New Evidence in Oncology is an independent medical news reporting service providing educational updates on current medical events. Views expressed are those of the participants and do not necessarily reflect those of the publisher or the sponsor. Support for development and distribution of this report was provided by AMGEN Oncology Canada and Abraxis Oncology through an unrestricted grant without conditions and under written agreement that ensures independence. Any therapies mentioned in this report should be used in accordance with the recognized prescribing information. No claims or endorsements are made for any products, uses, or doses presently under investigation. Information provided herein is not intended to serve as the sole basis for individual care. Our objective is to facilitate physicians’ and allied health care providers’ understanding of current trends in medicine.
Welcome to the first issue of 2007. We are pleased to bring you coverage from the American Society of Hematology meeting and the San Antonio Breast Cancer Symposium, the two major oncology conferences that brought 2006 to a close.

*New Evidence in Oncology* is committed to providing an educational yet engaging publication for Canadian healthcare professionals working the field of oncology. The beginning of 2007 is a fitting time to introduce the members of the *New Evidence* Advisory Board and recognize them for their efforts in moving this publication forward. The Advisory Board has played an integral part in further defining and shaping the third-party nature of *New Evidence*, and ensuring that the publication is meeting the needs of its readers.

Your interest in *New Evidence* is appreciated. We hope you enjoy reading this issue and connecting with your oncology community.

**Our Mission:** *New Evidence in Oncology* is a publication for Canadian healthcare professionals. Our concentrated effort provides busy oncology specialists with concise, timely, credible, and objective scientific data, focusing 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 the ways the latest international developments may shape how oncology patients are treated and managed in Canada.
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Medical oncologist with Cancer Care Ontario at The Ottawa Hospital Regional Cancer Centre (TOHRCC)
Assistant Professor, Department of Medicine, University of Ottawa

With an academic specialty in breast cancer, melanoma, and sarcoma, Dr. Verma chairs the disease site groups in each of these areas at the University of Ottawa, and is chair or a member of these groups at the provincial level. He is a principal investigator in numerous research and educational projects at the ORCC and the Ottawa Regional Women’s Breast Health Centre. He frequently presents papers on drug therapies for breast cancer and on breast cancer management, and speaks on breast cancer advocacy issues.

Henry Krieger, MD

Hematologist/Oncologist, Scarborough Hospital

Dr. Krieger is a hematologist/oncologist at Scarborough Hospital, the General division. Scarborough Hospital is involved in clinical trials with NCIC and other industry funded trials. Dr. Krieger has maintained an active clinical practice for the last 31 years, and previously headed a community oncology group called COMET in the metro Toronto area for a number of years. He continues to be an active member of the group. He is also a member of ASCO, ASH and CAMO.

Pierre Laneuville, MD, FRCPC

Associate Professor of Medicine and Oncology, McGill University
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Royal Victoria Hospital, Montreal
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Chairman, Canadian Consensus Group on the Management of Chronic Myeloid Leukemia (CCGM-CML)

Dr. Laneuville has focused his clinical and laboratory research activities on hematological malignancies. He is best known for his research on the molecular mechanisms underlying the genesis and transformation of chronic myelogenous leukemia. He has served on numerous basic and clinical research panels including the Medical Research Council of Canada, the Leukemia Research Fund of Canada, the National Cancer Institute of Canada Clinical Trials Hematology Executive, and the Canadian Blood and Marrow Transplant Group.
Plugged in

5th International Symposium on Targeted Anticancer Therapies
March 08 – 10, 2007
Amsterdam, The Netherlands

St. Gallen Oncology
Primary Therapy of Early Breast Cancer
10th International Conference
March 14 – 17, 2007
St. Gallen, Switzerland

St. Gallen Oncology
Primary Therapy of Early Breast Cancer
10th International Conference
March 14 – 17, 2007
St. Gallen, Switzerland

ASCO
43rd American Society of Clinical Oncology
Annual Meeting
June 01 – 05, 2007
Chicago, IL

ECCO
The 14th European Cancer Conference
September 23 – 27, 2007
Barcelona, Spain

MASCC
Multinational Association of Supportive Care in Cancer
June 28 – 30, 2007
St. Gallen, Switzerland

PMH
7th Princess Margaret Hospital Conference
New Developments in Cancer Management
The 4th ISC International Conference on Cancer Therapies
November 15 – 17, 2007
Toronto, Ontario

ASH
49th American Society of Hematology Annual Meeting
December 2007
Orlando, FL

SABCS
30th San Antonio Breast Cancer Symposium
December 2007
San Antonio, Texas

7th World Congress on Gastrointestinal Cancers
June 15 – 18, 2007
Barcelona, Spain
Nanotechnology in Cancer Imaging, Diagnostics, and Therapeutics

Meenakshi Kashyap

What is nanotechnology?
Nanotechnology (derived from the Greek word *nano* meaning dwarf) is a rapidly evolving, multidisciplinary scientific field that applies engineering and manufacturing principles at the molecular level. This field of research deals with the engineering and creation of things from materials that are less than 100 nanometres (one-billionth of a metre) in size, especially single atoms or molecules. Nanomedicine, a branch of nanotechnology, includes rapidly developing fields such as: a) the construction of nanoscale-sized structures for diagnostics, biosensors, and local drug delivery; b) genomics, proteomics and nano-engineered microbes; and c) the creation of molecular machines capable of identifying and eliminating host pathogens, replacing/repairing cells or cellular components in vivo. Recent advances in the design of novel therapies such as peptidic drugs and siRNA therapy have further increased the need for progress in this field.

Applications of nanotechnology in medicine
Significant strides in nanotechnology have been made in the fields of imaging, diagnostics, and clinical therapies.

Most recent advances in imaging and diagnostics include progress in technologies for:
- designing bioactivated nanoprobes for molecular imaging of cancer and monitoring cell death
- developing nanofluidic devices for rapid, single-cell analysis of tumour cell signalling and migration
- targeting magnetic nanoparticles for brain tumour imaging and therapy

In clinical therapies, progress is being made in:
- magnetically guiding delivery of drugs in photodynamic therapy
- targeting tumour endothelium
- delivery of antigens for vaccination
- delivery of drugs into the brain
- enhancing antitumour vaccine activity
- designing nanotubes and nanoshells for in vivo cancer detection and treatment
- pulmonary delivery of drugs
- developing controlled-release drug reservoirs with microchips
- anticancer gene therapy
- developing polymer nanoparticles and quantum dots for siRNA delivery
- improving blood stem cell transplants
- homing peptide-nanoparticle complexes to tumours
- designing nanoparticles for delivering therapeutics directly to bone metastases
- creating novel nanoscale sensors for rapidly screening potential anticancer drugs in single cells

Nano-scale diagnostic and imaging technologies currently approved by the US Food and Drug Admin-
istration (FDA) are the CellTracks® kit for rare cell isolation, and gadolinium chelate (Gd-DTPA Dimeglumine) and iron oxide particles (Feridex®) for MRI imaging. Currently approved nanoscale therapeutics for cancer are liposome enclosed doxorubicin (Doxil®) and daunorubicin (DaunoXome®), and nab-paclitaxel (Abraxane®). Doxil® and DaunoXome® both use lipid nanoparticles that incorporate a PEG drug formulation for the treatment of refractory ovarian cancer (Doxil®) and AIDS-related Kaposi’s sarcoma (DaunoXome®). This technology not only improves absorption of the drugs, but also masks the drugs from the host immune system. Abraxane® uses albumin nanoparticles to deliver high concentrations of paclitaxel to breast tumours. This technology eliminates the use of the solvent mixture that itself can be very toxic, which can result in limited utility of this powerful anticancer agent. Patients treated with Abraxane® suffer fewer side effects and have significantly improved outcomes as compared to those who receive other formulations of paclitaxel. The drug is also being tested in other cancers such as advanced non–small-cell lung cancer, ovarian cancer, melanoma, and cervical cancers. Other nab applications in development are nab-doxetaxel, nab-17AAG, nab-rapamycin, and nab-thiocolchicine dimers.

Advantages of nanotechnology

Nanotechnology based chemotherapy offers several advantages over conventional chemotherapy, such as:

- nanoparticulate drug carriers bypass organs that normally impede delivery of drugs to the desired target, which makes them ideal for targeted peptide, protein, and siRNA administration. Enhanced delivery leads to superior performance characteristics of the product
- minimizing the use of expensive drugs results in reduced cost of the product, and
- since nanoparticles can be designed for oral or intravenous delivery, nanotechnology is opening up new therapeutic opportunities for agents that conventionally cannot be used effectively due to poor bioavailability or drug instability.

Summary

Nanotechnology is heralding a new era in the development of novel diagnostic, imaging, and therapeutic products. Further refinements in this technology are expected to transform clinical decision making and cancer treatment by allowing early diagnosis, monitoring of effectiveness of therapy, and efficacious delivery of chemotherapeutic drugs and new generation biologics with minimal side effects, which in turn will lead to better patient compliance and improved quality of life for patients with cancer.

Several aspects of the treatment of non-Hodgkin’s lymphoma, myelodysplastic syndrome (MDS), anemia, and other hematological conditions received particular emphasis at the recent 48th Annual Meeting of the American Society of Hematology (ASH), held December 9–12 in Orlando, Florida. During the last several years the treatment of these conditions has improved, mostly related to the introduction of the anti-CD20 monoclonal antibody rituximab for lymphoma, the application of DNA methylation inhibitors in MDS, and the improved evaluation of patients who would benefit from erythropoiesis-stimulating agents. These and other developments are highlighted in this issue of *New Evidence in Oncology*. 
**Background**

- Patients older than 65 years with aggressive NHL have worse outcomes than younger patients; treatment of these patients is associated with a lower complete response (CR) rate and a worse overall survival (OS).
- Efforts have been made to improve the outcome by adding rituximab to standard CHOP chemotherapy or by intensifying CHOP from 21 days to 14 days intervals (two-weekly CHOP, CHOP 14).
- The Dutch HOVON and the Scandinavian Nordic groups performed a prospective, multicentre, randomized phase 3 trial to compare eight cycles of CHOP 14 chemotherapy with or without six administrations of rituximab (R-CHOP 14), supported by G-CSF in previously untreated, older patients with intermediate or high-risk B-cell NHL.

**Study Design**

- Inclusion criteria were mantle cell lymphoma, follicular lymphoma grade 3 or diffuse large B-cell lymphoma; intermediate or high age-adjusted IPI score; CD20-positive NHL; age greater than 65 yrs; World Health Organization (WHO) performance status ≤2.
- Exclusion criteria were prior treatment, severe organ failure, or inadequate cardiac function.
- The primary endpoint was failure-free survival (FFS).
- Secondary endpoints were complete response (CR), overall survival (OS), and toxicity.
- At final analysis 252 patients were eligible and evaluable.
- Median follow up was 23 months.

**Key Findings**

- Superior response rates were observed with R-CHOP 14 versus CHOP 14 after adjusting for age (Table 2).
- For FFS, the hazard ratio (HR) was 0.60 (95% confidence interval [CI]: 0.42–0.86; P=0.004).
- A trend towards longer OS was observed; HR: 0.70 (95% CI: 0.47–1.00; P=0.07).
- CR and FFS were not affected by age (Table 3).
Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CHOP 14 (n=127)</th>
<th>R-CHOP 14 (n=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>64.5</td>
<td>65.8</td>
</tr>
<tr>
<td>Median age, yrs</td>
<td>73.5</td>
<td>72.5</td>
</tr>
<tr>
<td>65–69 yrs, %</td>
<td>32.2</td>
<td>36.0</td>
</tr>
<tr>
<td>70–74 yrs, %</td>
<td>28.3</td>
<td>36.0</td>
</tr>
<tr>
<td>75–85 yrs, %</td>
<td>39.4</td>
<td>28.0</td>
</tr>
<tr>
<td>WHO performance score 0–1, %</td>
<td>82.7</td>
<td>78.4</td>
</tr>
<tr>
<td>Histology, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>82.7</td>
<td>80.0</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>14.2</td>
<td>12.8</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>3.1</td>
<td>7.2</td>
</tr>
<tr>
<td>Ann Arbor stage III–IV, %</td>
<td>89.7</td>
<td>84.8</td>
</tr>
<tr>
<td>B symptoms present, %</td>
<td>34.6</td>
<td>37.6</td>
</tr>
<tr>
<td>Abnormal LDH level, %</td>
<td>67.7</td>
<td>57.6</td>
</tr>
<tr>
<td>Age-adjusted IPI, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High intermediate</td>
<td>51.2</td>
<td>47.2</td>
</tr>
<tr>
<td>High</td>
<td>11.8</td>
<td>12.8</td>
</tr>
</tbody>
</table>

LDH, lactate dehydrogenase; R-CHOP, rituximab + CHOP

Table 2: Patient outcomes on CHOP 14 versus R-CHOP 14

<table>
<thead>
<tr>
<th></th>
<th>CHOP14 (n=127)</th>
<th>R-CHOP14 (n=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycles achieved (%)</td>
<td>62</td>
<td>66</td>
</tr>
<tr>
<td>CR (%)</td>
<td>41</td>
<td>52</td>
</tr>
<tr>
<td>CRu (%)</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>CR + CRu (%)</td>
<td>47</td>
<td>66*</td>
</tr>
<tr>
<td>PR (%)</td>
<td>38</td>
<td>26</td>
</tr>
</tbody>
</table>

*P < 0.01 CR, complete response; CRu, complete response unconfirmed; PR, partial response

Table 3: Outcomes according to age group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Age 65–69 Yrs (n=86)</th>
<th>Age 70–74 Yrs (n=81)</th>
<th>Age 75–85 Yrs (n=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of patients receiving 8 cycles</td>
<td>77</td>
<td>60</td>
<td>54</td>
</tr>
<tr>
<td>Proportion of patients achieving CR</td>
<td>42</td>
<td>51</td>
<td>48</td>
</tr>
<tr>
<td>Proportion of patients achieving PR</td>
<td>38</td>
<td>35</td>
<td>22</td>
</tr>
<tr>
<td>Toxicity-related discontinuations</td>
<td>10</td>
<td>20</td>
<td>29</td>
</tr>
<tr>
<td>CTC grade 3/4 infections</td>
<td>12</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

CTC: common toxicity criteria
This study confirms that rituximab improves response rate and time to progression when used in combination with chemotherapy. Standard care in Canada is R-CHOP 21 as defined in the Coiffier study. Since a large number of patients tolerated the increased dose intensity, a study comparing R-CHOP 14 vs. R-CHOP 21 would be informative, but I think the issue of maintenance rituximab following induction therapy is a more important issue and should be answered in clinical trials.

Background

• Autologous stem cell transplant may be able to replace immune cells that were destroyed by the chemotherapy.

• It is not yet known if giving more than one drug (combination chemotherapy) plus autologous stem cell transplant is more effective with or without monoclonal antibody therapy in treating non-Hodgkin’s lymphoma.

• HOVON 44 is a randomized, multicentre phase 3 trial designed to assess the effectiveness of chemotherapy plus peripheral stem cell transplant with or without rituximab therapy in treating patients with relapsed non-Hodgkin’s lymphoma.

• More patients achieved CRu after eight cycles with R-CHOP 14 vs. CHOP 14 (50% vs. 29%, respectively).

• Toxicity-related discontinuations increased with age as 22% of patients went off treatment because of toxicity, of which 2% were cardiovascular.

• Fourteen percent of patients experienced CTC grade 3/4 infections.

• Significantly fewer older patients received the full regimen (P=0.003).

• Age had no impact on rituximab efficacy.

Key Conclusions

■ In an elderly population (median age 72 years) with highly aggressive NHL, the CHOP 14 regimen is tolerable and achievable in >60% of patients.

■ The addition of rituximab results in a significant improvement in CR rate, a trend towards improved OS, and improved FFS.

■ R-CHOP 14 supported by G-CSF is a feasible and manageable protocol in elderly patients with aggressive NHL.


Rituximab Enhances Treatment Results of DHAP-VIM-DHAP Followed by ASCT in Relapsed/Progressive Aggressive NHL

Background

Specifically, this trial compared the partial and complete response rates in patients treated with dexamethasone, cisplatin, and cytarabine in combination with etoposide, ifosfamide, and methotrexate (DHAP-VIM) with or without rituximab followed by carmustine, etoposide, cytarabine, melphalan, and autologous peripheral blood stem cell transplantation (ASCT).

Study Design

• Eligibility criteria included
  ◦ Age: 18–65 years
  ◦ Histologically confirmed relapsed B-cell non-Hodgkin’s lymphoma (NHL)

Table 1: Outcomes

<table>
<thead>
<tr>
<th></th>
<th>FFS</th>
<th>DFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHAP-arm*</td>
<td>21%</td>
<td>46%</td>
<td>48%</td>
</tr>
<tr>
<td>R-DHAP arm*</td>
<td>52%</td>
<td>82%</td>
<td>62%</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.40</td>
<td>0.32</td>
<td>0.61</td>
</tr>
<tr>
<td>P-value log rank test</td>
<td>&lt;0.001</td>
<td>0.003</td>
<td>0.03</td>
</tr>
</tbody>
</table>

* 2-year estimate; FFS, failure-free survival; DFS, disease-free survival; OS, overall survival
Diffuse large cell B-cell lymphoma
Grade 3 follicular centre-cell lymphoma
Primary mediastinal B-cell lymphoma
CD20-positive
Documented remission of at least three months after first-line chemotherapy
WHO performance status 0–1
At least one month since prior chemotherapy or radiotherapy

Patients were well balanced for risk factors and had no prior exposure to rituximab.

Patients were randomly assigned to receive either DHAP-VIM-DHAP followed by BEAM and autologous stem cell re-infusion (ASCT) (DHAP-arm, n=106) or DHAP-VIM-DHAP in conjunction with rituximab (375 mg/m²) and ASCT (R-DHAP arm, n=110). Patients in both arms also received G-CSF during following induction chemotherapy.

Only patients with CR/PR after two courses of intensive chemotherapy were eligible for ASCT.

Median follow-up was 24.5 months.

The primary outcome measured was overall survival (OS).

Secondary outcomes were disease-free survival (DFS) and failure-free survival (FFS).

Key Findings
PR/CR was obtained in 49% of the patients in the DHAP arm and 77% in the R-DHAP arm (P<0.01; intention to treat analysis) after two courses of chemotherapy.

Post-transplantation PR/CR was obtained in 41% and 58% of the patients respectively (P=0.40).

Rituximab significantly improved FFS, OS, and DFS (P<0.05, Table 1).

There was no difference between the two arms in infection rate.

Key Conclusions
Rituximab significantly improved treatment results of DHAP-VIM-DHAP followed by ASCT in relapsed/progressive aggressive CD20-positive NHL.

Studies are needed to test whether that same benefit can be achieved in patients who have had rituximab in induction therapy.

References: Vellenga E et al. Rituximab (Mabthera®) improves the treatment results of DHAP-VIM-DHAP and ASCT in relapsed/progressive aggressive CD20+ NHL. A Prospective Randomized HOVON Trial. Program and abstracts of the 48th Annual Meeting of the American Society of Hematology; December 9–12, 2006; Orlando, Florida; Abstract 328.

Canadian Perspective by Dr. Krieger
This study demonstrated that rituximab is safe and effective when added to salvage chemotherapy in relapsed and progressive patients not previously exposed to rituximab, who then went on to an autologous transplant. All patients would now be treated with rituximab up front, so these results would not be applicable to most patients in Canada with aggressive lymphoma, but it assures us of being able to safely transplant relapsed patients.

CPOP Combination Results in a High Response Rate in Aggressive Lymphoma

Background
Pixantrone is a novel aza-anthracenedione with superior activity compared with doxorubicin and mitoxantrone in various tumour models, including hematologic malignancies.

Single-agent pixantrone led to major responses in patients with aggressive lymphoma including diffuse large B-cell lymphoma (DLBCL).

In a phase I dose-ranging study of pixantrone (80 to 180 mg/m²) replacing doxo-rubicin (CPOP) in a CHOP-like regimen, the optimal dose (RD) from that study was found to be 150 mg/m².

This multicentre phase 2 study assessed the efficacy and safety of the CPOP regimen in patients with relapsed DLBCL, transformed follicular lymphoma (tFL), and mantle cell lymphoma (MCL).

Study Design
Thirty patients were given CPOP (cyclophosphamide 750 mg/m² dL, pixantrone 150 mg/m² dL, vincristine 1.4 mg/m² dL, limited to 2 mg, and prednisone 100 mg/dL) for a total of six cycles administered every 21 days.

Hematopoietic growth factors were not permitted for the first cycle, but could be used thereafter according to ASCO guidelines.
Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CPOP (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years</td>
<td>66 (26–76)</td>
</tr>
<tr>
<td>Median International Prognostic Index</td>
<td>2</td>
</tr>
<tr>
<td>Previous lines of chemotherapy</td>
<td>2 (1–7)</td>
</tr>
<tr>
<td>Median time since last chemotherapy, months</td>
<td>14</td>
</tr>
</tbody>
</table>

Table 2: Patient outcomes on CPOP

| Cycles achieved (%)                      | 62          |
| Overall Response Rate (ORR) (%)         | 73          |
| CR (%)                                  | 41          |
| CR + CRu (%)                            | 47          |
| PR (%)                                  | 26          |
| Response duration, months               | 10.3 (2.5–27) |

CR: complete response; CRu: CR unconfirmed; PR: partial response

Table 3: Reported Grade 3/4 adverse events in thirty patients

<table>
<thead>
<tr>
<th>Number of events (%)</th>
<th>Number of events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>29 (97%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>9 (30%)</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Infection</td>
<td>5 (17%)</td>
</tr>
<tr>
<td>Nonhematologic</td>
<td></td>
</tr>
<tr>
<td>LVEF ↓ 10–20%</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>LVEF ↓ ≥20%</td>
<td>2 (6%)</td>
</tr>
</tbody>
</table>

Canadian Perspective by Dr. Krieger

Pixantrone is an aza-anthracenedione that appears to have a high response rate in relapsed patients and causes very little cardiotoxicity in patients pretreated with anthracyclines. Studies with this class of drugs and pegylated anthracyclines compared with standard doxorubicin in a first-line setting may be a way to reduce possible late-onset cardiotoxicity in young lymphoma survivors.

Key Findings

- Inclusion criteria included at least one but not more than two previous lines of chemotherapy containing an anthracycline with a cumulative dose of less than 450 mg/m² of doxorubicin, a left ventricular ejection fraction (LVEF) >50%, absence of CNS lymphoma, and negative HIV serology.

Key Conclusions

- The results of the CPOP regimen with 150 mg/m² of pixantrone indicate a high response rate in patients with relapsed anthracycline-refractory aggressive B-cell lymphoma.

- The CPOP regimen exhibits an acceptable toxicity profile and can be administered safely in an outpatient setting, even in this cohort of elderly, anthracycline-pretreated patients.

- Further studies to determine the agent’s role in combination therapy in this disease are ongoing.

- A randomized phase 2 study comparing CPOP-rituximab with CHOP-rituximab in patients with untreated DLBCL has been initiated.

Follicular Lymphoma

Lesley McKarney

First-Line R-CHOP Significantly Improves Outcomes in Older Patients with Advanced-Stage Follicular Lymphoma

Background
• Follicular lymphoma (FL) is an indolent disease and represents 22% of all new diagnoses of NHL.¹
• It is typically a disease of the elderly, with more than 40% of patients with FL being older than 60 years at diagnosis and an age-specific incidence peaking above 75 years.¹
• The role of up-front rituximab-based immunochemotherapy in the management of follicular/low-grade NHL has been investigated.
• A comparison of rituximab (R) in combination with CHOP versus CHOP alone as the initial therapy of follicular/low-grade NHL was the goal of a prospective randomized trial conducted by the German Low Grade Lymphoma Study Group.²

Study Design
• This phase 3 randomized study allocated 221 patients to either CHOP or R-CHOP (rituximab 375 mg/m² d0–1; cyclophosphamide 750 mg/m² d1; doxorubicin 50 mg/m² d1; vincristine 1.4 mg/m² d1; prednisone 100 mg/m² d1–5), with a secondary randomization to either autologous stem cell transplantation or two additional cycles of R-CHOP with either standard dose or intensive interferon maintenance.
• Eligibility criteria for patients included:
  ◦ Age ≥60 years
  ◦ Untreated stage 3 or 4 FL
  ◦ Follicular Lymphoma International Prognostic Index (FLIPI) 2 or 3
• Patient characteristics were well balanced between the treatment groups, also with regard to the distribution of the FLIPI risk groups (> three adverse factors in 73% and 66% in the R-CHOP and CHOP arm, respectively).
• Study endpoints included time to treatment failure and overall remission rate.

Key Findings
• First-line therapy with R-CHOP resulted in higher overall response rates and significantly prolonged the time to treatment failure (TTF) compared to CHOP (Table 1).


### Key Conclusion

- **Rituximab in combination with CHOP significantly improves the outcome for older patients with previously untreated advanced stage FL without adding major side effects.**

**References:**
2. Buske C et al. Front-line combined immuno-chemotherapy (R-CHOP) significantly improves the time to treatment failure and overall survival in elderly patients with advanced stage follicular lymphoma; results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). Program and abstracts of the 48th Annual Meeting of the American Society of Hematology; December 9–12, 2006; Orlando, Florida; Abstract 482.

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### Rituximab with Chemotherapy Improves Responses in Previously Untreated Follicular Lymphoma Patients

#### Background

- Cyclophosphamide, vincristine, and prednisone (CVP) is standard first-line therapy for follicular lymphoma.
- Single-agent rituximab has been shown to induce a high response rate in follicular lymphoma patients.
- Rituximab added to eight cycles of CVP (R-CVP) chemotherapy improves time to progression and duration of response in previously untreated patients with stage III/IV CD20-positive follicular NHL compared with CVP alone; however, the effect on survival in this study was unclear.
- The following results are from a pre-planned analysis of this study after a median follow-up of 53 months.

#### Study Design

- Inclusion criteria included age ≥ 18 years; stage III or IV CD20-positive FL; Eastern Cooperative Oncology Group performance score 0-2; and white blood cell count of < 25 x 10⁹/L.
- The regimens consisted of cyclophosphamide 750 mg/m² (day 1), vincristine 1.4 mg/m² (day 1), and prednisolone 40 mg/m² (days 1–5) (CVP) as a 21-day cycle for eight cycles; or the same regimen with rituximab 375 mg/m² on day 1 of each cycle (R-CVP).
- The primary endpoint of the study was time to treatment failure (TTF).
- Secondary endpoints included overall response rate (ORR), duration of response, time to progression (TTP), disease-free survival (DFS), and overall survival (OS).

### Table 1: First-line response to R-CHOP vs. CHOP Treatment

<table>
<thead>
<tr>
<th>Response</th>
<th>CHOP (%) (n=112)</th>
<th>R-CHOP (%) (n=109)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to treatment failure, median (years)</td>
<td>5</td>
<td>2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Response duration at 4 years (%)</td>
<td>62.2</td>
<td>27.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Estimated 4-year overall survival (%)</td>
<td>90</td>
<td>81</td>
<td>0.039</td>
</tr>
</tbody>
</table>
### Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CVP (n=159)</th>
<th>R-CVP (n=162)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years</td>
<td>53</td>
<td>52</td>
</tr>
<tr>
<td>Lymphoma grade, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>142 (89)</td>
<td>146 (90)</td>
</tr>
<tr>
<td>3</td>
<td>13 (8)</td>
<td>15 (9)</td>
</tr>
<tr>
<td>FLIPI score, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1 (good prognosis)</td>
<td>24 (15)</td>
<td>31 (19)</td>
</tr>
<tr>
<td>2 (intermediate prognosis)</td>
<td>59 (37)</td>
<td>66 (41)</td>
</tr>
<tr>
<td>3–5 (poor prognosis)</td>
<td>75 (47)</td>
<td>65 (40)</td>
</tr>
<tr>
<td>Elevated LDH level, n (%)</td>
<td>41 (26)</td>
<td>41 (26)</td>
</tr>
</tbody>
</table>

FLIPI, Follicular Lymphoma International Prognostic Index; LDH, lactate dehydrogenase

### Table 2: Patient outcomes on R-CVP vs. CVP for follicular lymphoma

<table>
<thead>
<tr>
<th>Median Treatment Outcome, months</th>
<th>CVP (n=159)</th>
<th>R-CVP (n=162)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTF</td>
<td>7</td>
<td>27</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>TTP, relapse, or death</td>
<td>15</td>
<td>34</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>FLIPI 0–1</td>
<td>22</td>
<td>NR</td>
<td>0.0288</td>
</tr>
<tr>
<td>FLIPI 2</td>
<td>17</td>
<td>37</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>FLIPI 3–5</td>
<td>11</td>
<td>26</td>
<td>0.0009</td>
</tr>
<tr>
<td>Time to new treatment</td>
<td>12</td>
<td>49</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Duration of response</td>
<td>14</td>
<td>38</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Survival</td>
<td></td>
<td></td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Disease free</td>
<td>21</td>
<td>NR</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Overall</td>
<td>NR</td>
<td>NR</td>
<td>0.0290</td>
</tr>
</tbody>
</table>

NR, not reached

### Table 3: Comparison of reports of Grade 3 or 4 toxicities between arms

<table>
<thead>
<tr>
<th>Grade 3/4 Hematologic Toxicity, n (%)</th>
<th>CVP (n=159)</th>
<th>R-CVP (n=162)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>30 (18.8)</td>
<td>19 (12)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>23 (14.5)</td>
<td>39 (24)</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (1.9)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>2 (1.2)</td>
</tr>
</tbody>
</table>
Key Findings

- There was significantly more response to induction therapy in the rituximab arm (P < 0.0001).
  - ORR: 81% vs. 57%, R-CVP vs. CVP respectively
  - CR/CR unconfirmed: 41% vs. 10%, respectively
- In patients achieving a complete response (CR) or CR unconfirmed (CRu), DFS was significantly prolonged (P=0.0001, log rank).
- Estimated 4-year DFS rate was 54% for patients receiving R-CVP compared with 17% for CVP.
- Grade 3/4 toxicities were comparable between treatment arms, and the addition of rituximab to CVP did not significantly increase toxicity over CVP alone.

Key Conclusion

- **Rituximab added to CVP as first-line chemotherapy in patients with follicular NHL improves TTP and DFS, and prolongs overall survival.**
  - Increased rate and duration of response
  - Extended time to treatment failure, progression, and new treatment
  - Prolonged disease-free and overall survival
- **The toxicity profile was not significantly affected by addition of rituximab.**
- **The investigators recommend R-CVP as a standard therapy for this patient population.**

References:
Rituximab + CHOP Is Most Effective for Patients with Untreated Follicular Lymphoma

Background

• Options for treating patients with untreated, advanced-stage follicular lymphoma include watchful waiting, single-agent and combination chemotherapy, monoclonal antibodies, and radioimmunotherapy.
• While rituximab (R) chemotherapy combinations have become commonly used for untreated patients with FL, to date, the optimal first-line therapy remains undefined.
• The current study involved a systematic literature review and a meta-analysis of first-line therapies for untreated FL that examined the effect of various chemotherapy regimens combined with R on response rates and survival in patients with untreated FL.

Study Design

• Search terms included follicular lymphoma, medications and treatment regimens (single agent R, R-CVP, R-CHOP, and fludarabine-combinations with R [R-Fcom]).
• Inclusion criteria for studies were as follows:
  1) Patients with untreated stage III/IV FL grades 1, 2, or 3
  2) Intervention with chemotherapy and/or immunotherapy, radioimmunotherapy, or watchful waiting
  3) Reporting in English of the following treatment outcome measures specifically for patients with FL: CR/CR-unconfirmed, overall response rate (OR), and at least one form of survival data.

Key Findings

• Of 3,135 abstracts reviewed, 11 studies met the inclusion criteria, which included data from 3,144 patients.
• Only one study presenting CR data for R-CVP (36%, 95% confidence interval: 28%–44%) met inclusion criteria.
• Estimated CR rate associated with single-agent R was 30% (95% CI: 20%–40%), R-CHOP was 62% (30%–94%), and R-Fcom was 85% (76%–94%).

Canadian Perspective by Dr. Krieger

The studies on follicular lymphoma confirm previous studies showing that rituximab in combination with chemotherapy significantly improves response rate, time to treatment failure, and time to progression compared to chemotherapy alone. The preplanned analysis of the Solal-Ceelligny study shows improved overall survival in first-line treatment of advanced follicular lymphoma patients. In Canada, most centres probably use R-CVP as first-line treatment. While there may be higher response rates using R-CHOP, which is used more often in Germany and the U.S., there is no conclusive evidence that this will improve overall survival.

Preliminary data suggest lower rates of transformation in patients receiving anthracyclines; however, there is increased toxicity with that approach. Further studies investigating the benefit of maintenance rituximab as well as comparing different rituximab-containing chemotherapy regimens will be needed to answer the question of the most appropriate chemotherapy to use.

Key Conclusions

■ R-CHOP and R-fludarabine combinations appear to produce the highest CR rates for untreated patients with FL.
■ Meta-analyses can aid clinicians in therapeutic decision-making as they weigh the risks and benefits of various regimens for newly diagnosed patients.

New Therapies

Lesley McKarney

Lenalidomide Monotherapy has Activity in Relapsed/Refractory Aggressive Non-Hodgkin’s Lymphoma

Background
- Lenalidomide is a novel immunomodulatory agent that has been approved for use in multiple myeloma and subsets of patients with myelodysplastic syndromes.
- It has also been shown to be active in chronic lymphocytic leukemia and cutaneous T-cell lymphoma in clinical trials.
- The current phase 2 multicentre, single-arm, open-label study was designed to evaluate the therapeutic potential and safety of lenalidomide oral monotherapy in patients with relapsed refractory aggressive NHL following one or more prior treatment regimens with measurable disease.

Study Design
- Inclusion criteria were relapsed/refractory aggressive NHL and measurable disease following at least one prior treatment regimen.
- Patients received 25 mg lenalidomide orally once daily on days 1 to 21 every 28 days and continued therapy for 52 weeks as tolerated or until disease progression.
- Response and progression after at least two cycles were evaluated using the IWLRG methodology.

<table>
<thead>
<tr>
<th>Table 1: Baseline Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristic</strong></td>
</tr>
<tr>
<td>Evaluable patients, n</td>
</tr>
<tr>
<td>Median age, years</td>
</tr>
<tr>
<td>Median interval from diagnosis, years</td>
</tr>
<tr>
<td>Median number of prior regimens</td>
</tr>
<tr>
<td>Histology (%)</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma (DLBCL)</td>
</tr>
<tr>
<td>Mantle cell lymphoma (MCL)</td>
</tr>
<tr>
<td>Follicular lymphoma (FL) grade 3</td>
</tr>
<tr>
<td>Transformed lymphoma</td>
</tr>
<tr>
<td>Disease stage (%)</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
<tr>
<td>Not known</td>
</tr>
</tbody>
</table>
Key Findings

- Preliminary results indicate that lenalidomide monotherapy has activity in relapsed/refractory aggressive NHL.
- Median progression-free survival has not yet been reached.
- Grade 3 or 4 adverse events were rare.
- Other events reported in one person each: cardiac infarction, febrile neutropenia, pulmonary embolism, intermittent rash, and anemia.

Key Conclusions

- Oral lenalidomide therapy is active in relapsed/refractory aggressive non-Hodgkin’s lymphoma, with an overall response rate of 41%.
- Activity was seen in all aggressive lymphoma subtypes evaluated.
- The regimen was well tolerated with few Grade 4 adverse events.
- Ongoing studies will evaluate lenalidomide in other settings.

Supportive Care

Lesley McKarney

Primary Prophylaxis with Pegfilgrastim Associated with Reduced Incidence of Febrile Neutropenia in Patients with NHL Undergoing Chemotherapy

Background
• Dose-dense chemotherapy is associated with a higher risk of neutropenia, which can be ameliorated by the daily administration of a recombinant granulocyte-colony stimulating factor (G-CSF).
• Pegfilgrastim is a long-acting form of G-CSF which simplifies neutropenia management with a fixed, once-per-cycle dose.

A recent study confirmed that single dose pegfilgrastim provides safe and effective supportive care for patients with diffuse large B-cell lymphoma receiving dose-dense R-CHOP 14 (rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone) every 14 days.¹

EORTC, NCCN, and ASCO guidelines recommend primary prophylaxis (PP) with G-CSF when the risk of chemotherapy-induced febrile neutropenia (FN) is ≥20%.

Without G-CSF prophylaxis, FN risk in patients with non-Hodgkin’s lymphoma (NHL) receiving CHOP is up to 50%, and over 50% of FN occurs in cycle 1.

Physicians often delay/reduce dose to manage neutropenia, potentially compromising CT efficacy.

The current study reported at ASH is a retrospective analysis of three prospective trials that assessed the effectiveness and safety of pegfilgrastim given in the first courses of chemotherapy in newly diagnosed patients with NHL receiving a dose-dense induction regimen.

Study Design
• The NeuCuP project is an integrated analysis of three phase 2 to 4 studies in which patients with NHL were treated with CHOP, CHOEP, or CNOP with or without rituximab in three- or four-weekly cycles.

Patients who had received at least one chemotherapy regimen plus a pegfilgrastim injection as primary prophylaxis were evaluated.

CHOP: Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
CHOEP: Cyclophosphamide, Doxorubicin, Vincristine, Etoposide, Prednisone
CNOP: Cyclophosphamide, Mitoxantrone, Vincristine, Prednisone

Patients who had received at least one chemotherapy regimen plus a pegfilgrastim injection as primary prophylaxis were evaluated.

CHOP: Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
CHOEP: Cyclophosphamide, Doxorubicin, Vincristine, Etoposide, Prednisone
CNOP: Cyclophosphamide, Mitoxantrone, Vincristine, Prednisone

282 patients of all NHL stages were included in this analysis; 163 patients (58%) had received six chemotherapy cycles.

Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total population (n=282)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>43</td>
</tr>
<tr>
<td>Mean age ± SD, years</td>
<td>65±12.5</td>
</tr>
<tr>
<td>WHO performance score 0–1, %</td>
<td>82.7</td>
</tr>
<tr>
<td>Histology, %</td>
<td></td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>26</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>5</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>3</td>
</tr>
<tr>
<td>No prior chemotherapy, %</td>
<td>72</td>
</tr>
<tr>
<td>Ann Arbor stage, %</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>13</td>
</tr>
<tr>
<td>II</td>
<td>21</td>
</tr>
<tr>
<td>III</td>
<td>32</td>
</tr>
<tr>
<td>IV</td>
<td>34</td>
</tr>
</tbody>
</table>

SD: standard deviation

Table 2: Percentage of patients with WHO grade 3/4 hematological toxicities over all cycles

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 3, %</th>
<th>Grade 4, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median absolute neutrophil count (ANC)</td>
<td>13</td>
<td>54</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Platelet count</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>White blood cell count (WBC)</td>
<td>24</td>
<td>39</td>
</tr>
</tbody>
</table>
The primary outcome measure was the proportion of patients developing FN.

Secondary endpoints were: febrile neutropenia per cycle, hospitalizations due to neutropenia, anti-infective therapy, chemotherapy delay and dose reduction, relative dose intensity, and hematologic toxicities.

Key Findings

- In all, 280 patients started the first cycle of CT, of whom 275 (98%) received pegfilgrastim as PP and were included in the present analyses.
- 272 (96%) of the patients received CHOP; the others received CNOP chemotherapies.
- There was a low overall incidence of FN: 45 patients (16%) (95% CI, 12–20%).
- Of these cases, almost half occurred in the first cycle (45%) (7% of 16% total); and dropped to 1–4% for cycles two to six.
- 83% of patients received a relative dose intensity (RDI) of over 90% across all cycles.
- The myelosuppressive effects of chemotherapy were most evident in the older population:
  - Patients over 65 years of age (n=172) had an FN rate of 18% compared to 13% of the 110 patients under 65 years.
  - Hospitalization due to FN occurred in 13% of patients ≥65 years and 6% aged <65 years.
  - RDI and the incidence of dose delay were similar between the two age groups.
  - Over all cycles, 15% of patients were hospitalized due to a neutropenic event and 11% were hospitalized due to FN.
  - Anti-infectives were prescribed for 60% of patients across all cycles.

Key Conclusion

- Compared to the usual management of secondary prophylaxis, primary prophylaxis lowered the rate of febrile neutropenia from 22–50% to 16%.
- Data suggest that primary prophylaxis with pegfilgrastim enables a high proportion of patients (83%) to complete the necessary chemotherapy regimen with the desired relative dose intensity (≥90% RDI).
- This analysis supports the new guidelines regarding the G-CSF prophylaxis, which suggest the benefit of G-CSF for patients with a risk of FN of ≥20%.

Myelodysplastic Syndrome

Myelodysplastic Syndrome: Incidence

Lesley McKarney

Incidence of Myelodysplastic Syndrome and Chronic Myeloproliferative Disorders Established for U.S. Population

Background

- A recent change in the classification of myelodysplastic syndrome (MDS) by the World Health Organization resulted in the inclusion of MDS in the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) Program and other central cancer registries in 2001.
- Prior to that, incidence rates for MDS and chronic myeloproliferative disorders (CMD) in the United States were not available.
- The current study examined U.S. incidence rates for 2001–2003 to establish a baseline for future studies of MDS and CMD and identify trends according to demographic factors.

Study Design

- SEER (www.seer.cancer.gov) is a population-based cancer registry established and run by the NCI.
- Investigators collected incidence data for MDS and CMD cases from 2001–2003 in 18 SEER areas.
- Information on stage at diagnosis and patient survival was also collected.
- Incidence rates stratified by disease subtype according to French-American-British Classification.
- Incidence of disease subtypes further stratified by sex, age, race, and World Health Organization 5q deletion category at time of diagnosis.
- Incidence rates were extrapolated to the entire U.S. population.

<table>
<thead>
<tr>
<th>Disease</th>
<th>SEER Cases, n</th>
<th>Predicted Cases in Total U.S. Population, n</th>
<th>Incidence Rate per 100,000 Individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMD</td>
<td>1,421</td>
<td>5,813</td>
<td>2.0</td>
</tr>
<tr>
<td>MDS</td>
<td>2,538</td>
<td>9,673</td>
<td>3.6</td>
</tr>
<tr>
<td>Refractory anemia (RA)</td>
<td>420</td>
<td>1,613</td>
<td>0.6</td>
</tr>
<tr>
<td>Refractory anemia with ringed sideroblasts (RARS)</td>
<td>288</td>
<td>1,117</td>
<td>0.4</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts (RAEB)</td>
<td>342</td>
<td>1,491</td>
<td>0.5</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia</td>
<td>123</td>
<td>361</td>
<td>0.2</td>
</tr>
<tr>
<td>Treatment-related MDS</td>
<td>34</td>
<td>161</td>
<td>0.1</td>
</tr>
<tr>
<td>Survival</td>
<td>35</td>
<td>179</td>
<td>0.1</td>
</tr>
<tr>
<td>MDS NOS</td>
<td>1,257</td>
<td>4,750</td>
<td>1.8</td>
</tr>
</tbody>
</table>

NOS: not otherwise specified
Table 2: 2003 SEER incidence rate per 100,000 individuals

<table>
<thead>
<tr>
<th>Race</th>
<th>MDS*</th>
<th>CMD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>White, non-Hispanic</td>
<td>4.2</td>
<td>2.4</td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>2.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.0</td>
<td>0.7</td>
</tr>
<tr>
<td>American Indian/Alaskan</td>
<td>0.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>1.9</td>
<td>1.1</td>
</tr>
</tbody>
</table>

*P for race differences = 0.2; †P for race differences = 0.5

Key Findings

- Incidence rates from 2001–2003 were stable.
- Estimated incidence of MDS in the U.S. population was 3.6/100,000; estimated total number of cases was 9,673.
- Estimated incidence of CMD was 2/100,000; estimated total number of cases was 5,813.
- The incidence rate of MDS with 5q deletion was 0.1/100,000.
- After adjusting for age, CMD was more common in males than females (2.4 vs. 1.7 per 100,000 individuals [P<0.0001]).
- Similarly, MDS was more common in males and there was no difference across subtypes (4.5 vs. 2.7 per 100,000 individuals [P<0.0001]).
- Incidence in both sexes increased significantly with advancing age.

MDS: 36.3/100,000 in 80 and above age group compared with 0.7/100,000 in the 40 to 49 age group (P=0.01)
CMD: 12.2/100,000 in 80 and above age group compared with 1.2/100,000 in the 40 to 49 age group (P=0.001)

- There was a non-significant higher incidence of MDS and CMD among white and non-Hispanic populations, while American Indians and Alaskans had the lowest incidence.
- Investigators also reported that the overall incidence rate (per 100,000 individuals) of MDS in United States was consistent with incidence rates reported in other countries:
  - United States: 3.6
  - United Kingdom: 3.6
  - Germany: 4.1
  - Sweden: 3.6
  - France: 3.2
  - Japan: 1.0

Canadian Perspective by Dr. Laneuville

There is no reliable data available on the incidence and prevalence of myelodysplastic syndromes (MDS) and chronic myeloproliferative disorders (CMD) in Canada. It has thus been difficult to estimate the resources that might be necessary to provide for the growing number of therapeutic options recommended for this patient population. This information was also not systematically collected by the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) Program in the US until 2001. In this report, US national age-adjusted incidence rates observed between 2001 and 2003 for MDS were 4.5/100,000 males and 2.7/100,000 females, while those for CMD were 2.4/100,000 males and 1.7/100,000 females. These results are very similar to those reported in Europe. In Canada, the incidence reported in the US would translate to approximately 1,200 new cases of MDS and 650 new cases of CMD per year. The figures probably underestimate the true incidence, and the prevalence of these disorders would be expected to be several folds greater.

Key Conclusions

- In the U.S., the estimated incidence rate of MDS is 3.6/100,000 and 2/100,000 for CMD.
- Male sex and advanced age appear to be important demographic risk factors for the development of CMD and MDS.
- Diagnostic recording differences may underestimate the total annual U.S. MDS and CMD case burden.
- The identification of a potentially higher incidence of MDS and CMD in white and non-Hispanic groups requires further investigation.
- Questions were raised about poor access to health care for certain ethnic minorities.

Treatment of Myelodysplastic Syndrome

Lesley McKarney

Combined 5AC/MS-275 Inhibition of DNA Methylation Leads to Cytogenetic Responses

Background

- Aberrant methylation of CpG islands in the promoter region has been observed for many differentiation- and cancer-related genes in a number of tumour types, resulting in the silencing of their expression.
- Over the past decade, there has been increasing interest in the use of demethylating agents to either restore normal gene expression or cause apoptosis of cancer cells.
- Optimal re-expression of silenced genes has been shown to require sequential exposure to a methyltransferase inhibitor followed by an HDACi.
- A methyltransferase inhibitor, 5-azacytidine (5AC), has been shown to inhibit cell growth and to induce apoptosis in certain cancer cells.
- MS-275 is a benzamide histone deacetylase inhibitor (HDACi) that leads to sustained induction of histone hyperacetylation.
- MS-275 is an orally bioavailable HDACi with a 50-hour half-life.
- The present phase 1 dose-finding, single-arm prospective study examined whether the addition of HDACi to 5AC could augment the latter’s clinical activity in MDS, CMML, and AML.

Study Design

- Subcutaneous 5AC (30, 40, or 50 mg/m²/dose) was self-administered daily for 10 days.
- MS-275 (2, 4, 6, or 8 mg/m²/dose) was administered on days 3 and 10 of each 28-day treatment cycle.
- A total of 32 patients were enrolled
  - Median age: 63 years (35–84)
  - MDS: 15 patients
  - CMML: 4 patients
  - AML: 13 patients
- A total of 27 patients were evaluable for response.
  - Declining performance status was experienced by two patients.
  - One patient died of sepsis.
  - Two patients had recurrent dose-limiting toxicity (DLT).
- DLT occurred in four patients treated with the MS-275 8 mg/m²/dose (5AC 40 and 50 mg/m²/dose).
  - Laryngeal edema (2), delayed neutrophil recovery >21 days (1), asthenia (1)
- Other side effects of MS-275 included constipation, nausea, transient marrow suppression, and fatigue.
Key Findings

- In this study, 12 of 27 (44%) patients responded.
  - Four complete responses, four partial responses, six demonstrated hematologic improvement in two or more cell lines
  - MDS (7), CMMoL (1), AML-TLD (3), and relapsed AML (1)
- Median time to first objective hematologic response was two cycles (1–5).
- Median time to best hematologic response was four cycles (2–9).
- Median number of cycles administered was 14 (6–26).
- Six out of twelve responders have continued on the study.
- Twenty patients had clonal cytogenetic abnormalities, including six clinical responders; all six had a minimum decrease in abnormal metaphases of 50%, with four cytogenetic CR.

Key Conclusions

- The combination of SAC/MS-275 is clinically tolerable and leads to substantive cytogenetic remissions.
- This study suggests a benefit of the addition of MS-275 to SAC, though SAC scheduling may also be the reason for the responses.
- The apparent optimal dose of the combination is SAC 50 mg/m²/dose and MS-275 4 mg/m²/dose.
- Histone deacetylation and DNA damage was induced by both drugs.
- A randomized phase 2 trial has been initiated (U.S. Intergroup E1905) comparing SAC/MS-275 with the comparable dose schedule of SAC alone.
- The underlying molecular mechanisms of the SAC/MS-275 combination are under investigation.

Canadian Perspective by Dr. Laneuville

Myelodysplasia and AML are thought to, in part, result from epigenetic silencing of certain genes through promoter methylation. This preclinical study has shown that the optimal re-expression of genes silenced through this mechanism can be achieved by combined treatment with a DNA methyl transferase. Overall, a 50% objective hematological response was observed in MDS/AML patients with acceptable toxicity. An Intergroup study of SAC/MS-275 vs. SAC is ongoing and, if positive, could result in changes to current therapeutic recommendations.

Erythropoietin and G-CSF Improve Overall Survival in Patients with Myelodysplastic Syndrome

Background

• Erythropoiesis-stimulating agent (ESA) plus granulocyte-colony stimulating factor G-CSF improves anemia and quality of life (QoL) in MDS with low-transfusion need and low EPO levels.1

• A study of a large cohort of MDS patients treated with the ESA epoetin (EPO) and G-CSF demonstrated a 60% erythroid response rate, with a two-year median response duration in patients with low transfusion needs and low serum-EPO levels.1

• In contrast, only 6% in the poor predictive group (high transfusion need and high serum-EPO level) responded to treatment, and the response was short-lived (three months).1

• A recent study evaluating EPO and G-CSF treatment in patients with MDS vs. historical controls indicates that the treatment can be given safely as chronic administration.

• The present study compared treated patients in three Nordic MDS Group studies with untreated patients from Pavia, Italy to assess the effects of EPO and G-CSF treatment on survival outcome in patients with different probability of response.2

Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Untreated (n=268)</th>
<th>EPO-G-CSF Treated (n=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>63</td>
<td>56</td>
</tr>
<tr>
<td>Median age, yrs (range)</td>
<td>66 (22–92)</td>
<td>72 (43–87)</td>
</tr>
<tr>
<td>Transfusion dependent, %</td>
<td>45</td>
<td>70</td>
</tr>
<tr>
<td>WHO group, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA/RARS/Sq</td>
<td>37</td>
<td>26</td>
</tr>
<tr>
<td>RCMD+/-RS, MDS-U</td>
<td>29</td>
<td>35</td>
</tr>
<tr>
<td>RAEB I</td>
<td>14</td>
<td>26</td>
</tr>
<tr>
<td>RAEB II</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>IPSS classifications, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>55</td>
<td>58</td>
</tr>
<tr>
<td>Intermediate</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>Poor/Unknown</td>
<td>32</td>
<td>24</td>
</tr>
</tbody>
</table>

IPSS: International Prognostic Scoring System; RA, refractory anemia; RAEB, refractory anemia with excess blasts; RARS, refractory anemia with ringed sideroblasts; RCMD+/-RS, refractory cytopenia with multilineage dysplasia with or without ringed sideroblasts; MDS-U, unclassifiable myelodysplastic syndrome.
Study Design
• EPO–G-CSF treated patients from three Nordic trials (n=121) were compared with untreated patients from an Italian cohort (n=268).
• All patients were either transfusion dependent or had Hb <100 g/L.
• Major prognostic indicators recorded at baseline:
  ◦ World Health Organization (WHO) MDS classification
  ◦ Level of transfusion need
  ◦ Serum erythropoietin level
• Prognostic variables that were assessed included overall survival (OS), multivariate Cox analysis with delayed entry, and progression to acute myeloid leukemia (AML).
• Patient groups were well balanced with respect to WHO and IPSS criteria.

Key Findings
• EPO–G-CSF treatment induced an erythroid response rate of 39%.
  ◦ Major response from 96% of responders
  ◦ Median duration of transfusion independence was 23 months (range: 3–116).
• EPO–G-CSF treatment significantly increased OS (hazard ratio (HR): 0.61; P=0.002).
  ◦ Survival benefit was observed for patients with a low transfusion need (<2 U of red blood cells per month) (HR: 0.44; P<0.001); no benefit was observed in patients with higher transfusion need (HR: 0.92; P=0.89).
• No increased risk of leukemic transformation was observed in patients with either high (P=0.21) or low (P=0.75) transfusion requirements.
• Not all patients were treated from the time of diagnosis; multivariate Cox analysis revealed that age and karyotype had an impact on survival, while baseline serum EPO levels had no impact.


Key Conclusions
■ EPO–G-CSF-treated patients with MDS showed a better overall survival than untreated patients.
• The effect was significant in patients with lower need for transfusion.
■ Chronic EPO–G-CSF treatment does not appear to increase risk of transformation of MDS to AML.
■ This is the first study of its kind showing an effect of this treatment on outcome in patients with MDS.
  • Whether this effect is mediated by limiting the iron overload or counteracting other negative effects of chronic anemia remains to be investigated.

Darbopoetin Alfa in the Management of Anemia in Myelodysplasia

Background
• Previous studies have shown that erythropoiesis-stimulating agent (ESA) darbopoetin alfa 150 mcg/wk or 300 mcg/wk appears to be safe and efficacious in treating anemia related to MDS.1,2
• Darbopoetin alfa can raise hemoglobin (Hb) levels in low-risk MDS patients.1
• The current study is a prospective, multicentre, phase 2 study of the effectiveness of darbopoetin alfa 500 mcg administered every three weeks to patients with MDS, which may increase patient convenience through a reduction in clinic visits.

Study Design
• The study enrolled 206 patients, 62 of whom had previous ESA treatment and 144 were ESA-treatment naïve.
• The patient population consisted primarily of MDS patients with IPSS classification of low or intermediate-1 with FAB classifications of refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS).
• Eligibility criteria included ≥18 years, anemia (Hb ≤110 g/L).
• The primary endpoint was erythroid response (International Working Group criteria) by week 13.
• Secondary 53/55-week endpoints included incidence of erythroid responses, incidence of transfusions, the
### Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ESA naïve (n=144)</th>
<th>Prior ESA treatment (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Median age, yrs (range)</td>
<td>76 (51, 93)</td>
<td>76.5 (55, 94)</td>
</tr>
<tr>
<td>Transfusion dependent at screening, %</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Baseline hemoglobin, mean (g/L)</td>
<td>97</td>
<td>100</td>
</tr>
<tr>
<td>FAB group, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>56</td>
<td>61</td>
</tr>
<tr>
<td>RARS</td>
<td>37</td>
<td>32</td>
</tr>
<tr>
<td>RAEB</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>IPSS classification, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>65</td>
<td>71</td>
</tr>
<tr>
<td>Intermediate</td>
<td>31</td>
<td>23</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Baseline erythropoietin category, (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100 mU/mL</td>
<td>67</td>
<td>64</td>
</tr>
<tr>
<td>≥100 and &lt;500 mU/mL</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>≥500 mU/mL</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

*IPSS, International Prognostic Scoring System; RA, refractory anemia; RAEB, refractory anemia with excess blasts; RARS, refractory anemia with ringed sideroblasts*

### Table 2: Outcomes

<table>
<thead>
<tr>
<th></th>
<th>ESA naïve (n=144)</th>
<th>Prior ESA treatment (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude % (95% CL) patients with a major erythroid response at week 53/55</td>
<td>59 (51, 67)</td>
<td>34 (22, 46)</td>
</tr>
<tr>
<td>Crude % (95% CL) patients with a minor erythroid response at week 53/55</td>
<td>15 (9, 20)</td>
<td>16 (7,25)</td>
</tr>
<tr>
<td>Mean (SD) Hb maintained after target achieved, g/L</td>
<td>116 (80)</td>
<td>117 (80)</td>
</tr>
<tr>
<td>Crude % (95% CL) patients achieved target Hb (110g/L)</td>
<td>71 (64, 79)</td>
<td>46 (33, 59)</td>
</tr>
<tr>
<td>Mean (SD) change in FACT-F score to week 53/55</td>
<td>6.2 (9.4)</td>
<td>6.2 (8.8)</td>
</tr>
<tr>
<td>KM% median (95% CL) time to target Hb, weeks</td>
<td>7 (5, 9)</td>
<td>24 (9, not estimable)</td>
</tr>
</tbody>
</table>

*SD: standard deviation; KM%= Kaplan-Meier percentage*
change in Hb levels and FACT-F score from baseline, and adverse events.

- Treatment consisted of darbopoetin alfa 500 mcg administration every three weeks (Q3W) with consideration of increasing dose frequency; if patients did not respond by week seven, the dosing frequency was escalated to every two weeks (Q2W).
- End of study (EOS) was week 53 (Q2W dosing) or week 55 (Q3W dosing).

**Key Findings**

- Patients who had not been treated previously with an ESA had a major response rate of 59%, with 15% having a minor response rate, compared to 34% and 16%, respectively, for patients who had previous treatment with ESA.
- Both ESA-N and ESA-T patients had a clinically meaningful rise (≥3 points) in FACT-F score from baseline.
- Incidence of treatment-related adverse events (AEs) was 11% in ESA-naïve patients and 8% in prior ESA-treated patients.
- The most common AEs were musculoskeletal and injection site pain, and connective tissue disorders such as arthralgia and bone pain.
- Percentage of patients with any adverse event (treatment-related and treatment-unrelated) was 93% in the ESA-naïve and 89% in the prior ESA-treated group; the percentage of patients with serious adverse events was 28% and 34%, respectively.
  - Most common serious adverse events were infections and infestations (pneumonia).

### Key Conclusions

- These results suggested that darbopoetin alfa 500 mcg Q3W was well tolerated.
- Darbopoetin alfa effectively increased Hb levels in the low-risk MDS patients.
- By week 53/55, most patients had achieved an erythroid response.
- Quality of life also improved on darbopoetin alfa treatment, as the mean change in FACT-F score in both ESA-pretreated and ESA-treatment-naïve patients was clinically significant.
- ESA-naïve patients appear to have a more robust response to darbopoetin alfa; the reason for this is unclear.
- A better understanding of previous ESA treatments would assist in determining whether patients can still respond well to darbopoetin alfa if previous treatment with another ESA failed, or if there were dosage or administration issues.
- Further studies should address whether the Q3W extended dosing paradigm increases quality of life in this patient population.


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**Canadian Perspective by Dr. Laneuville**

The Groupe Francophone des Myelodysplasies (GFM) reported on 419 MDS patients who received Epoetin/Darbopoetin + GSCF. A serum G-CSF <200 IU/l, and <2 units PRBC/month were shown to be the two most important determinants of erythropoietin response while multiple lineage dysplasia and >10% blasts were predictive of a shorter duration of response. A major erythroid response was observed in up to 50% of low/Int-1 MDS patients treated with single agent darbopoetin alfa 500 ug Q3W in a multi-site US study. In 389 MDS patients from the Nordic MDS and Pavia Italy Group studies, it was shown that 39% of patients with relatively low transfusion requirements (<2 units months) became transfusion independent and had improved OS when treated with G-CSF and epoetin.

Together, these findings suggest that epoetin/darbopoetin alfa + G-CSF can have a major impact on promoting red cell transfusion independence and improving OS in early stage MDS. This treatment has very little toxicity and is feasible in most Canadian jurisdictions.
Iron Overload in Transfusion-Dependent MDS

Lesley McKarney

Iron Chelation Improves Survival in Myelodysplastic Syndrome

Background
- One of the consequences of the abnormal bone-marrow function in MDS is that patients develop chronic anemia.1
- At diagnosis, approximately half of patients have a hemoglobin level of less than 100 g/L.1
- More than 90% of MDS patients with chronic anemia eventually require regular blood transfusions.2
- Blood transfusions themselves may cause hemosiderosis or iron overload, and that itself can cause clinical adverse effects on cardiac function.1,2
- Iron overload can lead to liver damage, cardiac arrhythmias, infections, skin pigmentation, and malignancies.1,2
- One way to address the problem of iron overload is the use of iron chelation therapy, which helps to prevent iron-related cell damage.
- However, there is some controversy over which patients with MDS should receive iron chelation therapy and whether the treatment is worthwhile, since there have been no data showing the effect on clinical outcomes.1
- In the present study, investigators in British Columbia conducted a retrospective review of patients with MDS who underwent iron chelation therapy (ICT) to determine the impact of iron overload on clinical outcomes in MDS and whether iron chelation therapy improves clinical outcomes in MDS patients with iron overload.2

Study Design
- A retrospective review of data from the Iron Chelation Program of British Columbia database was conducted.

Key Findings
- Clinical evidence of iron overload (serum ferritin > 2000 mcg/L) was determined in 22 patients
- Clinically defined iron overload
  - Congestive heart failure: 5 (3%)
  - Liver disease: 18 (10%)
  - Endocrine dysfunction: 4 (2%)
  - Other: 4 (2%)
- Overall, 18 of the 22 patients were selected to undergo iron chelation therapy (ICT) because of either elevated ferritin levels (13 patients), clinical and biochemical evidence of iron overload (3 patients), or the number of transfusions already received (2 patients).
  - Median duration: 15 months (range: 0.1–37)
  - All 18 patients were considered to be low or intermediate-1 risk according to the International Prognostic Scoring System (IPSS).
- ICT patients generally showed higher baseline levels of ferritin compared with patients who did not undergo ICT (median levels, 4,215 mcg/L vs. 1,647 mcg/L).
- ICT patients also had significantly lower post-ICT ferritin levels (median levels, 2,659 mcg/L vs. 3,188 mcg/L).
### Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median age at cancer diagnosis</th>
<th>Gender</th>
<th>MDS diagnosis, n (%)</th>
<th>ECOG performance status, n (%)</th>
<th>Median absolute neutrophil count</th>
<th>Median hemoglobin</th>
<th>Platelet count</th>
<th>Cytogenetic risk profile (n=150), n (%)</th>
<th>IPSS classification (n=133), n (%)</th>
<th>Ferritin ≥1000 mcg/mL</th>
<th>Received &gt;20 red blood cell units</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>69 years (range: 18–94)</td>
<td>Male: 105</td>
<td>36 (20%)</td>
<td>Refractory anemia</td>
<td>25 (14%)</td>
<td>96.5 g/L (range: 33–155)</td>
<td>115 x 10^9/L (range: 7–644)</td>
<td>107 (60%)</td>
<td>Low risk</td>
<td>16 (8%)</td>
<td>85 (47%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female: 73</td>
<td>42 (24%)</td>
<td>Refractory anemia with ringed sideroblasts</td>
<td>133 (75%)</td>
<td>115 x 10^9/L (range: 7–644)</td>
<td>115 x 10^9/L (range: 7–644)</td>
<td>22 (12%)</td>
<td>Intermediate-1 risk</td>
<td>4 (25%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>28 (16%)</td>
<td>Refractory anemia with excess blasts</td>
<td>17 (10%)</td>
<td>96.5 g/L (range: 33–155)</td>
<td>115 x 10^9/L (range: 7–644)</td>
<td>21 (8%)</td>
<td>Intermediate-2 risk</td>
<td>10 (10%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16 (9%)</td>
<td>Refractory anemia with excess blasts in transformation/acute myeloid leukemia (AML)</td>
<td>17 (10%)</td>
<td>96.5 g/L (range: 33–155)</td>
<td>115 x 10^9/L (range: 7–644)</td>
<td>17 (10%)</td>
<td>High risk</td>
<td>10 (10%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25 (14%)</td>
<td>Chronic myelomonocytic leukemia</td>
<td>10 (1%)</td>
<td>96.5 g/L (range: 33–155)</td>
<td>115 x 10^9/L (range: 7–644)</td>
<td>17 (10%)</td>
<td>Other</td>
<td>4 (25%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>31 (17%)</td>
<td>Other</td>
<td>10 (1%)</td>
<td>96.5 g/L (range: 33–155)</td>
<td>115 x 10^9/L (range: 7–644)</td>
<td>21 (8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**IPSS,** International Prognostic Scoring System

### Table 2: Baseline characteristics of patients who received iron chelation therapy vs. patients who did not

<table>
<thead>
<tr>
<th>Characteristic at Diagnosis, %</th>
<th>Iron Chelation Therapy (n=18)</th>
<th>No Iron Chelation Therapy (n=160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPSS low/intermediate-1</td>
<td>100</td>
<td>51</td>
</tr>
<tr>
<td>&lt; 65 yrs of age</td>
<td>61</td>
<td>29</td>
</tr>
<tr>
<td>Ferritin &gt; 1000 mcg/L</td>
<td>50</td>
<td>4</td>
</tr>
<tr>
<td>Clinical iron overload</td>
<td>33</td>
<td>10</td>
</tr>
<tr>
<td>Major infection</td>
<td>22</td>
<td>29</td>
</tr>
</tbody>
</table>

### Table 3: Overall survival in MDS patients with and without iron chelation therapy (ICT)

<table>
<thead>
<tr>
<th>Overall survival</th>
<th>ICT (%)</th>
<th>Non-ICT (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>Not reached at 160 months</td>
<td>40.1</td>
<td>0.03</td>
</tr>
<tr>
<td>4-year</td>
<td>80</td>
<td>44</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Key Findings, cont.

- Overall survival was significantly longer for patients who received ICT.
- In Cox regression analysis, the only factors significant for OS were:
  - IPSS score (P<0.008)
  - ICT (P<0.02)
- There were 71 documented deaths among patients not receiving ICT:
  - Twenty-two patients died from acute leukemia
  - Twenty-one from MDS complications
  - Eighteen from infection/sepsis
  - Ten from non-MDS-related causes
- There were fewer deaths in the ICT group:
  - Three patients died; one from acute leukemia, one from MDS complications, and one from iron overload.

Key Conclusions

- This study provides the first data documenting improvement in clinical outcome in patients with MDS receiving chelation therapy.
- The 4-year survival rates were 80% in patients on ICT compared with only 44% among non-ICT patients.
- International Prognostic Scoring System (IPSS) score and ICT significantly and independently associated with survival.
- There was no evidence of a decrease in organ dysfunction in patients receiving ICT for MDS.

2. Leitch HA et al. Improved Survival in Patients with Myelodysplastic Syndrome (MDS) Receiving Iron Chelation Therapy. Program and abstracts of the 48th Annual Meeting of the American Society of Hematology; December 9–12, 2006; Orlando, Florida; Abstract 249.

Canadian Perspective by Dr. Laneuville

The consequences of chronic red cell transfusions and iron overload on end-organ damage, morbidity, and mortality in MDS patients has been poorly described. Although evidence of end-organ damage from iron overload could be documented in a large US health-insurance claims database of MDS and other acquired hematopoietic disorders (n=7,113),1 less than 1% of patients received deferoxamine. Data presented from the Iron Chelation Program of British Columbia demonstrated for the first time a significant improvement in overall survival in patients with MDS receiving chelation therapy with deferoxamine. Oral iron chelation therapy may be more convenient, however, and studies with deferasirox (Exjade®) have shown that serum ferritin can be stabilized using a dose of 20 mg/kg/day, or progressively reduced using a dose of 30 mg/kg/day. Safety and tolerability of deferasirox appears to be very acceptable after up to 2.5 years of observation.2

References: 1. Delaea TE et al. Retrospective, nested, case-control study of the association between transfusion frequency and potential complications of iron overload in patients with myelodysplastic syndrome and other acquired hematopoietic disorders. Program and abstracts of the 48th Annual Meeting of the American Society of Hematology; December 9–12, 2006; Orlando, Florida; Abstract 968. 2. Cappellini MD et al. Long-term safety and tolerability of the once-daily, oral iron chelator deferasirox (Exjade®, ICL670) in patients with transfusional iron overload. Program and abstracts of the 48th Annual Meeting of the American Society of Hematology; December 9–12, 2006; Orlando, Florida; Abstract 1768.
Anemia

Background
Chemotherapy-induced anemia is by far the most common hematological adverse event reported by patients with cancer. The grade of anemia varies, depending on the type of cancer and treatment regimen. Anemia is associated with significant healthcare costs as well as decreased quality of life (QoL). If left untreated, severe anemia can result in a delay in cancer treatment and reduced QoL, which may result in suboptimal chances of a cure or long-term survival. Current therapies to ameliorate chemotherapy-induced anemia include supplemental iron therapy, blood transfusions, and/or erythropoietic-stimulating agents (ESAs). Several studies at the ASH meeting in Orlando on December 11, 2006, addressed critical issues regarding quality of life associated with anemia and fatigue, treatment of anemia, and the identification of patients at high risk of developing anemia.

Carpin et al. conducted a review of the published literature on the economic and quality-of-life (QoL) issues of anemia in patients with cancer.1

- The authors carried out a systematic search of trials published between 1990 and 2006 that were designed to examine the burden of illness, direct and/or indirect medical costs, cost drivers, or QoL outcomes associated with anemia and its treatment in patients with cancer.
- Fatigue is one of the most pronounced and prevalent clinical symptoms of anemia.
- Patients with Hb >120 g/L reported significantly less fatigue, fewer non-fatigue anemia symptoms, better physical and functional well-being, and higher general QoL than those with Hb <120 g/L.

- Up to 60% of the total cost of care for patients with cancer may be attributable to anemia, which results in substantial economic and QoL issues for these patients.
- This burden is particularly pronounced for hematological malignancies compared to solid tumours.

Henry et al. assessed the prevalence of fatigue in patients with cancer and examined the relationship between fatigue, anxiety, depression, and somatization.2

- The authors conducted a cross-sectional survey of 1,569 patients. Inclusion criteria were 18 years of age or over, diagnosis of cancer, and receiving chemotherapy and/or radiotherapy during the 12 months prior to the survey.
- Fatigue was by far the most common side-effect of chemotherapy and/or radiotherapy reported in this survey (79%), and yet was found to be largely undertreated (27%).
- Higher levels of fatigue were significantly associated with higher levels of anxiety (P <0.0001), depression (P<0.0001), somatization ((P<0.001), and the global symptom severity (P<0.001).
- Less fatigue was associated with better health status (P<0.0001).
- Fatigue was more prevalent among females, unemployed patients, non-whites, younger patients, and those currently receiving chemotherapy.

Wang and colleagues presented results from their study on early hemoglobin response to erythropoiesis-stimulating therapies (ESTs) and outcomes in cancer patients with anemia.3

- The objective of the study was to evaluate early hemoglobin response (ER) (increase of ≥ 10 g/L within...
four weeks of initiating ESAs) and improved clinical outcomes (e.g., lower transfusion requirements, better overall hematologic rates) between patients achieving an ER and those not achieving an ER.

- Data were analyzed from the Dosing and Outcomes Study of Erythropoiesis-Stimulating Therapies (D.O.S.E) Registry, an ongoing, prospective registry collecting data on real-world practice patterns and outcomes in cancer patients treated with ESAs, epoetin alfa, and darbepoetin alfa.
- Of the 494 patients that were eligible for analysis, 59% achieved an ER within four weeks. This group of patients had shorter mean treatment duration (60.5 vs. 69.2, P=0.0003) and a significantly lower proportion of patients required RBC transfusion compared to patients without an ER (Table 1) (9% vs. 17%, P=0.009).
- A higher proportion of patients were found to achieve an Hb increase of ≥ 20 g/L, an Hb ≥ 110 g/L (85% vs. 40%, P<0.0001), and also a shorter time to achieving Hb ≥ 110 g/L compared to the no-ER group.
- Data from this prospective, observational study demonstrates that patients with an ER had significantly better outcomes than patients without an ER, making ER a desirable goal (19 days vs. 39 days, P<0.0001).

Dr. Lyman and his colleagues conducted a prospective nationwide study to develop and validate risk models for hematologic toxicities of chemotherapy (Table 2). The authors presented a predictive model for early anemia in patients receiving cancer-chemotherapy.

- The analysis was based on 3,640 patients with cancer of the breast, lung, colon, or ovary, or malignant lymphoma receiving a new regimen at 117 randomly selected U.S. practices.
- A logistic regression model for Hb <100 g/L was developed and validated using a 2:1 random selection split-sample methodology.
- The predictive model exhibited good performance characteristics and identified chemotherapy patients at increased risk for developing clinically significant anemia who may be candidates for early targeted intervention with an ESA.

Delarue et al. presented preliminary safety results for the LNH03-6B randomized GELA study. The study involved assessment of the safety of prophylactic use of darbepoetin alfa in older patients with diffuse large B-cell lymphoma treated with R-CHOP 14 or R-CHOP 21.

- Elderly patients between the ages of 66 to 80 years with aggressive lymphoma were randomized to first-line darbepoetin alfa (n=63) in order to maintain hemoglobin levels between 130 and 150 g/L or classical treatment (n=67) of chemotherapy-induced anemia, including transfusions and epoetin alfa therapy according to usual practices.
- The number of serious adverse events (SAE) of any cause was found to be lower in the first-line darbepoetin alfa arm. The number of patients receiving red blood cell transfusions was also significantly lower in this arm (P<0.01) (Table 3).
- These preliminary studies provide encouraging results about the safety of a prophylactic use of darbepoetin alfa and support the accrual to draw definite conclusions about safety and efficacy.

### Table 1: Hemoglobin response after erythropoiesis-stimulating agents

<table>
<thead>
<tr>
<th></th>
<th>ER (n=293)</th>
<th>No ER (n=201)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% requiring RBC transfusion</td>
<td>9</td>
<td>17</td>
<td>0.0009</td>
</tr>
<tr>
<td>Mean treatment duration</td>
<td>61 days</td>
<td>69 days</td>
<td>0.0003</td>
</tr>
<tr>
<td>% achieving Hb ≥120 g/L or Hb increase ≥20 g/L</td>
<td>85</td>
<td>40</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% achieving Hb increase ≥20 g/L</td>
<td>70</td>
<td>29</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% achieving Hb ≥110 g/L</td>
<td>94</td>
<td>73</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean time to achieving Hb ≥110 g/L</td>
<td>19 days</td>
<td>39 days</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Summary of Main Findings

- Anemia results in substantial economic and quality of life (QoL) burdens in patients with cancer.
- Severity of anemia is correlated with the degree of fatigue and QoL impairment.
- A validated predictive model of anemia risk has been developed to help identify patients undergoing chemotherapy who are at high risk of developing clinically significant anemia.
- Patients with early response to erythropoiesis-stimulating agents exhibit better clinical outcomes as compared to patients who do not achieve an early response.
- Preliminary results of the GELA study provide reassuring data on the safety and efficacy of prophylactic use of the erythropoiesis-stimulating agent, darbepoetin alfa.


Table 2: Grade 3/4 hematological toxicity

<table>
<thead>
<tr>
<th></th>
<th>R-chemotherapy + darbepoetin alfa</th>
<th>R-chemotherapy + transfusions or epoetin alfa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (%) (&lt;80 g/L)</td>
<td>22</td>
<td>39</td>
</tr>
<tr>
<td>WBC (%) (&lt;2,000/mm³)</td>
<td>80</td>
<td>79</td>
</tr>
<tr>
<td>ANC (%) (&lt;1,000/mm³)</td>
<td>79</td>
<td>73</td>
</tr>
<tr>
<td>Platelets (%) (&lt;30,000/mm³)</td>
<td>22</td>
<td>37</td>
</tr>
<tr>
<td>Patients receiving red blood cell transfusions (%)</td>
<td>29</td>
<td>55</td>
</tr>
<tr>
<td>Patients with at least one episode of febrile neutropenia (%)</td>
<td>23</td>
<td>36</td>
</tr>
<tr>
<td>Median Hb (g/L)</td>
<td>120.5</td>
<td>106.5</td>
</tr>
</tbody>
</table>

Table 3: Cardiac and vascular serious adverse events (SAE)

<table>
<thead>
<tr>
<th></th>
<th>R-chemotherapy + darbepoetin alfa</th>
<th>R-chemotherapy + transfusions or epoetin alfa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number and causes of vascular SAE, %</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Cerebral ischemia</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Bleeding</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Number and causes of cardiac SAE, %</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Coronary atheroma</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>
August 2003 is still a blur of medical events for Patricia Plummer. An active, healthy 40-something Patricia found out that her sudden renal failure was caused by a rare form of non-Hodgkin’s lymphoma. Kidney dialysis and chemotherapy treatments translated into countless trips to and from the cancer centre, repeated testing, and transfusion dependency with long hours attached to machines and IV tubes.

Just as Patricia started to feel better after each chemotherapy treatment, it was time for the next one. The side effects of the cancer therapy were challenging to say the least and made daily activities of normal life nearly impossible.

“I experienced a whole range of chemotherapy side effects. The chemo destroyed my immune system, and I spent about four weeks in the hospital because of a really bad infection. The neuropathy was difficult to deal with too. Some of the feeling still hasn’t come back. To top it all off, severe anemia, which was initially caused by the kidney failure, was made worse by chemotherapy. The drugs used to treat my cancer were taking away my ability to live. Anemia left me so exhausted that moving from one room of my house to another was an enormous physical feat. It robbed me of one of my favourite pleasures: walking my dog, Shadow. My anemia affected him too. He used to be thinner.”

Anemia is a common but little understood symptom of chronic disease that adversely affects the quality of life of thousands of Canadians. Anemia diminishes the ability to work, perform daily tasks, and participate in family or social activities. It remains an under-diagnosed and under-treated side effect of cancer treatments.

Treatment of anemia results in significant improvements in energy, activity, and overall quality of life. Primarily, anemia is treated with red-blood-cell transfusions, or by intravenous or subcutaneous administration of erythropoietic stimulating agents (ESAs). In the last decade, ESAs have been integrated worldwide into standard care for chemotherapy-related anemia in patients with non-myeloid malignancies. Two ESA therapies are currently available in Canada: epoetin alfa and darbepoetin alfa.

**Cancer patient defines ESA therapy as “life-giving”**

Patricia and her dog, Shadow
In addition to raising hemoglobin levels, and consequently improving patient quality of life, ESA therapy decreases transfusion requirements.\(^1\) In Patricia’s case, it meant that she no longer required transfusions. Once Patricia was taken off dialysis, she was able to continue her ESA therapy at home. Her daily life improved remarkably. Gone were the visits to the treatment centre where she sat for five or six hours just to receive two units of blood. Instead, her hemoglobin level was easily maintained by simple subcutaneous injections that her husband, Gary, administered to her in the comfort of their home.

“It was such a relief to be able to get this treatment at home. The trips to the treatment centre for transfusions were a burden and major inconvenience not only to me, but to the lives of my family and friends. Now, no one has to drive me to the hospital and spend the day waiting for me to be done. Gary can just give me my shot at home. It’s so quick and so simple.”

Shortly after starting ESA therapy, Patricia noticed a change in her energy level. The fatigue began to lift and she was able to walk her dog with her husband and do things around the house. With renewed energy, she was able to focus on her battle with cancer. While the cancer never actually reached remission, Patricia was told in June 2004 that the lymphoma cells had dropped below the active level. No further cancer treatments were required. She continued ESA treatments at home to maintain her hemoglobin level.

This past summer, Patricia took sick again very quickly. Tests showed that the lymphoma had become active, and she needed another eight rounds of chemotherapy. She had fought this cancer before and resolved to do it again. She found it helpful to know that there were medications out there, such as ESA therapies.

“This ESA medication really reminds me that there are many positive times during these darker moments. My biggest fear with the re-diagnosis was that I would have to go back on dialysis and be dependent on machines and long visits to the cancer centre. Chemotherapy and kidney dialysis are life-saving, but treatments like ESA are life-giving.”

Given the significant impact that anemia has on the lives of cancer patients, it is important that healthcare professionals and the general public understand the seriousness of anemia — its causes, effects, diagnosis, and treatment.

“It would be great if my hemoglobin level would eventually improve to the point that I no longer need ESA injections. But if it doesn’t, then it is so nice to know that there is something that helps me to live a somewhat normal life and that I don’t have to go to the hospital to get the treatment.”

_Just before Christmas, Patricia successfully completed her eighth cycle of chemotherapy. She continues to administer darbepoetin alfa as required at home. Her future plans include returning to work in the spring. But for now, the daily walks with Gary and Shadow are what she savours most._


“My biggest fear with the re-diagnosis was that I would have to go back on dialysis and be dependent on machines and long visits to the cancer centre. Chemotherapy and kidney dialysis are life-saving, but treatments like ESA are life-giving.”
The 29th annual San Antonio Breast Cancer Symposium, held on December 14 to 17, 2006, attracted more than 8,100 participants from 79 countries. The ongoing exploration of tamoxifen in breast cancer prevention was one of several themes at the meeting. Of particular note were studies examining the toxicities and treatment duration of adjuvant regimens for HER2-overexpressing breast cancer, as well as treatment options after failure of non-steroidal aromatase inhibitors. The meeting also featured new data regarding the use of alternative therapies to bisphosphonates to reduce bone turnover in patients with metastatic breast cancer. Finally, the latest data from studies of nab-paclitaxel continue to confirm its role in the metastatic breast cancer setting.
Radiotherapy

Lesley McKarney

Radiotherapy in Older Patients: What’s the Value?

**Background**

- Although breast irradiation is relatively well tolerated, it is not without its side effects.\(^1\)
- A 2004 study reported that breast pain, skin fibrosis, edema, cosmesis, skin color, and shoulder and arm stiffness were worse among older women who had undergone breast irradiation than in women who did not.\(^1\)
- The same study also demonstrated that among women 70 years of age or older who have early, estrogen-receptor–positive breast cancer, the addition of adjuvant radiation therapy to tamoxifen had no impact on the rate of mastectomy for local recurrence, and did not increase the survival rate or increase the rate of freedom from distant metastases after a median follow-up of five years.
- The current CALGB 9343 study updates the results at a median follow-up of 7.9 years.\(^2\)

**Study Design**

- Eligibility criteria included:
  - Age 70 years or older
  - Clinical stage I breast cancer (T1N0M0 according to the tumor–node–metastasis classification system)
  - No history of cancer other than *in situ* cervical cancer or nonmelanoma skin cancer within five years before randomization.
  - Tumor size ≤2 cm
  - ER-positive
  - Node-negative following lumpectomy
- At study entry 636 patients were randomly assigned to receive tamoxifen 20 mg daily for five years (Tam, n=319) alone or with radiation therapy (TamRT, n=317).
- Primary end points were:
  - time to locoregional recurrence
  - frequency of mastectomy for recurrence
  - breast-cancer-specific mortality
  - time to distant metastasis
  - all-cause mortality

**Key Findings**

- The benefit of radiotherapy at 7.9 years of follow-up was small but significant in terms of locoregional recurrence (\(P<0.001\))(Table 1).
- There was no difference in overall survival detected between groups.
- The benefit of radiotherapy is summarized below:
  - Locoregional recurrence \(5.9\%\)
  - Ultimate breast conservation \(no\ \text{effect}\)
  - Distant metastases \(no\ \text{effect}\)
  - Death from breast cancer \(no\ \text{effect}\)
  - Death from all causes \(no\ \text{effect}\)

**Key Conclusions**

- **Radiation produces a 5.9% decrease in breast recurrence in this population.**
- **Radiation does not impact ultimate breast conservation, distant metastases or death from other causes**
- The five-year data are durable.
- The cohort may be too small to test overall survival.
- **Tamoxifen without radiation is a reasonable option for women 70 years and older with T1 N0 estrogen-receptor–positive breast cancer.**

Table 1: Outcomes

<table>
<thead>
<tr>
<th></th>
<th>TamRT (n=317)</th>
<th>Tam (n=319)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locoregional recurrence</td>
<td>3 (1%)</td>
<td>23 (7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>3 (1%)</td>
<td>9 (3%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>9 (3%)</td>
<td>11 (3%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Breast cancer-specific mortality</td>
<td>5 (2%)</td>
<td>5 (2%)</td>
<td>0.823 - 0.987</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>86 (27%)</td>
<td>82 (26%)</td>
<td>0.841</td>
</tr>
</tbody>
</table>

Canadian Perspective by Dr. Verma

This was a well-conducted study. Patients had been followed long enough to assess the critical endpoint of in-breast recurrences. The investigators concluded radiation significantly reduced breast recurrence in patients treated with partial mastectomy and tamoxifen. However a reduction in breast conservation, distant metastases, or deaths from other causes was not observed. Therefore it may well be appropriate to start changing the treatment paradigm in older women. These results would apply to women 70 years or older with T1 N0 stage disease. My suspicion is that, in Canadian practice, this will evolve down to women with < 1 cm tumours.

There is still a lot of concern about any in-breast recurrence, however, and what it means to women. But if we can demonstrate that there is no impact on mortality, as this study does, then it is justified to avoid radiation in selected women with ER-positive tumours.

Radiation Boost Increases Risk of Fibrosis without Adding Survival Benefit: 10-Year Results

**Background**

- Radiotherapy prevents local recurrence of breast cancer after breast-conserving surgery.
- Many guidelines limit the dose of radiation to 50 Gy when the excised tumour has microscopically negative margins.1
- A European Organisation for Research and Treatment of Cancer (EORTC) study published in 2001 investigated the benefits and risks of adding an additional 16 Gy dose to this standard 50 Gy irradiation of the whole breast in patients with completely excised early breast cancer.1
- It found that, at 5-year follow-up, a supplementary boost radiation of 16 Gy to the primary tumour area nearly halved the annual odds of local recurrence (hazard ratio, 0.59), particularly in patients younger than 40.
- The current study provides the 10-year data on the impact of boost radiation on local control, fibrosis and survival for patients enrolled in the aforementioned equivalence trial of boost versus no boost.2

**Study Design**

- Eligibility: patients with breast cancer of clinical stage T1–2,N0–1,M0
- Exclusion criteria included patients >70 years of age, or those with pure carcinoma in situ, multiple tumor foci in more than one quadrant, a history of other cancers, an ECOG performance score >2, residual microcalcifications on mammography, or gross residual disease in the breast after lumpectomy were ineligible.
- After breast-conserving surgery, all 5,318 patients received 50 Gy of radiation to the entire breast.
- Half the patients also received a 16 Gy radiation boost (n=2,661) to the area of the cancer.
- The remaining patients (n=2,657) received no further radiation therapy.
• At randomization, patients were stratified according to age, menopausal status, the presence or absence of an intraductal component in and around the invasive tumour, clinical tumour size, clinical nodal status, and centre.
• Median follow-up was 10.75 years.

Baseline Characteristics
• Median age was 55 years
• Patient and tumour characteristics, published previously,1 were well balanced between the two groups; 90% of cases were cN0 and 78% were pN0.
• The boost and no boost groups were also balanced with regards to the proportion of patients receiving adjuvant chemotherapy (12% in each group).

Key Findings
• Ten-year survival was 82% in both study groups (P=0.93).
• The ten-year risk of cancer recurrence within the breast was 6.2% in patients who received boost radiation and 10.2% in the no-boost group (P<0.0001).
• Young women (those under the age of 40) experienced the greatest reduction in recurrence risk following boost radiation.
• Absolute risk reduction per age group at 10 years:
  ≤40 years: 23.9% to 13.5% (P=0.0014)
  41–50 years: 12.5% to 8.7% (P=0.0099)
  51–60 years: 7.8% to 4.9% (P=0.0157)
  >60 years: 7.3% to 3.8% (P=0.0008)
• Severe fibrosis occurred in 4.4% of patients treated with boost radiation, compared with only 1.6% of patients who did not receive boost radiation (P<0.0001).

Canadian Perspective by Dr. Verma

This was an interesting study in that it showed that women who had received radiation and then a boost had better local control regardless of their stage. However, this disease control came at a cost of increased fibrosis. The predominant benefit was seen in younger women 40 years or less. Less benefit of the boost was seen in older women, which is consistent with previous reports from the same study group.

The EORTC has been very diligent in looking at the role of boost in the adjuvant radiation setting. It has been shown that younger women are at higher risk of relapse, and this is a group we should be paying more attention to. It is doubtful whether the results of this study will penetrate Canadian practice in a significant way, except perhaps for the message that we should be looking for cosmetic results and long-term effects of radiation, and recording and measuring them.

Key Conclusions

- A boost irradiation of 16 Gy significantly reduced the incidence of local failure from 12% to 7% (HR, 0.59).
  • The greatest impact was for patients ≤40 years of age.
- The benefit of boost irradiation in local control decreased with advancing age.
  • The benefit in local control at 10 years amounts roughly 10% in patients 40 years old or younger, 4% in patients aged 41–50 years, and 3% in patients older than 50 years.
- Boost irradiation had no impact on survival or mortality.
- The improved local control was at the cost of a small increase in severe fibrosis.

Breast Cancer Prevention

Lesley McKarney

Effect of Tamoxifen and Raloxifene Is Similar in Development of Noninvasive Breast Cancer

Background

- All women with significant risk for future breast cancer development are potential candidates for chemoprevention.
- Tamoxifen was approved largely based on the findings of the NSABP-P1 trial, a randomized, double-blinded trial conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP).¹
- In this trial, women with a projected risk of breast cancer of greater than 1.66% over a 5-year period received either tamoxifen or a placebo for a period of 5 years.¹
- However, the NSABP-P1 trial made no determinations regarding the age at which tamoxifen chemoprevention therapy should begin, the recommended duration for this therapy, related quality-of-life measures, or how it compared with other breast cancer risk-reduction and ovarian cancer risk-reduction strategies.
- Though both agents are selective estrogen receptor modulators, tamoxifen has an associated increased risk of endometrial cancer, while raloxifene has no such associated risk.
- The purpose of the STAR (Study of Tamoxifen and Raloxifene) trial, which is overseen by the NSABP, is to determine if raloxifene may be an alternative to tamoxifen in a chemoprevention role in high-risk women.²

Study Design

- In this large, randomized trial, 19,747 postmenopausal women (average age 57.8 years) with increased 5-year breast cancer risk (mean 4.03 ± 2.17 % as calculated by the Gail model) received five years of daily oral tamoxifen 20 mg or raloxifene 60 mg.
- Primary outcome measures were the development of invasive breast cancer, uterine cancer, noninvasive breast cancer, bone fractures, and thromboembolic events.
- Median follow-up was 47 months. Average age at follow-up was 47.3 years.

Key Findings

- The incidence of invasive breast cancer was similar in the two treatment arms, with 163 cases occurring in the tamoxifen arm and 168 in the raloxifene arm (Table 1):
  - Incidence 4.30 per 1,000 vs. 4.41 per 1,000; RR = 1.02, 95% CI = 0.82–1.28
- The cumulative incidence of noninvasive breast cancer, both LCIS and DCIS, appeared to favour tamoxifen; however, the significance was borderline:
  - Incidence 8.2 vs. 11.7 per 1,000, P=0.052
  - About 36% of the cases were LCIS and 54% were DCIS, with the balance being mixed types.

Reference

2. Vogel VG et al. The effects of tamoxifen versus raloxifene on the risk of developing noninvasive breast cancer in the NSABP study of tamoxifen and raloxifene (STAR) P-2 trial. Proceedings from the 29th Annual San Antonio Breast Cancer Symposium; December 14-17, 2006; San Antonio, Texas; Abstract 33.

Key Conclusion

- Tamoxifen and raloxifene may have similar effects on incident in situ carcinomas, but both the clinical impact and significance of these findings remains to be determined.

Table 1: Annual rate by treatment group

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Number of events</th>
<th>Rate per 1,000</th>
<th>Risk ratio</th>
<th>RR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tamoxifen</td>
<td>Raloxifene</td>
<td>Tamoxifen</td>
<td>Raloxifene</td>
</tr>
<tr>
<td>DCIS</td>
<td>30</td>
<td>44</td>
<td>0.79</td>
<td>1.16</td>
</tr>
<tr>
<td>LCIS</td>
<td>21</td>
<td>29</td>
<td>0.56</td>
<td>0.76</td>
</tr>
<tr>
<td>Mixed</td>
<td>6</td>
<td>7</td>
<td>0.16</td>
<td>0.18</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
<td>80</td>
<td>1.51</td>
<td>2.11</td>
</tr>
</tbody>
</table>

DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ
Chemoprevention with Tamoxifen Confirmed in Long-Term IBIS-I Study Follow-Up

Background
- The International Breast Cancer Intervention study (IBIS-I), a randomized, double-blind, placebo-controlled, multicenter, phase 3 chemoprevention trial, enrolled over 7,000 women between the ages of 35 and 70 who had a family history of breast cancer.
- Early results published in 2002 found that women taking tamoxifen had a 32% lower risk of developing breast cancer compared to those taking placebo.  
- There was a nonsignificant increase in incidence of endometrial cancer (11 vs. 5; P=0.2), while thromboembolic events were significantly increased with tamoxifen (43 vs. 17; OR: 2.5 [1.5-4.4], P=0.001).
- Hence, the overall risk to benefit ratio for the use of tamoxifen in prevention is still unclear.
- The present study reports the detailed findings of long-term follow-up of this study.  

Study Design
- 7,145 women were randomly assigned to receive either 20 mg/day tamoxifen (n=3,579) or matching placebo (n=3,575) for five years (Table 1).
- The primary outcome measure was the incidence of breast cancer (including ductal carcinoma in situ).
- Secondary endpoints included other cancers, breast cancer mortality, all-cause mortality, adverse events.
- Median follow-up was 95.6 months (eight years)

Key Findings
- There was a 29% reduction in the incidence of breast cancer in the tamoxifen arm versus placebo (HR: 0.71; CI, 0.56-0.89) (Table 2).
- Risk reduction was most evident in invasive ER-positive breast cancer
- Tamoxifen appears to have long-lived effects in preventing new tumours
- Reduction in risk with tamoxifen, Year 5
  + All breast cancers: 1.1% (2.2% vs. 3.3%)
  + ER-positive breast cancer: 0.5% (1.5% vs. 2.0%)
- Reduction in risk with tamoxifen, Year 10
  + All breast cancers: 1.7% (4.7% vs. 6.4%)
  + ER-positive breast cancer: 1.4% (2.9% vs. 4.3%)

| Table 1: Baseline characteristics |
| Characteristics | Tamoxifen (n=3,579) | Placebo (n=3,575) |
| Mean age, yrs (SD) | 50.7 (7) | 50.8 (6.7) |
| Postmenopausal, % | 49.3 | 48.8 |
| HRT, % |
| Never | 58.4 | 59.3 |
| Current | 25.4 | 26.3 |
| Prior | 15.8 | 14.1 |
| Hysterectomy, % | 34.5 | 36.0 |

HRT, hormone replacement therapy; SD, standard deviation

| Table 2: Breast cancer incidence |
| New Breast Cancer, n | Tamoxifen (n=3,579) | Placebo (n=3,575) | Odds Ratio (95% CI) |
| Invasive | 124 | 166 | 0.73 (0.57-0.94) |
| ER-positive | 87 | 129 | 0.66 (0.49-0.88) |
| ER-negative | 35 | 35 | 0.99 (0.60-1.64) |
| Noninvasive (DCIS) | 17 | 27 | 0.62 (0.32-1.19) |
| Total | 142 | 195 | 0.71 (0.56-0.89) |

DCIS, ductal carcinoma in situ
### Key Conclusions

- The updated analysis confirms the reduction in invasive ER-positive breast cancer by daily treatment with tamoxifen for five years.
- The effect is continued after cessation of tamoxifen.
- Benefit is seen in the last five years as well as the first.
- Most side effects are only apparent during treatment.
- Suggests that the risk-to-benefit ratio of tamoxifen used for breast cancer prevention improves with longer follow-up.
- Benefit is possibly greatest in premenopausal women
- Likely optimal strategy: tamoxifen in premenopausal phase followed by aromatase inhibitor in postmenopausal phase.

#### Reference:
2. Cuzick J, on behalf of the IBIS Investigators. Long term efficacy of tamoxifen for chemoprevention: results of the IBIS-I study. Program and abstracts of the 29th Annual San Antonio Breast Cancer Symposium; December 14-17, 2006; San Antonio, Texas; Abstract 34.

### Table 3: Breast cancer incidence

<table>
<thead>
<tr>
<th>Invasive Breast Cancer Characteristics, n</th>
<th>Tamoxifen (n=3,579)</th>
<th>Placebo (n=3,575)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50</td>
<td>86</td>
<td>129</td>
<td>0.79 (0.58-1.06)</td>
</tr>
<tr>
<td>&lt;50</td>
<td>56</td>
<td>35</td>
<td>0.64 (0.45-0.91)</td>
</tr>
<tr>
<td>Tumour grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>41</td>
<td>50</td>
<td>0.81 (0.52-1.26)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>53</td>
<td>81</td>
<td>0.64 (0.44-0.93)</td>
</tr>
<tr>
<td>Low</td>
<td>26</td>
<td>27</td>
<td>0.96 (0.53-1.71)</td>
</tr>
<tr>
<td>Nodal status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>37</td>
<td>44</td>
<td>0.83 (0.52-0.96)</td>
</tr>
<tr>
<td>Negative</td>
<td>81</td>
<td>112</td>
<td>0.71 (0.52-1.33)</td>
</tr>
<tr>
<td>Size, cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>38</td>
<td>51</td>
<td>0.74 (0.47-1.15)</td>
</tr>
<tr>
<td>1–2</td>
<td>40</td>
<td>62</td>
<td>0.64 (0.41-0.97)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>38</td>
<td>37</td>
<td>1.02 (0.63-1.66)</td>
</tr>
</tbody>
</table>

- The benefit was greater in premenopausal women < 50 years of age.
- There was a nonsignificant trend for lower risk of breast cancer in women in the tamoxifen arm who had never used HRT, which requires further investigation.
- There was a higher risk of cataracts after tamoxifen treatment (odds ratio: 1.87 [95% CI: 1.06–3.41]).
- There was no long-term difference in deaths from all causes (25 Tam vs. 11 placebo, P=0.36).
- There was an increased risk of thromboembolic events during treatment with tamoxifen (OR: 2.98, 95% CI: 1.78–5.16).
- The incidence diminishes after treatment is stopped (OR: 1.30, 95% CI: 0.79-2.15).
- Cardiac effects may persist after treatment with tamoxifen.
- There was no statistical difference in overall incidence of endometrial cancers (17 Tam vs. 11 placebo, OR: 1.54, P=0.25).
- Most cases of endometrial cancer were seen during tamoxifen treatment.

### Canadian Perspective by Dr. Verma

This data continues to uphold the contention that estrogen-receptor-positive breast cancer can be prevented. In practice, physicians should be much more sophisticated about selecting women at risk for breast cancer. Does this role fall to oncologists? Certainly it does. But this knowledge should also be translated to surgeons and general practitioners, so that we may all become more familiar with all of the tools that are available to help identify women at risk, counsel these women on risks and benefits of the different treatments, and consider initiation of therapy raloxifene or tamoxifen in high-risk women.
Adjuvant Therapy in HER2-Positive Patients

New Data Challenges Necessity of Anthracyclines in Adjuvant Therapy of HER2-Positive Breast Cancer

**Background**
- Anthracyclines have formed the backbone of adjuvant treatment for breast cancer.
- Approximately 25% of individuals with breast cancer are HER2-positive.
- HER2 is associated with poorer clinical prognosis than absence of HER2.
- Trastuzumab is a monoclonal antibody to the HER2 receptor, with demonstrated efficacy in combination with adjuvant chemotherapy.
- The present study is the second interim analysis of randomized, phase 3 trial Breast Cancer International Research Group 006, which was designed to assess the role of trastuzumab in combination with a docetaxel-containing chemotherapy regimen with or without an anthracycline (doxorubicin).
- Close monitoring of trastuzumab-containing arms will assess cardiac safety.

**Study Design**
- HER2-positive (FISH) breast cancer patients with axillary lymph node positive or high-risk negative patients were randomly assigned to either standard doxorubicin/cyclophosphamide (AC) followed by docetaxel (T) or two trastuzumab-containing regimens:
  - AC followed by T with trastuzumab for one year or TCarboplatin with trastuzumab for one year.
- All patients with hormone-receptor–positive tumours received five years of hormone-directed therapy following chemotherapy.
- A very small subset of patients (n=17; 1.6%) assigned to doxorubicin and cyclophosphamide followed by docetaxel (AC→T) crossed over to receive trastuzumab.
- The primary endpoint was disease-free survival (DFS).
- Secondary endpoints include overall survival (OS) and safety/toxicity (which includes analysis of extensive cardiotoxicity such as symptomatic events and asymptomatic left ventricular ejection fraction [LVEF] decline).
- Subanalysis compared outcomes between patients with or without topoisomerase II (TOPO II)-alpha coamplification with HER2.
- Median follow-up for second interim analysis was 36 months.

![Diagram of treatment regimens](attachment:image.png)

*AC, doxorubicin/cyclophosphamide; T, docetaxel; H, trastuzumab*
Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>AC → T (n=1,072)</th>
<th>AC → TH (n=1,076)</th>
<th>TCH (n=1,074)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs (range)</td>
<td>49 (23–74)</td>
<td>49 (22–74)</td>
<td>49 (23–73)</td>
</tr>
<tr>
<td>Karnofsky performance score = 100, %</td>
<td>80</td>
<td>79</td>
<td>80</td>
</tr>
<tr>
<td>Prior treatments, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td>60</td>
<td>63</td>
<td>60</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>63</td>
<td>61</td>
<td>63</td>
</tr>
<tr>
<td>After chemotherapy</td>
<td>62</td>
<td>61</td>
<td>62</td>
</tr>
<tr>
<td>To left chest*</td>
<td>32</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>50</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td>Number of tumour nodes, %</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>29</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>1–3</td>
<td>38</td>
<td>38</td>
<td>39</td>
</tr>
<tr>
<td>4–10</td>
<td>22</td>
<td>24</td>
<td>23</td>
</tr>
<tr>
<td>&gt;10</td>
<td>11</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Tumour size (cm), %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>41</td>
<td>38</td>
<td>40</td>
</tr>
<tr>
<td>&gt;2 and ≤5</td>
<td>53</td>
<td>55</td>
<td>54</td>
</tr>
<tr>
<td>&gt;5</td>
<td>6</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Estrogen and/or progesterone-receptor-positive, %</td>
<td>54</td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td>Cardiovascular risk factors, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity (BMI ≥30)</td>
<td>20</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

BMI, body mass index
*Potential cardiovascular risk factor

Key Findings
- The results confirm the findings of the first interim analysis, as both experimental groups had significantly better outcomes than the control group in reducing the risk for death and improving disease-free survival.
- The differences between the two experimental groups were not statistically significant.
- The number of observed events at second interim analysis was significantly greater.
  - AC → T regimen vs. AC → TH regimen (P=0.000011) or TCH regimen (P=0.00028)
- The number of observed events were comparable between AC → TH and TCH regimens (P=0.42).
- A total of 17 patients (1.6%) of 1,073 assigned to the ITT control arm (AC-T) crossed over to receive trastuzumab.
- OS was significantly improved with trastuzumab-containing regimens (Table 2).
- The number of deaths was significantly greater with AC → T regimen vs. AC → TH regimen (P=0.004) or TCH regimen (P=0.017).
- The number of deaths was comparable between AC → TH and TCH regimens (P=0.58).
- Patients with lymph-node-negative disease appeared to do better on trastuzumab-containing regimens, with no apparent difference in OS between TCH and AC → T regimens (Figures 1 and 2).
- In terms of safety, the TCH regimen was the least toxic of the three regimens while the AC → TH was most toxic (Table 3).
- The TCH group showed significantly less neutropenia and leukopenia but more anemia and thrombocytopenia.
Secondary leukemia developed in both of the anthracycline-containing groups – in three patients in the AC → T and in one patient in AC → TH, but no cases have been reported in TCH group.

No cardiac-associated deaths were reported in any arm; however, there were significant differences in Grade 3/4 cardiotoxicity between the two trastuzumab-containing regimens (Table 4).

Five times lower in the nonanthracycline-containing regimen than the arm receiving both trastuzumab and an anthracycline.

Grade 3/4 cardiac left ventricular function impairment (indicative of congestive heart failure) and LVEF impairment significantly more common in patients treated with AC → TH vs. either TCH or AC → T (all P<0.01).

No significant difference in cardiac impairment was observed between AC → T and TCH arms.

Amplification of topoisomerase II (TOPO II) alpha is predictive for improved response to anthracyclines among breast cancer patients.

Patients with coamplified HER2 and TOPO II alpha demonstrated better DFS than patients with no TOPO II alpha coamplification at both first and second interim analyses.

TOPO II alpha coamplification vs. no coamplification: HR 1.44, 95% CI: 1.16-1.78

| Table 2: Disease-free and overall survival in lymph-node negative patients |
|---------------------------------|---------------------------------|---------------------------------|
| Survival Events                 | AC → T (n=309)                 | AC → TH (n=310)                 | TCH (n=309)                 |
| DFS                             |                                 |                                 |                              |
| Number of events, n             | 35                              | 12                              | 17                           |
| Hazard ratio (95% CI)           | Reference                       | 0.32 (0.17-0.62)                | 0.47 (0.26-0.83)             |
| P value                         | —                               | 0.0007                          | 0.0096                       |
| OS                              |                                 |                                 |                              |
| Number of deaths, n             | 12                              | 2                               | 5                            |
| Hazard ratio (95% CI)           | Reference                       | 0.16 (0.04-0.73)                | 0.42 (0.15-1.2)              |
| P value                         | —                               | 0.018                           | 0.106                        |
### Table 3: Hematologic and nonhematologic toxicities

<table>
<thead>
<tr>
<th>Toxicity, %</th>
<th>AC → T (n=1,050)</th>
<th>AC → TH (n=1,068)</th>
<th>TCH (n=1,056)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-grade nonhematologic toxicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>52.8</td>
<td>55.5</td>
<td>38.6*</td>
</tr>
<tr>
<td>Nail changes</td>
<td>49.2</td>
<td>43.6</td>
<td>28.7*</td>
</tr>
<tr>
<td>Neuropathy, sensory</td>
<td>48.3</td>
<td>49.7</td>
<td>36.1*</td>
</tr>
<tr>
<td>Neuropathy, motor</td>
<td>5.2</td>
<td>6.3</td>
<td>4.2*</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0.0</td>
<td>0.0</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Grade 3/4 nonhematologic toxicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irregular menses</td>
<td>27.1</td>
<td>24.2</td>
<td>26.4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7.0</td>
<td>7.3</td>
<td>7.2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6.1</td>
<td>6.8</td>
<td>3.4*</td>
</tr>
<tr>
<td>Nausea</td>
<td>6.0</td>
<td>5.7</td>
<td>4.8</td>
</tr>
<tr>
<td>Myalgia</td>
<td>5.2</td>
<td>5.2</td>
<td>1.8*</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>3.6</td>
<td>3.1</td>
<td>1.4*</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3.2</td>
<td>3.3</td>
<td>1.4*</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.0</td>
<td>5.7</td>
<td>5.5</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>1.9</td>
<td>1.4</td>
<td>0.0*</td>
</tr>
<tr>
<td>Creatinine elevation</td>
<td>0.6</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Grade 3/4 hematologic toxicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>63.3</td>
<td>71.3</td>
<td>66.2*</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>51.5</td>
<td>60.2</td>
<td>48.2*</td>
</tr>
<tr>
<td>Neutropenic infection</td>
<td>11.3</td>
<td>12.0</td>
<td>11.0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>9.1</td>
<td>11.0</td>
<td>9.8</td>
</tr>
<tr>
<td>Anemia</td>
<td>2.5</td>
<td>3.1*</td>
<td>5.8</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1.0</td>
<td>1.2*</td>
<td>5.4</td>
</tr>
<tr>
<td>Leukemia</td>
<td>0.3 (n=3)</td>
<td>0.1 (n=1)</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*Statistically significant in comparison with AC → TH or TCH.

### Table 4: Cardiotoxicity

<table>
<thead>
<tr>
<th>Cardiovascular Event, n</th>
<th>AC → T (n=1,050)</th>
<th>AC → TH (n=1,068)</th>
<th>TCH (n=1,056)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 3/4 left ventricular dysfunction, n</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First interim analysis</td>
<td>3</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>Second interim analysis</td>
<td>4</td>
<td>20</td>
<td>4*</td>
</tr>
<tr>
<td><strong>&gt;10% LVEF decline, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First interim analysis</td>
<td>9 (n=1,012)</td>
<td>17.3 (n=1,040)</td>
<td>8 (n=1,029)</td>
</tr>
<tr>
<td>Second interim analysis</td>
<td>10 (n=1,014)</td>
<td>18 (n=1,042)</td>
<td>8.6 (n=1,030)</td>
</tr>
</tbody>
</table>

*P=0.0015 vs. AC → TH.
Interestingly, the controversy as to whether anthracyclines should be included when trastuzumab is employed in adjuvant therapy remains a relevant issue. When used without trastuzumab, adjuvant anthracyclines result in low rates of clinically important rates of cardiac toxicity. This risk is substantially augmented with the addition of trastuzumab and is not observed when non anthracycline combinations such as TCH are used. In the first analysis, AC→TH and TCH produced significant improvement in DFS a compared to AC→T. Although AC→TH was slightly superior to TCH, there was a significant difference in cardiac toxicity. In the updated analysis more events have been observed and the differences in outcomes between AC→TH and TCH are no longer significant. The cardiac toxicity data continues to favour TCH. Previously the investigators also reported that AC→TH might be the preferred therapy in patients with coamplification of HER2 and TOPOII. However, in the updated analysis, this no longer holds true. TCH and AC→TH are equivalent regardless of HER2 and TOPOII amplification. This coupled with the lower cardiac toxicity would make TCH the preferred choice in the adjuvant therapy setting.

Key Conclusions

- Updated results show a nonsignificant difference in the number of disease-free survival events and breast cancer deaths in favour of the AC→TH regimen.
- However, one must consider the number of critical adverse events, including CHF, loss of cardiac function, and anthracycline-related leukemia.
- The trial demonstrates that endocrine-responsive tumours can be treated effectively with trastuzumab, which has similar efficacy and milder toxicity than anthracycline.
- In view of this data and that of a recently published trial, which showed significantly superior efficacy in breast cancer for an anthracycline-free regimen of docetaxel plus cyclophosphamide compared with doxorubicin plus cyclophosphamide (Jones SE et al. J Clin Oncol. 2006;24:5381), Dr. Slamon raised the provocative question of whether anthracyclines were necessary for adjuvant therapy.

Background

- Third-generation aromatase inhibitors (AIs) such as anastrozole and letrozole are rapidly becoming the standard for hormonal therapy in postmenopausal women with hormone-receptor–positive (HR+) breast cancer.
- Although response rates are high, many patients ultimately stop responding to first-line nonsteroidal AIs, at which point disease progression occurs.
- Fulvestrant is a selective estrogen receptor downregulator.
- Exemestane is a steroidal AI.

Study Design

- The EFECT trial is a multicentre randomized, double-blind phase 3 trial designed to compare the efficacy of these two agents as second-line therapy in postmenopausal with advanced breast cancer when prior treatment with a nonsteroidal AI has failed.

Study Design

- Inclusion criteria included
  - Estrogen receptor (ER)– and/or progesterone receptor (PgR)–positive tumour
  - Postmenopausal
  - Progression during treatment with nonsteroidal AI for advanced breast cancer or recurrence on nonsteroidal AI used for adjuvant treatment or within six months after completing treatment
  - Measurable bone lesions or disease

- About 60% of the women in the trial had received two or more previous endocrine therapies, and 60% had visceral involvement (Table 1).

- To achieve a rapid steady state in the blood, fulvestrant was administered (I.M. injection) on days 0, 14, and 28, followed by monthly therapy.

- Exemestane was given on a standard dosing schedule.
- All patients received corresponding placebo medication.
- The primary endpoint was time to progression (TTP)
- Secondary endpoints included: objective response rate (ORR), duration of response (DoR), clinical benefit rate (CBR) [RECIST criteria] and tolerability.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exemestane (n=342)</th>
<th>Fulvestrant (n=351)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>≥2 prior therapies, %</td>
<td>53.8</td>
<td>53.8</td>
</tr>
<tr>
<td>Site of distant metastasis, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>66.4</td>
<td>67.2</td>
</tr>
<tr>
<td>Lung</td>
<td>36.3</td>
<td>34.5</td>
</tr>
<tr>
<td>Liver</td>
<td>32.2</td>
<td>31.1</td>
</tr>
<tr>
<td>Visceral involvement, %</td>
<td>56.1</td>
<td>57.9</td>
</tr>
<tr>
<td>Hormone receptor status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER-positive and/or PgR-positive</td>
<td>98.5</td>
<td>99.7</td>
</tr>
<tr>
<td>ER-positive and PgR-positive</td>
<td>67.5</td>
<td>56.4</td>
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<tr>
<td>Race, %</td>
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<tr>
<td>White</td>
<td>91.2</td>
<td>89.0</td>
</tr>
<tr>
<td>Black</td>
<td>3.8</td>
<td>3.1</td>
</tr>
<tr>
<td>Asian</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>Other</td>
<td>3.8</td>
<td>6.6</td>
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</table>
### Table 2: Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Exemestane (n=270)</th>
<th>Fulvestrant (n=270)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to progression, months</td>
<td>3.7</td>
<td>3.7</td>
<td>0.6531</td>
</tr>
<tr>
<td>ORR, %</td>
<td>6.7</td>
<td>7.4</td>
<td>0.7364</td>
</tr>
<tr>
<td>CBR, %</td>
<td>18.5</td>
<td>23.3</td>
<td>0.1687</td>
</tr>
<tr>
<td>Median duration of response, months</td>
<td>9.8</td>
<td>13.5</td>
<td></td>
</tr>
<tr>
<td>Median duration of clinical benefit, months</td>
<td>10.4</td>
<td>11.7</td>
<td></td>
</tr>
</tbody>
</table>

CBR, clinical benefit rate; ORR, overall response rate

* Only includes patients with measurable disease

### Table 3: Safety Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Exemestane (n=342)</th>
<th>Fulvestrant (n=351)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE, %</td>
<td>88.8</td>
<td>88.9</td>
</tr>
<tr>
<td>Drug-related AE or serious AE, %</td>
<td>49.4</td>
<td>47.0</td>
</tr>
<tr>
<td>Withdrawal due to AE, %</td>
<td>2.6</td>
<td>2.9</td>
</tr>
<tr>
<td>≥Grade 3 AE, %</td>
<td>22.6</td>
<td>21.7</td>
</tr>
<tr>
<td>Serious AE, %</td>
<td>12.4</td>
<td>11.4</td>
</tr>
<tr>
<td>Any AE-related death (none drug-related), %</td>
<td>0.9</td>
<td>0.9</td>
</tr>
</tbody>
</table>

### Canadian Perspective by Dr. Verma

This was a well-conducted trial presented for the first time here at San Antonio and it basically demonstrated that in women with metastatic breast cancer who progress on an AI, the options are exemestane or fulvestrant. While it was disappointing that no clear ‘winner’ was identified in this study, the overall low response rate observed in the third-line setting was particularly dismaying. I think we have to seriously question whether third-line hormonal therapy after tamoxifen and one AI is actually the best approach to consider or whether some women would be best off treated with chemotherapy. However strictly from the perspective of this trial, it is fair to offer women who have progressed after an AI exemestane or fulvestrant. In my view, taking a tablet is still preferable to getting an intramuscular injection once a month. A lot of arguments have been made regarding compliance in women who take pills but generally this is not a huge problem in women with metastatic breast cancer as adherence rates remain fairly high.

### Key Findings

- No difference in TTP was observed between treatment arms.
- There was also no difference in ORR or CBR (defined as objective response + stable disease for at least 24 weeks).
- Both treatments were well tolerated.
- Adverse events (AEs) were also similar between the two study arms.
- Most common AEs for both agents included joint disorders, nausea/vomiting, and injection-site reactions.

### Key Conclusions

- This is the first phase 3 clinical trial in this patient population, and it confirms the comparable efficacy and safety of fulvestrant and exemestane when used in patients who have shown disease progression on nonsteroidal AIs.
- Fulvestrant loading-dose offers a potentially effective and well-tolerated treatment option for postmenopausal women with ABC who have progressed/recurred on non-steroidal AI therapy.

Reference: Gradishar W et al. Fulvestrant versus exemestane following prior non-steroidal aromatase inhibitor therapy: first results from EFECT, a randomized, phase III trial in postmenopausal women with advanced breast cancer. Proceedings from the 29th Annual San Antonio Breast Cancer Symposium; December 14-17, 2006; San Antonio, Texas; Abstract 12.
Treatment of Metastatic Breast Cancer: New Drugs

Albumin-Bound Paclitaxel Is More Effective and Less Toxic than Docetaxel

Background

- Solvents such as Tween 80 and Cremophor, which are used as vehicle formulations for highly hydrophobic drugs, have serious side effects that can often limit drug efficacy, including prolonged and sometimes irreversible neuropathy, myelosuppression, hypersensitivity reactions, and excessive fluid retention.\(^1,2\)
- Drug entrapment in micelles also limits bioavailability and impairs dose-dependent activity.\(^3\)
- A novel class of compounds combining human albumin in the nanoparticle state with water-insoluble cancer drugs has been developed (Nanoparticle albumin-bound [nab]-paclitaxel)\(^4\) (Figure 1).
- Two trials, CA012 (ABRAXANE\(^\text{TM}\), nab-paclitaxel) and TAX311 (Taxotere\(^\text{®}\), docetaxel), had a common control arm (solvent-based paclitaxel 175 mg/m\(^2\) given every three weeks [Q3W]).\(^1,5\)
- A cross-trial analysis suggested comparable antitumour activity of nab-paclitaxel and docetaxel, but showed that nab-paclitaxel was better tolerated.\(^6\)
- The current study\(^7\) presents the third interim analysis of randomized, phase 2 trial designed to compare toxicity and preliminary efficacy data for
  - solvent-free nab-paclitaxel vs. solvent-based docetaxel
  - nab-paclitaxel every week vs. every three weeks and
  - nab-paclitaxel weekly in high doses vs. low doses (Figure 2).

Study Design

- Patients had no prior chemotherapy for metastatic disease, Stage IV adenocarcinoma of the breast, and adequate organ function (Table 1).
- Patients were enrolled from November 2005 to June 2006.

Figure 1: Nanoparticle Albumin Bound (nab) Platform
### Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nab-paclitaxel 300 mg/m² Q3W (n=76)</th>
<th>Nab-paclitaxel 100 mg/m² QW (n=76)</th>
<th>Nab-paclitaxel 150 mg/m² QW (n=74)</th>
<th>Docetaxel 100 mg/m² Q3W (n=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sites of metastases, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>13</td>
<td>13</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>20</td>
<td>24</td>
<td>18</td>
<td>26</td>
</tr>
<tr>
<td>Lung/thoracic</td>
<td>70</td>
<td>64</td>
<td>67</td>
<td>78</td>
</tr>
<tr>
<td>Hepatic/liver</td>
<td>28</td>
<td>36</td>
<td>30</td>
<td>34</td>
</tr>
<tr>
<td>Bone</td>
<td>29</td>
<td>33</td>
<td>44</td>
<td>34</td>
</tr>
<tr>
<td>Prior adjuvant/neoadjuvant chemotherapy, %</td>
<td>43</td>
<td>38</td>
<td>38</td>
<td>46</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>26</td>
<td>20</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td>43</td>
<td>38</td>
<td>36</td>
<td>46</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>43</td>
<td>36</td>
<td>36</td>
<td>42</td>
</tr>
<tr>
<td>Vinca alkaloids</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Q3W, every 3 weeks; QW, weekly

### Table 2: Incidence of neutropenia

<table>
<thead>
<tr>
<th>Neutropenia</th>
<th>Nab-paclitaxel 300 mg/m² Q3W (n=76)</th>
<th>Nab-paclitaxel 100 mg/m² QW (n=76)</th>
<th>Nab-paclitaxel 150 mg/m² QW (n=74)</th>
<th>Docetaxel 100 mg/m² Q3W (n=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>20</td>
<td>28</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>30</td>
<td>35</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>16</td>
<td>28</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>3</td>
<td>7</td>
<td>74</td>
</tr>
<tr>
<td>P value vs. docetaxel</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>-</td>
</tr>
<tr>
<td>P value vs. nab-paclitaxel, 100 mg/m² QW</td>
<td>0.002</td>
<td>-</td>
<td>0.003</td>
<td>-</td>
</tr>
</tbody>
</table>

### Table 3: Incidence of fatigue among treatment arms

<table>
<thead>
<tr>
<th>Fatigue</th>
<th>Nab-paclitaxel 300 mg/m² Q3W (n=76)</th>
<th>Nab-paclitaxel 100 mg/m² QW (n=76)</th>
<th>Nab-paclitaxel 150 mg/m² QW (n=74)</th>
<th>Docetaxel 100 mg/m² Q3W (n=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>12</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>9</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>P value vs. docetaxel</td>
<td>0.13</td>
<td>&lt;0.001</td>
<td>0.08</td>
<td>-</td>
</tr>
<tr>
<td>P value vs. nab-paclitaxel, 100 mg/m² QW</td>
<td>0.01</td>
<td>-</td>
<td>0.02</td>
<td>-</td>
</tr>
</tbody>
</table>
• Mean age was 53.6 yrs, and 73% of the women in the study were postmenopausal.
• The third interim analysis was conducted in November, 2006.
• Primary study outcomes were antitumour response (evaluated every eight weeks by RECIST criteria) and toxicity.
• Secondary outcome measure was progression-free survival (PFS).

Key Findings
• Weekly nab-paclitaxel (100 and 150 mg/m^2) increased tumour response rate by greater than 60%, compared to the response rate of docetaxel given every three weeks (Figure 3).
• Both doses of nab-paclitaxel weekly were superior to nab-paclitaxel given every three weeks.
• Response rates for nab-paclitaxel (300 mg/m^2) and docetaxel (100 mg/m^2) dosed every three weeks were similar.
• Although the data are not yet mature, preliminary analysis of PFS (33% of potential events) showed that all nab-paclitaxel doses were superior to docetaxel (Figure 4).
• The most common adverse events (occurring in >5% of patients) were neutropenia, peripheral neuropathy, fatigue, stomatitis/mucositis, and arthralgias.
• Myelosupression was significantly higher in the docetaxel arm (Table 2).

• No differences were observed in peripheral neuropathy between the nab-paclitaxel arms and docetaxel
  ○ the 100 mg/m^2 arm was associated with the least peripheral neuropathy
• Fatigue was significantly lower in the low-dose weekly nab-paclitaxel arm compared with the docetaxel arm (P< 0.001).
• No Grade 3 fatigue was reported for the weekly 100 mg/m^2 arm of nab-paclitaxel.
• Grade 1/2 stomatitis/mucositis was significantly more common in the docetaxel arm compared to the nab-paclitaxel arms (P<0.001 for all comparisons).
  ○ No significant differences were observed between nab-paclitaxel arms.
• Grade 1/2 arthralgias were significantly more common in every-three-weeks (P=0.01) and high-dose weekly nab-paclitaxel (150 mg/m^2) arms (P=0.03) compared to docetaxel.
  ○ Among nab-paclitaxel arms, arthralgias were significantly more common in the every-three-weeks arm (P=0.002) and high-dose weekly arm (P=0.003) compared to the low-dose weekly arm.
• The low-dose weekly arm appeared to be the most tolerable of the three nab-paclitaxel arms.

Figure 2: Study design

<table>
<thead>
<tr>
<th>300 1st line MBC patients randomized to 4 arms:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comparisons</strong></td>
</tr>
<tr>
<td>nab-paclitaxel vs. docetaxel (A, B, C, vs. D)</td>
</tr>
<tr>
<td>weekly vs. every-3-weeks nab-paclitaxel (B, C vs. A)</td>
</tr>
<tr>
<td>low vs. high dose weekly nab-paclitaxel (B vs. C)</td>
</tr>
<tr>
<td><strong>RANDOMIZE</strong></td>
</tr>
<tr>
<td><strong>Arm A</strong>: nab-paclitaxel 300 mg/m^2 Q3W</td>
</tr>
<tr>
<td><strong>Arm B</strong>: nab-paclitaxel 100 mg/m^2 weekly 3 out of 4</td>
</tr>
<tr>
<td><strong>Arm C</strong>: nab-paclitaxel 150 mg/m^2 weekly 3 out of 4</td>
</tr>
<tr>
<td><strong>Arm D</strong>: docetaxel 100 mg/m^2 Q3W</td>
</tr>
</tbody>
</table>
Figure 3: Objective confirmed response rate

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Response Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg/m² Q3W</td>
<td>33%</td>
</tr>
<tr>
<td>100 mg/m² QW 3/4 weeks</td>
<td>58%</td>
</tr>
<tr>
<td>150 mg/m² QW 3/4 weeks</td>
<td>62%</td>
</tr>
<tr>
<td>Docetaxel 100 mg/m² Q3W</td>
<td>36%</td>
</tr>
</tbody>
</table>

P<0.001, B vs. A  
P<0.001, C vs. A  
P=0.004, B vs. D  
P=0.016, C vs. D

Figure 4: Progression-free Survival

P=0.018, nab-Paclitaxel 300 mg/m² Q3W vs. docetaxel  
P=0.041, nab-Paclitaxel 100 mg/m² QW vs. docetaxel  
P<0.001, nab-Paclitaxel 150 mg/m² QW vs. docetaxel
Canadian Perspective by Dr. Verma

There is a wealth of data emerging on nab-paclitaxel. From the perspective of treating women with taxanes, acute hypersensitivity reactions remain problematic, regardless of the type of taxane being given. In a comparison with paclitaxel, nab-paclitaxel had a favourable toxicity profile. This particular study compares weekly or three-weekly nab-paclitaxel to standard three-weekly docetaxel, and the results presented here showed that Q3W nab-paclitaxel has a comparable response rate and, more impressively, very low rate of hypersensitivity reactions compared to Q3W docetaxel. The weekly program was clearly more interesting because of the higher response rate observed at both the 100 and 150 mg/m² doses of nab-paclitaxel, compared to the three-weekly program of either drug. There was significantly less febrile neutropenia compared to docetaxel, also an important observation.

No survival data were presented; however, the point of this trial was to show that nab-paclitaxel is as good as docetaxel and is associated with fewer serious toxicities. I think this is a drug that really does need to enter the clinic soon. It also has a shorter infusion time than docetaxel, so we may gain some time in the chemotherapy suites.

Key Conclusions

- Response rates of nanoparticle albumin-bound (nab)-paclitaxel every three weeks and docetaxel were comparable.
- Weekly dosing of nab-paclitaxel demonstrated almost double the response rate of nab-paclitaxel or docetaxel given every three weeks.
- Response rates were comparable between low-dose and high-dose nab-paclitaxel administered weekly.
- Preliminary data suggests superior progression-free survival with all doses and schedules of nab-paclitaxel versus Q3W docetaxel.
- Adverse events such as neutropenia, febrile neutropenia, and mucositis were less common with nab-paclitaxel than docetaxel.
- Toxicity data and response data for the low-dose (100 mg/m²) weekly nab-paclitaxel arm suggests that this may be the optimal regimen for further analysis in future clinical trials.

Combination Bevacizumab and Albumin-Bound Paclitaxel Is Active in Metastatic Breast Cancer

**Background**

- In the pivotal E2100 trial, Miller and colleagues demonstrated that adding bevacizumab to paclitaxel for the first-line treatment of metastatic breast cancer led to significant improvements in both response rate (RR) and progression-free survival (PFS).
- Less clear is the role of bevacizumab in combination therapy with other chemotherapy regimens and for patients who have already progressed on first-line treatment.
- The current pilot study combined nanoparticle albumin-bound (nab)-paclitaxel with bevacizumab to treat women with heavily pretreated metastatic breast cancer.²

**Study Design**

- The study enrolled 27 women with metastatic breast cancer who had had ≥3 prior chemotherapy regimens, including anthracyclines (n=26) and taxanes (n=24).
- Dosing regimen:
  - nab-paclitaxel
    - 80 to 125 mg/m²/day on days 1, 8, and 15
    - 170 to 200 mg/m²/every 14 days
  - 28-day cycle
  - bevacizumab 10 mg/kg every 14 days
- Patients received at least two courses of treatment
- Primary endpoint was clinical response
- Secondary endpoint was toxicity
- Patients were monitored using physical exam, tumour markers, and PET/CT fusion scanning.
- Length of follow-up was not specified.

**Key Findings**

- There was a documented and objective response rate of 59% (13 patients), consisting of both complete (CR: 11%) and partial responses (PR: 48%).
- Seven patients (26%) had stable disease (SD) and four (15%) progressed.
- The regimen appeared to be well tolerated.
  - One patient withdrew due to possible hemorrhage into a metastatic brain lesion.
  - Two patients had elevated liver transaminases.
  - Two patients had an increase in blood pressure that required antihypertensive medication.
  - One patient had a Grade 3 rash with desquamation

**Figure 1: Response rates for bevacizumab plus nab-paclitaxel**

![Response rates graph]

**Key Conclusions**

- Patients with metastatic breast cancer, whose disease has been treated with multiple chemotherapy agents, may have good responses to a combination of bevacizumab and nab-paclitaxel.
- The regimen is well tolerated and active in heavily pre-treated women with metastatic breast cancer.
- Therapy was discontinued in one patient due to possible hemorrhage into a metastatic brain lesion.


**Canadian Perspective by Dr. Verma**

The posters that were presented on nab-paclitaxel continue to cement its activity in metastatic breast cancer. It is active when it is given in combination with bevacizumab or capecitabine. So far, the data suggest that this drug is not inferior to the other taxanes. It has the same activity profile that we would expect of other taxanes and a comparable level of synergy with other agents. Should these combinations be applied in the clinic yet? No, because these are still phase-2 trials and we should await the results of larger randomized trials.
Weekly Nab-Paclitaxel and Capecitabine Shows Efficacy in First-Line Treatment of Metastatic Breast Cancer

**Background**
- Both nanoparticle albumin-bound paclitaxel and capecitabine have substantial single-agent activity in metastatic breast cancer.
- Taxane and anti-metabolite doublets improve response rate and time to progression (TTP) compared to singlet therapy.
- Nab-paclitaxel, given weekly, has an excellent safety and efficacy profile with maintenance of dose intensity.
- This small phase 2 study was designed to test the safety and efficacy of nab-paclitaxel plus capecitabine in a novel combination schedule, when administered to patients with metastatic breast cancer as first-line treatment.

**Study Design**
- In this open-label, multicentre study, all 50 patients enrolled thus far have received 125 mg/m² intravenous nab-paclitaxel on Days 1 and 8, in addition to 825 mg/m² of oral capecitabine twice daily on Days 1 through 14, every three weeks.
- Eligibility criteria included no prior chemotherapy or capecitabine for metastatic disease and no adjuvant fluoropyrimidine or paclitaxel therapy within six months prior to baseline.
- None of the patients had HER2-positive disease.
- Median age was 59 years (range 23.7 – 83.8).
- Half of the patients had received prior chemotherapy for non-metastatic disease.
- Prior radiotherapy had been given to 39.5%.
- The primary objective was objective response rate.
  - Responses evaluated after every two cycles.

**Key Findings**
- First interim results were reported after 213 cycles; 38 patients available for analysis.
- Four patients were not evaluable.
- 36.8% had received 1–4 cycles, 49.9% 5–9 cycles, and 13.1% received 10–14 cycles.
- Dose reductions were required for both agents:
  - Nanoparticle albumin-bound paclitaxel: n=3 (to 100 mg/m²)
  - Capecitabine: n=5 (3 to 650 mg/m², 2 to 550 mg/m²)
- Preliminary data suggest that progression-free survival is prolonged by the regimen.
  - Time to progression for the 25th quartile was 133 days.
- Overall, the treatment regimen was generally well tolerated.
  - Of the patients, 26.3% (n=10) had a grade 3 adverse event and 7.9% (n=3) had a grade 4 adverse event (Table 1).

**Table 1: CTC Grade 3/4 adverse events**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 3, n</th>
<th>Grade 4, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hand foot syndrome</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Breast pain</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

**Key Conclusions**
- Nanoparticle albumin-bound (nab)-paclitaxel in combination with capecitabine may be an effective first-line treatment option for patients with metastatic breast cancer.
- More than 50% of patients achieved at least a partial response, and there was a trend for prolonged progression-free survival.
- Longer follow-up is necessary to confirm the effectiveness of this treatment regimen.
- A future phase 3 clinical trial further evaluating this combination in these patients is warranted.
- The regimen was well tolerated with a relatively low incidence of Grade 3/4 toxicities.

Treating Patients with Bone Metastases

Denosumab Shows Decreased Bone Turnover in Patients with Metastatic Breast Cancer and Bone Metastases

Background

- Solvents such as Tween 80 and Cremophor, which are used as vehicle formulations for highly hydrophobic drugs, have serious side effects that can often limit drug efficacy, including prolonged and sometimes irreversible neuropathy, myelosuppression, hypersensitivity reactions, and excessive fluid retention.1,2
- Drug entrapment in micelles also limits bioavailability and impairs dose-dependent activity.3
- A novel class of compounds combining human albumin in the nanoparticle state with water-insoluble cancer drugs has been developed (Nanoparticle albumin-bound (nab)-paclitaxel or ABRAXANETM).4
- Two trials, CA012 (nab-paclitaxel) and TAX311 (docetaxel), had a common control arm (solvent-based paclitaxel 175 mg/m² given every three weeks [Q3W]).1,5
- A cross-trial analysis suggested comparable antitumour activity of nab-paclitaxel and docetaxel, but showed that nab-paclitaxel was better tolerated.6
- The current study7 presents the third interim analysis of randomized, phase 2 trial designed to compare toxicity and preliminary efficacy data for:
  - solvent-free nab-paclitaxel vs. solvent-based docetaxel
  - nab-paclitaxel every week vs. every three weeks
  - nab-paclitaxel weekly in high doses vs. low doses

Study Design

- Randomized phase 2 study, multi-site, prospective, current standard therapy as control
- Eligibility criteria were:
  - Aged ≥18 yrs
  - Histologically confirmed breast cancer
  - Radiographically confirmed BM
  - ECOG score of 0–2
  - No prior IV BP
- All patients were instructed to take 500 mg calcium and 400 IU of vitamin D daily.
- 255 patients who were receiving concurrent chemotherapy or hormonal therapy were randomly assigned to receive one of five double-blind denosumab-treated groups (30 mg, 120 mg, or 180 mg monthly; 60 mg or 180 mg every three months) or an open-label bisphosphonate arm. Patients were also stratified by chemotherapy or hormonal therapy.

Figure 1: Proposed mechanism of denosumab action

The investigators used urinary N-telopeptide (uNTx) as a surrogate marker for bone health, and compared changes from baseline in the denosumab and bisphosphonate arms. The primary endpoint was the percentage change from baseline to week 25 in the level of uNTx. Secondary endpoints evaluated were the percentage of patients with greater than or equal to a 65% decrease in uNTx from baseline, time to a 65% reduction in uNTx, incidence of SREs, and safety.

**Key Findings**
- All doses of denosumab led to rapid suppression of uNTx.
- The percentage of pooled denosumab patients with ≥1 on-study SRE was 12% (26/212) vs. 16% (7/43) of BP patients.
- The most frequent adverse events reported for denosumab-treated patients were nausea (22%), vomiting (18%), asthenia (18%), diarrhea (16%), fatigue (15%), and back pain (15%).
- No binding or neutralizing antibodies were detected.
- The most frequent adverse events reported for the IV bisphosphonate-treated patients were pyrexia (21%), arthralgia (28%), asthenia (28%), vomiting (21%), headache (21%), and nausea (23%).
- Grade 3 or 4 adverse events (AEs) were similar:
  - 16/43 (37%) for the IV BP arm
  - 79/211 (37%) for all denosumab arms
- Infection rate was also similar between arms:
  - 15/43 (35%) for the IV BP arm
  - 59/211 (28%) for all denosumab arms
- No serious or fatal AEs related to either denosumab or IV BP were reported.

**Key Conclusions**
- Denosumab is as effective as bisphosphonates in preventing skeletal-related events in patients with bone metastases.
- Denosumab caused rapid and sustained reduction of bone-turnover markers.
- The incidence of adverse events was similar for all denosumab cohorts and bisphosphonates.
- The data support further investigation at the phase 3 level.

**References:**
Clinical Benefit with Zoledronic Acid in Patients with Breast Cancer and Bone Metastases Is Durable

Background
- Approximately 65–75% of patients with advanced breast cancer develop bone metastases (BMs).  
- Skeletal complications resulting from BMs can be associated with debilitating bone pain and can negatively affect quality of life in women with advanced breast cancer.  
- Zoledronic acid has demonstrated durable reductions in skeletal morbidity and pain in patients with breast cancer and bone metastases.  
  - In a phase 3 randomized, controlled trial, zoledronic acid significantly reduced the overall risk of developing a skeletal-related event (SRE) at 25 months compared with pamidronate in patients with multiple myeloma or bone metastases from breast cancer.  
  - Moreover, the short infusion time (15 minutes) of zoledronic acid compared with pamidronate makes it a more convenient therapy.  
- This retrospective exploratory analysis of this trial examines the continuing benefit of zoledronic acid treatment in the subset of patients with breast cancer during months 13 to 25.

Study Design
- A total of 766 patients with breast cancer and bone metastases were treated with zoledronic acid 4 mg or pamidronate 90 mg.
  - 454 patients completed the 13-month core phase
  - 279 patients elected to enter the 12-month extension phase
- Treatment groups were well balanced.

Key Findings
- During the 13 to 25 month extension phase
  - The proportion of SREs was lower in the overall cohort of patients treated with zoledronic acid 4 mg than those treated with pamidronate 90 mg (20% vs. 29%; P=0.072).
  - The time to first SRE was significantly longer in the zoledronic acid group compared to the pamidronate group (median, 397 days vs. 224 days; P=0.067).
  - Zoledronic acid reduced the mean annual incidence of SREs by 17% relative to pamidronate (0.40 vs. 0.48, respectively; P=0.058).
  - Patients treated with zoledronic acid had a significant 41% reduction in risk of SRE compared with pamidronate (risk ratio=0.591; P=0.026), as assessed by multiple event analysis.
  - Zoledronic acid significantly reduced the overall risk of developing all SREs by an additional 29% over that achieved with pamidronate (HR=0.0711, P=0.015), in the hormonal therapy stratum.
  - In the stratum of patients treated with chemotherapy, zoledronic acid was at least as effective as pamidronate.

### Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Zoledronic acid (n=377)</th>
<th>Pamidronate (n=389)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs</td>
<td>58</td>
<td>57</td>
</tr>
<tr>
<td>Primary therapy, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>176 (47)</td>
<td>179 (46)</td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>201 (53)</td>
<td>210 (54)</td>
</tr>
<tr>
<td>Previous SRE, n (%)</td>
<td>232 (62)</td>
<td>244 (63)</td>
</tr>
<tr>
<td>Mean time to diagnosis of BM, months ± SD</td>
<td>17.5 ± 33.85</td>
<td>12.6 ± 21.68</td>
</tr>
</tbody>
</table>
Key Conclusions

- The data shows a continuing benefit of zoledronic acid in patients with breast cancer and bone metastases during long-term therapy.
- Zoledronic acid significantly reduced the risk of developing an SRE by an additional 41% compared with pamidronate (P=0.026).
- Zoledronic acid had the greatest clinical benefit in patients receiving hormonal therapy:
  - Reduced the percentage of patients developing a second SRE compared with pamidronate
  - Significantly delayed the time to second SRE compared with pamidronate (P=0.035)
  - Significantly reduced the mean annual incidence of SREs by 45% compared with pamidronate (P=0.049)
  - Significantly reduced the risk of developing subsequent SREs by an additional 31% (P=0.045)
- These analyses support the rationale for continuing long-term zoledronic acid therapy in patients with breast cancer throughout the course of their disease.


Canadian Perspective by Dr. Verma

Although the bisphosphonates (BP) have revolutionized the management of metastatic breast cancer, there remains much to be achieved in this area. Standard use of oral BP (clodrinate) or IV BP (pamidronate) has led to a significant reduction in skeletal events. However, such effects are not durable in the majority of patients, and newer strategies are required for patients whose disease ‘breaks through,’ whether it is clinically with increased pain or skeletal events, or biochemically with rising markers of bone metabolism, while being treated with standard BP. Both denosumab and zoledronic acid appear to have advantages in this area — the former due to a powerful and unique inhibitory effect on RANK ligand and the latter due to a more potent effect on bone metabolism compared to pamidronate.

The results of these trials confirm the superior activity of these agents, particularly the more durable effects of zoledronic acid when compared to pamidronate. This should eventually lead to the adoption of zoledronic acid as an appropriate standard of care.

New Evidence in Oncology | January 2007 65
Recent advances in the development of novel cancer drug therapeutics have resulted in a gap between the approval of certain cancer drugs by Health Canada and provision of funding for these drugs by provincial drug formularies. Provincial governments base funding decisions on various factors, such as evidence to support the efficacy of the drug and cost effectiveness. The absence of a national drug formulary has thus resulted in unequal funding for newer cancer drugs, such as rituximab and bevacizumab. These drugs have been demonstrated to improve patient outcomes and have been approved by Health Canada. Province-wide funding for these drugs, however, is unevenly distributed across the country.

For example, rituximab has been approved for the treatment of adult patients with relapsed or refractory CD20-positive low-grade or follicular B-cell non-Hodgkin’s lymphoma. Provinces that have approved funding for rituximab are British Columbia and Quebec. Rituximab is also covered by the Public Services Health Care Plan. In all other provinces, the drug is still under review.1

Bevacizumab has been shown to increase the life expectancy of patients with advanced colorectal
cancer by an average of 30% when combined with chemotherapy. Bevacizumab also plays a role in slowing cancer progression. Bevacizumab is covered according to eligibility criteria through the BC Cancer Agency, Newfoundland, and Labrador hospitals. Bevacizumab may be available through some Quebec hospitals according to eligibility guidelines set by the hospital and by the Public Services Health Care Plan.

Due to inherent delays and lengthy and complex bureaucratic processes, newer drugs such as nanoparticle albumin-bound (nab) paclitaxel that have been approved by Health Canada and clinical practice guidelines for breast cancer treatment could take anywhere from six to 24 months to gain government funding approval. A similar situation exists for drugs such as zoledronic acid. In Ontario Zoledronic acid is currently funded for treating prostate cancer metastases, but not for other types of metastases, to bone.

Within Ontario some hospitals, such as the Juravinski Cancer Centre in Hamilton and the Grand River Regional Hospital in Kitchener, have taken a leadership role in addressing these issues. Sandra Kagoma, Director of Pharmacy at Grand River Hospital, says that the hospital is working on a policy to allow patients to purchase unfunded chemotherapeutic drugs and have them infused in the hospital. The policy is awaiting approval from the Pharmacy and Therapeutics committee and the hospital board, but in the interim, the hospital has allowed two cancer patients to undergo infusion therapy.

“Cancer patients are vulnerable and cannot wait for two years to get treatment” says Dr. Sandees Sehdev, a practising medical oncologist. “Funding is a real barrier to drug accessibility and this is a real dilemma for doctors. It puts us in a bind because the drug maybe approved by Health Canada and recommended in clinical practice guidelines, but not funded by the provincial governments. Legally, morally, and ethically, we have to tell patients what the evidence is for a drug, if it is a benefit, and whether it’s funded or not,” Dr. Sehdev said. “We hate turning people away and not giving therapy. We care about them.”

Dr. Sehdev initially started a makeshift infusion clinic in his private office by providing infusion therapy for his patients that required rituximab. The process wasn’t easy, as he had to book a nurse to perform the infusion and also had to get a pharmacist experienced in reconstituting the drug to prepare the drug for infusion. “My office is a place for annual check-ups and patient consultation. It is not really an infusion clinic,” says Dr. Sehdev. He and his colleagues have now collaborated with Bayshore Infusion Clinics Inc. to provide infusion services for his patients. Ninety percent of patients being treated in the clinic at the moment are patients of Dr. Sehdev’s group. Bayshore is responsible for contacting the patient to schedule their infusions, providing specially trained and experienced nursing staff to administer the infusion, arranging for delivery of the medication from the pharmacy, and providing patient education. “It is a collaborative effort involving oncologists, nurses, and pharmacists,” states Dr. Sehdev. Dr. Sehdev and his colleagues also supervise infusions for other cancer patients, but the patients’ oncologists have the final say in their treatment. “We do not become involved in their treatment planning but we want to be here for emergencies.”

Bayshore is responsible for contacting the patient to schedule their infusions, providing specially trained and experienced nursing staff to administer the infusion, arranging for delivery of the medication from the pharmacy, and providing patient education.

Bayshore has been a provider of home and community health services since 1966. Bayshore’s skilled nurses have been providing IV infusion for infliximab, a drug used in the treatment of rheumatoid arthritis and inflammatory bowel disease, as well as many other infusibles for a number of years.

Due to the clinic’s expertise in infusion services, Bayshore has been contracted by McKesson Canada to provide infusion services for Roche oncology, hematology, and rheumatology drugs through the Roche Patient Assistance Program at community infusion clinics across Canada. “This program is not a permanent solution. It is only a stopgap measure until the public system can sort itself out and patients and doctors are able to get access to the drugs they need,” says Samantha Ouimet, Director of Corporate Affairs at Roche Canada.
Currently, 18 Bayshore infusion clinics are being established across Canada. Most Bayshore clinics are being set up with onsite physicians in collaboration with oncologists, rheumatologists, allergists, family and emergency physicians. This allows for optimum patient safety and comfort. Patient care is still provided by the referring physician. “Bayshore is proud of the professional level of training and expertise of our registered nursing staff who provide the highest level of quality care and compassion for all our patients. All of Bayshore’s nursing staff working at the infusion clinics under the Roche Patient Assistance Program have been trained and certified in Advanced Cardiac Life Support (ACLS),” explains Janet Daglish, Project Manager at Bayshore.

The Roche Patient Assistance Program has been designed as a single point of contact for patients (and their doctors) seeking reimbursement assistance options, possible financial assistance, and coordination of infusion services. Patients can access this program through their prescribing physician and are not charged for the infusion services. McKesson Canada pays for the cost of the infusion clinics and investigates reimbursement options and financial assistance options on behalf of patients who are enrolled in the Roche Patient Assistance Program.

Dr. Sehdev says of his patients’ response to the infusion clinic, “Our patients are very appreciative. They have been very politically active in addressing this issue and are quite relieved that they now have access to the drugs they need.” Dr. Sehdev is also committed to providing his patients access to oncology drugs manufactured by other companies and accessibility will not be limited to those manufactured by Roche alone.

There is a growing demand for patients to receive drugs such as rituximab and bevacizumab, both of which have been demonstrated to improve patient outcomes. Carolyn Khan, pharmacist and owner of Queens Lynch Pharmacy, is affiliated with Dr. Sehdev’s oncology practice. Ms. Khan says, “It would be ideal to have the drugs infused in hospitals, but because of funding issues, politics, red tape and boards, it is too difficult to do so at the moment. When somebody is diagnosed with cancer and they have all this information thrown at them, it would be nice to be able to go to the next room and get the drug.” She cautions that policies and procedures have to be followed while preparing chemotherapeutic drugs for infusion and the utmost care taken. “The drugs are toxic and we have to train our staff and protect them. It is an opportunity for pharmacists to demonstrate our skills and contribute to the well being of the patient. If the drug is not properly reconstituted, the patient is not going to benefit from receiving the drug.”

Ms. Khan feels it is unfortunate that the healthcare system is becoming a two-tier system. “However, the Roche Patient Assistance Program is able to provide funding for some of these drugs depending upon certain criteria, such as type of cancer and stage of disease, for patients who cannot afford to pay for the infusions. We are lucky that Bayshore is providing these services. It is a good thing that we are all able to work with oncologists in a way that benefits patients.”

Looking Back

Yesterday’s Findings Point the Way to the Future

INSTEAD THIS ISSUE

QUICK SKETCH

Bayshore Infusion Clinic provides essential service

ASH: New clinical data for myelodysplastic syndrome, non-Hodgkin’s lymphoma, and anemia

SABCS: Latest in breast cancer prevention and treatment, including adjuvant therapy for HER2-positive patients and new treatments for metastatic breast cancer

Nanotechnology in Cancer Imaging, Diagnostics, and Therapeutics