishing evidence-based nursing practice. Nurse leaders have an obligation to cultivate sound clinical practices leading to quality patient care. To this end, co-principal investigators Susan Robinson and Janice Wright from PMH, Toronto, initiated an exploratory study of oncology healthcare professionals’ knowledge, experiences, and attitudes of best practice use of advanced directives within an advanced care planning process. Details of the survey and the preliminary results were presented by Robinson during the session.

In their study, researchers set out to explore the current gaps in knowledge, skills, and attitudes of healthcare providers in oncology. The goals of the study are to:

1. Explore the knowledge, attitudes, and perceived skills of oncology nurses, physicians, social workers, and radiation therapists in advance care planning in a quaternary care comprehensive cancer centre (PMH);
2. Determine what is required for the development of a multi-professional model of support, education, clinical care, and research; and
3. Explore discipline-specific perceptions on the challenges and barriers to implementation of an advance directive philosophy within the model of patient-centred care.

The survey was conducted using KAESAD©, the research ethics-approved instrument designed to assess knowledge base and collect attitudes, a tool originally developed by Mary Ann Jezewski in the United States. Canadian researchers modified the 100-item

**Boiled Down**

- Advance care planning helps patients formulate and communicate their preferences regarding future care during critical illness.
- In order to effectively implement best practices, the entire interdisciplinary team needs to embrace the importance of advanced care planning.
- The oncology nursing community advocates taking a leadership position in helping to direct best practice guidelines.
- There is a growing movement towards establishing evidence-based nursing practice.
- PMH nurse leaders Susan Robinson and Janice Wright present preliminary results of an exploratory study of oncology health-care professionals’ knowledge, experiences, and attitudes of best practice use of advance directives within an advanced care planning process, using the using KAESAD© survey.
- Initial findings reveal
  - a significant lack of knowledge of ethical and legal principles of advance care planning,
  - a lack of clarity outlining roles and responsibilities of the members of the healthcare team, and
  - a discomfort with the communication skills they require to facilitate decision-making with patients and families.
- Nurse-led patient care is embraced at PMH.
survey to reflect Ontario law and expanded the range of survey participants to include not only oncology nurses, but also physicians, social workers, and radiation therapists.

Initial findings reveal a significant lack of knowledge of ethical and legal principles of advanced care planning. Provincial legislation outlines who, how, and when decisions can and must be made, yet few healthcare providers have received any formal education in the complexities of ethical and legal dilemmas that arise in practice. Additionally, the survey results show that the definition of roles and responsibilities remains unclear. Furthermore, among all professionals of the team, there was a sense that they lack the communication skills required to facilitate decision-making with patients and families.

The next phase of the study will involve a detailed analysis of the collected data in order to start the discussion process that will lead to the development of documentation standards and educational programs.

In a later session, presenters Laura Rashleigh and Samantha Mayo from PMH outlined the successes to date of the Malignant Hematology Nursing Professional Practice Council and their efforts to effect change for quality patient care and to support a nursing leadership role. The Council includes inpatient nurses in Malignant Hematology and the Apheresis Stem Cell Unit. Since the Council’s inception in 2000, it has made improvements to patient care processes and patient education. It has also implemented personal and professional development programs for staff nurses, including dissemination of education to other institutions in the greater Toronto area. By participating in programs offered by the Council, nurses are able to develop new skills and become leaders in their practice areas. In response to the nursing community’s recognition of the need for evidence-based data, the Council has set up a new initiative to explore ways to effectively move research into practice in order to promote change.

Mucositis Remains a Priority in Symptom Management

The oral session presented by Prisco Salvador, Registered Nurse, Malignant Hematology at PMH, highlighted the importance of oral care and evidence-based clinical practice guidelines for the management of oral mucositis. The challenge lies in the dissemination and implementation of evidence-based standards of care into clinical practice. Summarized in the table below are the 2005 updated guidelines developed by the Multinational Association of Supportive Care in Cancer (MASCC) Mucositis Study Group.

<table>
<thead>
<tr>
<th>Summary of Clinical Practice Guidelines for Care of Patients with Oral Mucositis¹,²,³</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Foundations of care</strong></td>
</tr>
<tr>
<td>1. Oral care protocols including patient education in an attempt to reduce the severity of mucositis from chemotherapy or radiation therapy.</td>
</tr>
<tr>
<td>2. Patient-controlled analgesia with morphine as the treatment of choice for oral mucositis pain in patients undergoing HSCT.</td>
</tr>
<tr>
<td><strong>Radiotherapy: prevention</strong></td>
</tr>
<tr>
<td>3. Use of midline radiation blocks and three-dimensional radiation treatment to reduce mucosal injury.</td>
</tr>
<tr>
<td><strong>Standard-dose chemotherapy: prevention</strong></td>
</tr>
<tr>
<td>6. Oral cryotherapy (30 min) in patients on bolus 5-FU chemotherapy.</td>
</tr>
<tr>
<td>7. Oral cryotherapy (20–30 min) in patients on bolus edatrexate chemotherapy.</td>
</tr>
<tr>
<td><strong>Standard-dose chemotherapy: treatment</strong></td>
</tr>
<tr>
<td>9. Chlorhexidine contraindicated for established oral mucositis.</td>
</tr>
<tr>
<td><strong>High-dose chemotherapy with or without TBI plus HSCT: prevention</strong></td>
</tr>
<tr>
<td>10. Pentoxifylline contraindicated for prevention of mucositis in patients undergoing HSCT.</td>
</tr>
<tr>
<td>11. LLLT to reduce the incidence of oral mucositis and its associated pain in patients on high-dose chemotherapy or chemoradiotherapy before HSCT.</td>
</tr>
<tr>
<td>12. Palifermin, a recombinant human keratinocyte growth factor, indicated to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support.</td>
</tr>
</tbody>
</table>

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

The National Oncology Pharmacy Symposium (NOPS) 2006 is an annual education event organised by the Canadian Association of Pharmacy in Oncology in cooperation with the National Cancer Institute of Canada’s Pharmacists’ Network. It brings together pharmacists from across the country to discuss topics in the areas of symptom management, new drug updates, pharmacy based research. The theme of this year’s meeting, held from October 13 – 15, 2006 in Montréal, QC was “The Dollars and Sense of Quality Cancer Care”.
The Dollars and Sense of Quality Cancer Care: Highlights from NOPS 2006

Lesley McKarney

In Canada, the wholesale cost of cancer drugs to pharmacies and hospitals is growing at a staggering rate. This is most evident with the new biological agents that are being developed and marketed.

After hospital care, Canada spends more on drugs, and oncology drugs in particular, than on any other major category of the healthcare system. In the last six years, the total public and private expenditure on prescription drugs has grown by approximately 12% annually.

The theme of this year’s annual meeting of the National Oncology Pharmacy Symposium (NOPS) focussed on the dollars and sense of cancer care in Canada. Below are some of the highlights of the meeting.

Coping with the Costs of New Cancer Therapies

- Annual growth in provincial oncology drug budgets is outstripping other areas of health care. In BC, it is projected to be 21% for 2005/06. An important driver of cost is the growth in the number of patients receiving cancer therapy, which has a dramatic impact on budget as well as on workloads of healthcare professionals. The aging population is another reason for the increased pressure on the budget for pharmaceuticals. Other cost drivers include acquisition costs, expanding indications and eligibility, longer treatment durations, wider treatment availability, changing public expectation, and greater treatment acceptance. In addition, many patients are staying on new targeted therapies such as imatinib much longer than expected. While they are doing well, this chronic treatment is putting a new strain on oncology budgets.

- Until recently, there has been limited coordination among provinces on determining which drugs are actually covered. From province to province, there is great variation in drug access, cancer treatment programs, and cancer mortality. Moreover, treatment guidelines tend to lag behind the evidence, and are continually “under construction.” It has been suggested that national guidelines should be established, and that Canada adopt the existing NCCN guidelines rather than reinvent the wheel. Oncologists, the Canadian Strategy for Cancer Control, CAPCA, CAPhO, and CANO must be active participants and partners in the development of national standards and guidelines. The Common Drug Review (CDR) has the potential to increase consistency between provinces of the drug plan listing decisions.

- The timeliness of drug approval at the federal level in Canada lags behind that of the US by four months to four and a half years. Fifteen of the 24 new drugs cost in excess of $20,000 (range $20,000 to $70,000) per course of treatment. Pharmacoeconomic evaluations describing the expenses in dollars per life year gained or per quality adjusted life year may assist us...
in comparing the cost effectiveness of some of these new therapies.

- As the new era of targeted therapies emerges it is going to be years before it is understood how to most effectively and economically exploit their activity. Moreover, post-marketing evaluation of drugs is essential to uncover possible long-term side effects.³

- Inconsistent interpretation of the Canada Health Act regarding self-payment for new therapies such as bevacizumab is a growing problem. How do we define “medically necessary”?²

- Prospective pharmacoeconomic evaluation will be critical as overall costs of new biological agents are high for several reasons: they are harder to produce and have been developed out of expensive basic research; the markets are small for individual agents; and chronic use, as well as the use of drugs in combination.²,⁴,⁵ A systematic framework to assess the relative costs and benefits of alternative healthcare interventions is necessary. The National Cancer Institute of Canada has created a working group to look into incorporating economic evaluations in clinical trials.⁵

- Provincial funding bodies need to find effective ways of directing their limited resources to those interventions that will have the greatest impact. Efforts must be made to weed out ineffective treatments that are either currently being reimbursed or have been submitted for a reimbursement decision.²

An Ethical and Social Perspective on Oncology Drug Use

Jean-François Bussières (Saint Justine Hospital, Montreal, QC) gave a very spirited presentation to conference attendees on the role pharmacists play in maintaining quality of care and treatment accessibility in light of the dramatic increases in cancer drug costs.⁶ Bussières raised the issue of ethics and how it relates to patient care. Putting ethics into practice is becoming increasingly challenging, he commented. By using the principles for the guidelines issued by the National Institute for Health and Clinical Excellence in the UK, he suggests there are six domains of ethics that pharmacists need to consider in their daily practice:

- Autonomy: This is an emerging principle, he said, that involves the pharmacist doing what he or she can to empower the patient so that they can make an informed decision. Respect for autonomy identifies what the patient subjectively considers to be in his or her best interests. This process may become more difficult as therapies become more complex, increasing the requirement that pharmacists also be educators.

  **Beneficence and nonmalfeasance:** Beneficence, meaning “doing good,” and nonmalfeasance, meaning “doing no harm,” are terms commonly known among healthcare professionals. Beneficence is usually considered to rely on an objective view of what would be best for the patient (e.g., how long to treat the patient). When a patient is unable to make an autonomous choice, the healthcare professional has the duty of beneficence; however, problems arise when the view of a competent adult patient as to what is in their best interests conflicts with medical opinion.

- Competence: Without question, Bussières said, pharmacists have an obligation to keep up their skill set and avoid making errors. True competence takes on a new meaning as treatment regimens become more complex. A pharmacist practising as a generalist in a community hospital will find it difficult to maintain true competence in oncology practice, possibly necessitating specialized training.

- Fidelity: It is important for the pharmacist to consider the patient’s medical history in detail to avoid making decisions that may not take into account past treatments.

- Justice: It is important to consider that health care does not only involve management of cancer. We must balance the need to adequately treat many other diseases and conditions against the rising costs in any one area. How can we live in a world of finite resources without making decisions to treat one disease and not another? Decisions to offer therapies need to be made not on a case by case basis, but rather on a societal basis. We need to decide on cut-off points or benchmarks for acceptable therapy costs per QALY.

- Veracity: Truth in medicine is critical. We must ensure that clinical trials are conducted in a manner that gives us information we need to safely treat patients with new therapies. Veracity in medicine also refers to full disclosure to patients of the benefits (without over-inflation) and risks (without minimization).

Drugs are not ordinary goods, argued Bussières, and should not be treated as such in direct-to-consumer campaigns such as those that are common in the US. Are all these new therapies being evaluated with a critical eye? Pharmacists and other health providers are trained in critical evaluation of the literature, yet evidence suggests that health providers are heavily influenced by...
marketing from pharmaceutical industries. If supposedly “critical” pharmacists are unable to truly make unbiased decisions, how can a patient living with cancer be expected to objectively evaluate the evidence? Oncology pharmacists, as well as doctors, should take a role in informing patients about drug therapy as honestly and openly as possible.

Bussières also questioned the trend among healthcare professionals to discard peer-reviewed, published studies older than two to three years as less relevant when compared to less than mature pre-market phase data on new drugs. Abstracts are a weak science, he says, and yet they are increasingly used to make arguments to support the use of new therapeutic agents. Evidence gathered through clinical trials in highly controlled environments limits the ability to predict a drug’s performance in the “real world,” and also provides little basis for assessing the benefits and risks of new medications relative to existing drug therapies. He urged pharmacists to use caution when considering unpublished data presented at conferences, particularly those studies sponsored by the pharmaceutical industry.


A Canadian Perspective by Dana Cole

Jean-François Bussières gave a highly relevant presentation on the ethical challenges facing pharmacists. I think it is important for pharmacists to regularly be reminded of these principles throughout our careers. Like other health professionals, we are influenced by industry marketing, and it is impossible for us to be completely divorced from this. He discussed what the important ethical considerations for pharmacists are in terms of patient care. It was interesting that he used the social-value judgments document derived from the development of the NICE guidance, which was created by the National Institute for Health and Clinical Excellence in the United Kingdom, to illustrate many of these ethical principles. In her discussion, Susan O’Reilly had an interesting take on these guidelines and pointed out that while they are important, they contain such complexity that applying them to every drug review imposes a challenge in terms of time limits—it can take approximately two years to review a drug submission. Many healthcare providers consider this simply too long to wait when there is an immediate need for that drug in the marketplace. It is a balance between thorough assessment and timely review.

I also found Bussières’ comments about the acceptance of evidence derived from abstracts to be very relevant. We all believe in evidence-based medicine, and yet these days we are often driven to act by findings presented in abstract form at large oncology symposiums. Research has been coming closer and closer to the bedside over the years, and this extends not only to large medical centres but also to small community clinics. This becomes an issue when unanticipated side effects are revealed over time and use. It raises the issue of whether we are moving too quickly ahead of the evidence sometimes, and not giving enough time for trials to fully mature before adopting new and expensive therapies. Innovative therapies are exciting and there is a demand from the public to make new therapies available quickly. It is sometimes difficult to make the decision to hold off on a using a new therapy. This is a real challenge for pharmacists and we do not have clear enough understanding of how to manage this issue.

Susan O’Reilly discussed some of the pharmacoeconomic work that the BC Cancer Agency regularly performs to evaluate therapies used in BC according to the incremental cost effectiveness per life year gained or the incremental cost for each percentage gained in five-year overall survival. The true cost of the drug therapy considers the effectiveness of use in day-to-day practice, not just in a
clinical trial setting. So while on paper it would appear to cost $47,000 to treat one woman with trastuzumab for one year, the true costs, considering effectiveness of therapy, indicate that it costs $400,000 for each additional patient who is disease free at two years. Another striking example was data on the use of maintenance rituximab, which was recently approved for use in BC. Although the cost for two years of treatment is ~$21,000, it only costs $11,000 for each progression-free life year gained because of the therapy, preventing the need for drug costs down the road.

The discussion around what constitutes a fair drug price was very thought provoking. There has been a slow creep upward in what we consider a reasonable cost. For years we used hemodialysis as a benchmark, which cost $45,000 – 60,000 per year to save a life, and therefore any new therapy that cost that or less was considered cost effective. Both O’Reilly and Bussières raised the point that what we used to consider an acceptable cost is now miniscule. In terms of the challenges of setting a fair drug price, I think the approach that most of the provinces have taken with thalidomide is very interesting. Thalidomide is a medication that was available relatively inexpensively for multiple myeloma for a number of years. When bortezemib came on the market it was priced similarly to other biological agents. Suddenly, the price of thalidomide increased exorbitantly, perhaps to be priced comparatively with bortezomib. Though thalidomide remains an effective agent, my understanding is that most of the provinces decided that the new pricing of thalidomide was unfair and funded bortezomib instead.

I think that the BC model of oncology drug approval is favourable in comparison with that of some other provinces in that we have been able to make newer therapies available relatively quickly. In BC, it is rare that we go through the self-pay or co-pay insurance situations that are increasingly common in other provinces. The concept of “medically necessary” treatments as outlined in the Canada Health Act was discussed at several points during the conference. Susan O’Reilly described the British Columbia Cancer Agency’s (BCCA) approach that if it is prescribed by a trained oncologist and this therapy is agreed upon by their peers (either in the development of a new therapy or on a case by case basis), then the drug must be medically necessary, and it should be funded. However, BCCA doesn’t take that approach with supportive care medications such as filgrastim, anti-nausea medications, or those medications for cancer-related anemia management, which are not funded and yet are also medically necessary. It is a situation of not being able to pay for everything.

During the panel session on the pharmacist’s role in assuring the quality of care while controlling drug costs, we heard from pharmacists working at all levels to provide affordable access to necessary drug therapies. Suzanne Taylor discussed the importance of employing pharmacoeconomic principles to evaluate the true effectiveness of drug therapies after they have been approved by a province, as is the practice in BC. Sean Hopkins discussed the challenges of treating individual patients in light of today’s and tomorrow’s economic constraints. He stressed that evaluations of the costs of therapies must consider the cost to the patient and to other areas of the healthcare sector. Sean also stressed that intensive monitoring and assessment by pharmacists can improve patient outcomes and save costs. Kathy Gesy outlined the challenges of managing a provincial oncology drug budget and Debbie Milliken from CCO discussed collaborative efforts with the western provinces to look at a common drug review for oncology products. I think that there are certainly some efficiencies to be gained there. It doesn’t mean that provinces are not going to be making their own independent decisions about which drugs to cover, but there is no sense in reinventing the wheel in terms of evaluating the drug for efficacy and toxicity; this is a process that could and should be shared. Perhaps we could even be collaborating on some pharmacoeconomic evaluations of the effectiveness of therapies such as those evaluations currently conducted in BC.
Quick Sketch

Dr. Verma is a medical oncologist at the Toronto Sunnybrook Regional Cancer Centre (TSRCC) and is an Assistant Professor at the University of Toronto. He did his Internal Medicine and Medical Oncology training at the University of Alberta and then went on to do a fellowship in breast cancer at the University of Toronto. He also completed his Master’s of Science in Medical Education from University of Southern California during his fellowship years.

Dr. Verma’s main clinical interests are in the treatment and management of breast cancer, and lung cancer. He also has key research interests in neoadjuvant and endocrine treatment of breast cancer, reducing toxicity of systemic treatment and developing novel therapies in breast and lung cancer. He is also the Director of Postgraduate Medical Oncology Education and the fellowship director for the breast fellowship program at TSRCC. He has led and created a number of innovative educational projects in oncology and has won numerous teaching awards. He is well published and is recognized nationally for his research and education leadership in breast and lung cancer.

Canada’s Education Website for Oncology Professionals

GOAL:
To serve as the primary portal for Oncology professionals to access educational resources

OBJECTIVES:
Provide optimal patient care by:

• delivering an optimal set of resources to oncology professionals
• improving medical oncologists, access to the information they need
• providing web-based learning through interactive online education courses
• promoting ongoing research and key updates by disease sites
• providing opportunities for collaboration and networking (e.g., clinical trials, fellowships, research opportunities)

We are currently finalizing the website based on a detailed national needs assessment. Thank you for all the input!

EXPECTED LAUNCH DATE: JANUARY, 2007

For questions and feedback regarding website, please e-mail sunil.verma@sunnybrook.ca or scott.berry@sunnybrook.ca
Canadians Collaborating on Turkish Soil

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