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A Canadian perspective by:

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A CANADIAN PERSPECTIVE

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Overview

From December 8 to 11, 2005, San Antonio hosted the 28th annual San Antonio Breast Cancer Symposium (SABCS). Every year, SABCS provides state-of-the-art information on the experimental biology, etiology, prevention, diagnosis, and therapy of breast cancer and premalignant breast disease to an international audience of physicians, researchers, and other healthcare professionals.

SABCS is a division of the Cancer Therapy & Research Center (CTRC). CTRC is an independent, non-profit institution directed by a volunteer Board of Governors committed to providing the highest quality cancer treatment, research, and education.

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A Canadian perspective provided by Shailendra Verma, MD, FRCP

Dr. Shailendra Verma has been a medical oncologist with Cancer Care Ontario at the Ottawa Regional Cancer Centre (ORCC) since 1985 and is an assistant professor in the department of medicine at the 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. Dr. Verma is a grant application reviewer for the Ontario, Alberta/NWT, and BC/Yukon Chapters of the Canadian Breast Cancer Foundation, and for the National Cancer Institute of Canada. He frequently presents papers on drug therapies for breast cancer and on breast cancer management, and speaks on breast cancer advocacy issues.

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Anemia and Fatigue: Commonly Neglected Complications of Chemotherapy

Anemia and fatigue remain common complications in breast cancer patients receiving adjuvant chemotherapy and are often neglected despite the availability of supportive care interventions, such as transfusion and erythropoiesis-stimulating agents (ESAs). Several studies presented at this year's SABC symposium focused on the causes and frequency of fatigue as well as the continuing need for diligent assessment and intervention of anemia.

Chemotherapy-related anemia, defined as a hemoglobin (Hb) level <120 g/L, adversely affects quality of life. Fatigue is the most commonly reported clinical manifestation of anemia in patients with cancer and many patients undergoing adjuvant chemotherapy rank fatigue ahead of pain as the primary distress affecting their quality of life.[1,2] The results of a recent Belgian study suggest that other metabolic factors in addition to anemia contribute to chemotherapy-induced fatigue in early-stage breast cancer patients.[3]

Twenty-seven early-stage breast cancer patients were treated with adjuvant CEF (cyclophosphamide, epirubicin, and fluorouracil) chemotherapy for six cycles and locoregional radiotherapy following surgery. With this study, Meulemans and colleagues were the first to demonstrate a clinically significant decline in the Functional Assessment of Cancer Therapy fatigue subscale (FACT-F) in early-stage breast cancer patients receiving adjuvant anthracycline-based chemotherapy. They concluded that chemotherapy not only induces anemia (decreased Hb levels [P=0.004]), but also decreases Hb oxygen saturation (P=0.031), and free carnitine (P=0.007) levels, and increases brachial arterial flow (P=0.017).

In the Canadian study[4] presented by Awad et al., investigators reported on the role of fatigue in mediating what patients call "chemo fog" — signs of cognitive decline during or shortly after chemotherapy treatment, experienced by up to 75% of breast cancer patients.[5,6] Changes in fatigue correlated significantly with changes in Hb level from pre- to post-treatment in a subset of 34 of the chemotherapy-treated patients (R=–0.37; P=0.03). Findings suggest that fatigue is a significant contributor to chemo fog and that fatigue in some patients may be related to declining Hb, which further suggests that maintenance of optimum Hb levels may help prevent chemo fog in early-stage breast cancer patients.

Two further studies presented at SABCS 2005 point to the necessity of proactive assessment and intervention of chemotherapy-induced anemia. In one study, researchers at the British Columbia Cancer Agency attempted to define the frequency and severity of anemia associated with adjuvant chemotherapy, and whether corrective interventions were undertaken to correct anemia.[7] They studied 702 breast cancer patients receiving adjuvant chemotherapy treatment and noted the dates of the first Hb levels in the ranges of 110–119, 100–109, 90–99 and <90 g/L. Also recorded were whether interventions (transfusion or epoetin alfa [EPO]) for the correction of anemia were discussed or administered.

Results showed that a Hb level of <100 g/L occurred in 54%, 27%, 12%, and 5% of women using CEF, AC→T (doxorubicin and cyclophosphamide followed by paclitaxel), FEC100 (5-fluorouracil, epirubicin, cyclophosphamide), and AC, respectively. Intervention rates increased as Hb declined (Table 1). Despite the rise in the prevalence of anemia, the condition was discussed with only a minority (15%) of patients with a Hb of 90–99 g/L and only half of patients (49%) with Hb <90 g/L. Intervention rates were relatively low at Hb values where evidence from randomized trials has shown treatment can improve quality of life.

Table 1: Interventions for Anemia by Hb Value					
Hb (g/L)	N	Anemia discussed	Transfuse only	EPO only	Both transfuse and EPO
110–119	443	1 (<1%)	0	0	0
100–109	340	6 (2%)	0	3 (1%)	0
90–99	190	28 (15%)	0	10 (5%)	2 (1%)
<90	99	49 (49%)	23 (23%)	11 (11%)	8 (8%)

Knowing that many oncologists acknowledge anemia to be unpredictable and that they usually act on a low Hb value once the patient is clinically anemic (i.e., reactively), Dranitsaris and colleagues set out to develop and validate a prediction model for grade III/IV anemia for breast cancer patients receiving adjuvant chemotherapy.[8] They surmised that patient care could be substantially improved if the occurrence of severe anemia could be accurately predicted through the use of validated mathematical models.

Precycle Hb, platelets ≤200 (103/mm), cycle number, patient age, type of adjuvant chemotherapy, and the use of prophylactic antibiotics were identified as being important predictors for grade III/IV anemia. An overall risk score of ≥24 for a given patient was identified as being the optimal cut off to maximize both the sensitivity (83.5%) and specificity (92.3%) of the prediction tool. Patients with a score of ≥24 would be considered at high risk for developing grade III/IV anemia following a particular cycle of chemotherapy. Researchers hope that the application and the planned continued refinement of this prediction tool will make it an important source of patient-specific risk information for the practising oncologist, thereby enhancing patient care by administering therapies to ameliorate anemia earlier — in a proactive rather than reactive manner.

Further to the endpoint of improving patient care, three studies presented as posters evaluated the administration of ESA therapy every three weeks to treat chemotherapy-induced anemia in breast cancer patients. Erythropoietic agents, such as epoetin alfa and darbepoetin alfa (DA), can effectively treat chemotherapy-induced anemia.[9] Because of its extended serum half-life, DA can be administered on an every-three-week (Q3W) schedule, which is compatible with many chemotherapy regimens.

In a randomized double-blind multicentre phase III study, European researchers evaluated the comparability (non-inferiority) of DA 500 mcg Q3W fixed-dose with DA 2.25 mcg/kg once weekly (QW) with respect to efficacy and safety.[10] Patients (n=705, breast cancer n=112) were randomized 1:1 to either a fixed dose of DA 500 mcg Q3W or DA 2.25 mcg/kg QW for up to 15 weeks. The unadjusted Kaplan-Meier percentage (95% CI) of all patients requiring transfusions from week 5 to end of treatment period (EOTP) was 23% (19 to 28) and 30% (25 to 35) for the Q3W and QW groups, respectively. The percentage (95% CI) of all patients achieving target Hb levels during the entire study was 84% (81 to 88) in the Q3W arm and 77% (72 to 81) in the QW arm. The mean difference (95% CI) in change in FACT-F scores at EOTP between groups was 0.75 (-0.97 to 2.46). The safety profile was similar between the two treatment groups.

Similarly, Glaspy et al. focused on the efficacy of DA 6.75 mcg/kg Q3W administered with Q3W chemotherapy in cancer patients with anemia (Hb ≥90 and ≤110 g/L) in a randomized multicentre open-label study.[11] This analysis compared response to Q3W DA therapy in patients with breast cancer compared with all patients enrolled in the study. Patients were randomized 1:1 to receive DA for 16 weeks on either an asynchronous schedule (begin chemotherapy day 15) or a synchronous schedule (begin chemotherapy day 1). Thirty-two (40%) of the total 81 patients had breast cancer (asynchronous, n=20; synchronous, n=12).

Regardless of synchronous or asynchronous timing, robust increases in Hb were observed, with mean Hb reaching the 110–130 g/L target range within four weeks. The percentage (95% CI) of patients who received a red blood cell transfusion was 9% (breast cancer) and 28% (all patients). The percentage (95% CI) of patients achieving a

hematopoietic response (≥20 g/L Hb increase from baseline or Hb ≥120 g/L) was 78% (breast cancer) and 74% (all patients). Median (95% CI) time to hematopoietic response was 43 days (breast cancer) and 49 days (all patients).

In a third poster, data from the breast cancer patient subset of a 16-week open-label single-arm study presented by Silberstein et al. also revealed results favouring Q3W administration.[12] The collective data of these three studies demonstrate that effective anemia management can be achieved with less frequent dosing of DA. The possibility of increased convenience created by synchronizing DA therapy with common chemotherapy regimens may be of particular importance for breast cancer patients, who are often younger than patients with other tumour types, are more likely to be working, and are frequently the primary caregivers for their families.

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Dr. Verma's perspective:

The management of anemia in cancer patients receiving chemotherapy has been the subject of considerable research in the last five years. Indeed, appropriate use of growth factors to improve or maintain Hb levels in such patients has been associated with reduced fatigue and improved quality of life. While there are no national standards for the treatment of chemotherapy-associated anemia, provincial guidelines are being revisited. Having national standards would be much more efficient. Although Canada has contributed to some research in this area, it has been necessary to rely largely on studies conducted in Europe or the US.

The need for improved efficiency in the clinic — planning and delivering care that is increasingly patient-centred — inspired the development of the prediction tool by Dranitsaris and colleagues. The tool aims to predict patients who are more likely to acquire myelopoietic conditions and attempts to make care more applicable to the individual. It is unlikely, however, that it will be applied universally as it is modelled to predict only severe cases of anemia.

The cost advantages of Q3W dosing of ESA therapy in the Canadian setting offers superb potential. Through the initial data gathering of Q3W safety and efficacy trials, researchers were able to demonstrate a meaningful shift to patient-centred care. Being able to potentially reduce the number and frequency of injections, and to coordinate Hb monitoring with a patient's scheduled clinic visits for chemotherapy will improve compliance and simplify the burden of supportive care supervision for healthcare professionals. The benefit to the patient is undeniable.

Dose-Dense Taxane Chemotherapy Associated with Higher Incidence of Cytotoxicity

The value of dose-dense (DD) chemotherapy — high drug doses combined with shortened time intervals between treatments[1] — in the adjuvant treatment of breast cancer remains an active area of debate.[2–4] Unfortunately, DD therapy is often associated with increased cytotoxicity. However, with the development of colony-stimulating growth factors, the routine use of increased doses of myelosuppressive agents in standard regimens is possible. In advanced breast cancer patients, DD therapy has resulted in positive response rates and favourable clinical outcomes, compared with historical controls,[5] and has led to the extensive exploration of high-dose chemotherapy in the treatment of a variety of solid malignancies.

Data presented at SABCS 2005 show promise that delivering chemotherapy more frequently than is done currently with standard regimens may result in better outcomes for women with high-risk breast cancer.[6] According to Hudis and colleagues, DD scheduling of chemotherapy once every two weeks (Q2W) is superior to Q3W treatment. The Intergroup Trial 9741 followed 1,972 evaluable patients who were randomized to a concurrent arm receiving doxorubicin, paclitaxel, and cyclophosphamide or a sequential arm receiving doxorubicin and cyclophosphamide followed by paclitaxel. In the sequential arm, duration of treatment was 22 weeks for the Q2W design, compared with 33 weeks for the three-week schedule; in the concurrent arm, treatment duration was 14 weeks and 21 weeks, respectively. The median follow-up of 6.5 years showed that, whether the drugs were administered sequentially or concurrently, giving treatment every two weeks resulted in significantly better disease-free survival (response rate [RR] 0.74, P=0.01) and overall survival (RR 0.69, P=0.013) than the Q3W schedule. A subsequent unplanned subset analysis demonstrated greatest benefit among patients with hormone receptor negative disease. Toxicity data of the four regimens remain unchanged from the 2003 report (Tables 2 and 3).[7] Namely, grade 4 neutropenia was more common in the three-week regimens and grade 3 or greater emesis was more common (7% vs. 3%) in the concurrent than sequential arms. Investigators also looked at several specific later-onset toxicities, including acute myelogenous leukemia and cardiac events, and found no association with either schedule or regimen.

Table 2: Hematological Related Toxicity (in % of patients during therapy)

Toxicity		Arm 1	Arm 2	Arm 3	Arm 4
		Single	DD Single	Comb	DD Comb
ANC	Gr3	0	0.2	0	0.2
	Gr4	24	3	43	9
Infection	Gr3	0.2	0	0	0.4
	Gr4	3	2	6	2
Febr. Neut. Hosp.		3	2	6	2
Platelets	Gr3	0	0	0.4	0.2
	Gr4	0.2	0	0	0.6
Hemoglobin	Gr3	0	0	0.2	0
	Gr4	0	0.2	0	0.2
Transfusion		0	3	4	3
Cycles delayed		7%	7%	8%	6%

Table 3: Non-Hematological Related Toxicity (in % of patients during therapy)					
Toxicity		**Arm 1**	**Arm 2**	**Arm 3**	**Arm 4**
		Single	DD Single	Comb	DD Comb
Nausea	Gr3	5	7	8	8
	Gr4	0.2	0.2	0.6	0
Stomatitis	Gr3	1	1	3	2
	Gr4	3	4	5	3
Cardiac Function	Gr3	1	1	0.2	0
	Gr4	0.2	0	0.2	0.2
Sensory	Gr3	4	4	5	4
	Gr4	0	0.2	0.4	0
Motor	Gr3	4	4	8	5
	Gr4	0	0	0.2	0
Skin	Gr3	2	3	0.4	2
	Gr4	0.2	0.6	0	0.2
Myalgias	Gr3	5	5	5	5
	Gr4	0	0	0.4	0

Data evaluating the relative benefits of adjuvant breast cancer chemotherapy with taxanes (docetaxel or paclitaxel) in combination with anthracycline, or given sequentially after an anthracycline-based regimen, were also presented during the symposium in two separate studies.

In a randomized multicentre phase III trial, Eiermann and colleagues compared docetaxel in combination with doxorubicin and cyclophosphamide (TAC) versus doxorubicin and cyclophosphamide followed by docetaxel (AC→T) in Her-2/neu negative early breast cancer patients with positive axillary lymph nodes.[8] The interim analysis of the BCIRG (Breast Cancer International Research Group) 005 study presented data on 3,298 patients whose baseline characteristics were as follows: less than 50 years of age (47%), one to three nodes (61%), hormone receptor positive (82%), tumour size greater than 2 cm (58%). The safety profiles of the two common docetaxel-based chemotherapy regimens are comparable with the exception of a higher incidence of febrile neutropenia with TAC (17.9% vs. 8.5%). Primary prophylaxis with G-CSF (granulocyte colony-stimulating factor) was given beginning cycle one in 16.4% of patients receiving TAC and 3.5 % of patients on AC→T. One septic death occurred in the TAC arm. Grade 3/4 neutropenic infections were equivalent (8.7% with TAC vs. 8.0%). Grade 3/4 non-hematological toxicity rates were fatigue (5.2% vs. 6.3%), nausea (4.5% vs. 4.1%), vomiting (4.2% vs. 4.1%), diarrhea (2.9% vs. 3.1%), stomatitis (2.6% vs. 3.0%), peripheral edema (1.3% vs. 2.6%), sensory-neuropathy (0.6% vs. 2.0%), and congestive heart failure (0.1% vs. 0.4%) in the TAC and AC→T arms, respectively. Efficacy data is not available at this time. Additional follow-up is required to evaluate the relative efficacy of combination vs. sequential docetaxel-containing chemotherapy in the adjuvant treatment of women with node positive, Her-2/neu negative breast cancer.

In another long-awaited study, Sparano et al. presented data of a phase III study designed to compare docetaxel and paclitaxel head-to-head in a standard three-week dosing schedule and independently to compare weekly taxanes to the longer treatment course for women with axillary node-positive or high-risk node-negative breast

cancer.[9] Patients received four cycles of AC (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2) every three weeks, followed by either: paclitaxel 175 mg/m^2 every Q3W x four, paclitaxel 80 mg/m^2 QW x 12, docetaxel 100 mg/m^2 every Q3W x four, or docetaxel 35 mg/m^2 QW x 12. While no differences in the primary endpoint of disease-free survival were reported, it was revealed that there was considerably more neutropenia in the three-week paclitaxel arm, leading to more febrile neutropenia and infection.

DD chemotherapy and the sequence of AC followed by a taxane are gaining acceptance as important treatments in adjuvant breast cancer. With the increased cytotoxicity often associated with these regimens, focus turns to studies of supportive care treatment options.

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Dr. Verma's perspective:

Anthracycline and taxane combinations — concomitant or sequential — in adjuvant treatment of breast cancer are here to stay. The updated Intergroup Trial 9741 study data further substantiate the efficacy and safety of DD doxorubicin, cyclophosphamide, and paclitaxel in this setting. The affirmation of a survival advantage is reassuring. This treatment has clearly penetrated practice across the US and Canada and is now established as one of the standards of care. The necessary additional cost of growth-factor support is counterbalanced by improved efficacy, decreased treatment time, and reduced toxicity.

Integration of the TAC treatment regimen in node positive, Her-2/neu negative breast cancer must await efficacy outcomes. The Eiermann et al. study shows TAC to be associated with a higher rate of febrile neutropenia, as was also demonstrated by the Breast Cancer International Research Group (BCIRG) 001 study, making growth-factor support an absolute necessity. However, if TAC is demonstrated to have significant superiority over AC→T, then it will require serious consideration in the future.

Comparing the Efficacy, Safety, and Cost-effectiveness of Endocrine Therapies

For more than 30 years, the selective estrogen receptor modifier tamoxifen has been the mainstay of endocrine therapy in postmenopausal women with breast cancer. In recent years, aromatase inhibitors (AI) have replaced megestrol acetate for use after failure of tamoxifen and are challenging tamoxifen as initial therapy in women with advanced disease.[1] Tamoxifen was the established adjuvant endocrine therapy for patients with hormone receptor-positive breast cancer until the first report of the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial in December of 2001.[2] Results of the trial prompted the National Comprehensive Cancer Network (NCCN) to modify their breast cancer treatment guidelines, accepting anastrozole as an alternative to tamoxifen in the adjuvant treatment of postmenopausal patients. Since the original publication of the ATAC trial results, several other large randomized studies involving AIs and tamoxifen, such as the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) MA. 17, Intergroup Exemestane Study (IES) and Breast International Group (BIG) I-98 trials, have reported data challenging standard practice.

One study presented as a poster at SABCS 2005 examined the treatment patterns of adjuvant endocrine therapy at NCCN institutions participating in the Breast Cancer Outcomes Database.[3] Researchers Svahn and colleagues discovered that use of AIs in place of tamoxifen increased rapidly after the first report of ATAC. However, they also noted that there was substantial variation between the institutions in the early adoption of AIs. Those patients who were older, who had a history of vascular disease, whose tumours overexpressed Her–2/neu, or who had more advanced-stage disease were more likely to be treated with AI therapy.

Given the recent focus on the AIs exemestane, anastrozole, and letrozole for the treatment of breast cancer, it was not unexpected that the efficacy, safety, and cost-effectiveness of AI use in the adjuvant setting were the focus of several studies presented at SABCS 2005.

Dr. Raimund Jakesz of the Vienna Medical School, Austria, presented updated results from the first tamoxifen-AI sequencing trial.[4] The results of the Austrian Breast and Colorectal Cancer Study Group 8 (ABCSG-8) trial suggest that switching from tamoxifen to an AI after two to three years of adjuvant therapy improves outcomes for patients compared with the standard five years of tamoxifen. In contrast to other switching trials, ABCSG Trial 8 randomized patients at diagnosis, rather than randomizing at the point of switch. The primary endpoint was event-free survival (EFS), including locoregional, contralateral, or distant metastatic recurrences. Secondary endpoints included safety and overall survival (OS). Eligible patients (n=3,700) were postmenopausal women with histologically verified G1 or G2, locally radically treated invasive or minimally invasive hormone receptor-positive breast cancer. After a median follow-up of 30 months, 158 events (local or metastatic recurrence, or contralateral breast cancer) were reported. The hazard ratio for EFS with tamoxifen followed by anastrozole versus tamoxifen was 0.68 (95% CI 0.49, 0.91; P=0.02), which represents a 32% reduction in the risk of disease recurrence for patients receiving tamoxifen followed by anastrozole. Regarding serious adverse events, there were a few cases of myocardial infarction in each group (three in the anastrozole group and two in the tamoxifen group). There were more instances of thrombosis, embolism, and endometrial cancer in tamoxifen-treated patients and a higher number of fractures in anastrozole-treated women.

Also supporting the policy of switching to anastrozole after two years of adjuvant tamoxifen therapy were the results of a meta-analysis investigating the use of an AI instead of tamoxifen as adjunctive therapy in postmenopausal women.[5] Dr. Walter Jonat from the University of Kiel, Germany, presented the latest data from three of the largest international trials — ABCSG-8 trial, the Arimidex-Nolvadex (ARNO 95) trial, and the Italian Tamoxifen Anastrozole (ITA) trial — that involved more than 4,000 patients and were similarly designed, allowing for a pooled analysis. The median duration of follow-up was 30 months; 2,009 women were switched to anastrozole therapy at two years, while 1,997 remained on tamoxifen for the five-year treatment period. With respect to disease-free survival (DFS), results showed a significant 41% improvement with anastrozole therapy (P<0.0001). There were fewer deaths among anastrozole-treated patients (n=66, 3.3%) compared to the tamoxifen group (n=90, 4.5%). Data also demonstrated a significant 29% OS benefit of switching therapy to anastrozole (P=0.038). The toxicity data showed that patients treated with anastrozole therapy suffered fewer serious side effects, such as an increased risk of endometrial cancer, thromboembolic events, and ischaemic cerebrovascular events, than those who were started on tamoxifen.[2] Like all AIs, anastrozole increases the risk of osteoporotic fracture compared with tamoxifen. However, it is possible to predict which women may be most at risk of fracture and manage them accordingly.

Health Canada's approval of letrozole as an extended adjuvant treatment in April 2005 was based largely on the results of the Canadian-led NCIC CTG MA. 17 trial in which letrozole therapy after the completion of standard tamoxifen treatment was shown to significantly improve DFS.[6] In the study, 5,187 postmenopausal women were originally randomized to receive letrozole or placebo after five years of adjuvant tamoxifen therapy. Because of the significant benefits of extended letrozole treatment observed at the first interim analysis, the study was unblinded early in October 2003.[7] At the time of the unblinding, women randomized to placebo were offered letrozole.

An updated analysis of the post-unblinding trial data was presented by Dr. Paul Goss at SABCS 2005.[8] He stated that the researchers set out to determine whether women who were previously given placebo and had opted to take the AI experienced any outcome benefit and to evaluate any treatment-related toxicity. Of the 2,594 patients in the

trial who had been randomized to placebo, 1,655 elected to take letrozole for up to five years. Most (95%) of the 2,593 patients who had been randomized to letrozole decided to continue treatment. Efficacy outcomes showed improved hazard ratios for DFS (0.31), distant DFS (0.28), OS (0.53), and rate of contralateral breast cancer (0.23) were all significantly in favour of AI treatment. The toxicity data only reported on those events occurring after the trial was unblinded. Excluded from the analysis were those patients in whom breast cancer recurred or who had died before the unblinding. Not surprisingly, the letrozole-treated patients were statistically more likely than those who took no more treatment to experience bone fractures, and the number of new osteoporosis diagnoses was higher in this group. Also, as expected, no differences in cardiac events between letrozole-treated patients and those who took no further treatment (n=612) were recorded. Optimal duration of treatment with letrozole remains an unanswered question as the MA. 17 trial was not designed to address this issue. In order to answer the question of duration, enrollment has begun for MA. 17R, a re-randomization of all participants completing five years of letrozole on MA. 17 to a further five years of treatment or placebo.

In a poster session, McCloskey and colleagues revealed the initial results of a direct comparison of safety parameters between AIs in healthy postmenopausal women.[9] The Letrozole, Exemestane, and Anastrozole Pharmacodynamics (LEAP) trial is an open randomized multicentre phase I comparing the effects of anastrozole, letrozole, and exemestane on serum markers of bone formation and resorption, lipid profiles, adrenal function, and safety in healthy postmenopausal women. Their analysis included differential effects on markers of bone turnover and cardiovascular effects, which may lead to differences in long-term safety profiles. Postmenopausal healthy women (n=90) from the United Kingdom and Hungary were randomized to anastrozole (1 mg/day), letrozole (2.5 mg/day), or exemestane (25 mg/day) orally, once daily for 24 weeks. Evaluation of serum lipid levels was based on fasting serum samples taken at baseline and after 2, 12, 24, and 36 weeks. Serum lipid measurements included total cholesterol, triglycerides, ratio of low-density lipoprotein cholesterol to high-density lipoprotein cholesterol (LDL-C:HCL-C), non-HDL-C, and ratio of apolipoprotein B to apolipoprotein A-1 (ApoB:Apo A-1). All patients had a slight increase in the LDL-C:HDL-C ratio at 24 weeks compared with baseline. Women receiving letrozole had a significantly increased percentage change in triglyceride levels from baseline to 12 weeks compared with those receiving anastrozole (+9.6 vs. –2.9, respectively; P=0.037), but no significant differences at 24 weeks. For women receiving exemestane, the percentage change from baseline of LDL-C:HDL-C ratio was significantly increased compared with those receiving anastrozole at both 12 weeks (+8.8 vs. –0.0, respectively; P=0.048) and 24 weeks (+17.0 vs. +4.6, respectively; P=0.047). At 24 weeks, the percentage change from baseline of ApoB:Apo A-1 for patients receiving exemestane was also associated with a significant increase compared with those receiving anastrozole (+9.0 vs. +0.0, respectively; P=0.023). The results of the analysis support those seen in non-comparative studies of the AIs, and show that anastrozole, exemestane, and letrozole have different effects on serum lipids. The researchers agreed that the differences warrant further investigation to determine if they are of clinical significance in the long-term management of breast cancer.

Although AIs are unseating tamoxifen as the most widely used hormonal agent in the treatment of breast cancer, they are considerably more expensive. Three poster sessions presented at the symposium undertook a cost-utility comparison of AIs versus tamoxifen to evaluate relative cost-effectiveness in terms of cost per quality-adjusted life year (QALY) gained. In the Canadian study by Risebrough and colleagues, treatments resulting in incremental cost per QALY below $20,000 CDN were considered to be cost-effective.[10] Using a Markov model with a 7.5-year time horizon, researchers sought to evaluate the cost-effectiveness of switching to exemestane at two to three years compared to remaining on tamoxifen for five years from a Canadian government payer perspective. Study results demonstrated that the total cost of tamoxifen treatment was $18,991 CDN compared to $20,810 CDN with exemestane. Life years (LY) and QALYs increased with the exemestane treatment strategy — from 6.37 and 5.64 with tamoxifen to 6.43 and 5.73 respectively with exemestane. The incremental medical cost per QALY gained with exemestane vs. tamoxifen was $19,124 CDN, while incremental cost gained per LY was $28,565 CDN. The sensitivity analysis showed results were robust to reasonable changes in probability and quality of life parameters, but were sensitive to distant recurrence costs. If the actual cost of recurrence was twice as high as in the base case

analysis ($14,927 CDN per six months), exemestane could be considered the dominant therapy with respect to better clinical outcomes and lower overall treatment cost.

An American study reviewing the cost-effectiveness of the same management strategy drew comparable conclusions.[11] Based on a Markov model with a 10-year time horizon for recurrence and a lifetime horizon for survival and costs, Thompson et al. determined that switching to exemestane was associated with increased recurrence-free survival (11.12 vs. 10.58 years), QALYs (8.45 vs. 8.23), and net costs of cancer care ($17,168 US per patient vs. $13,588 US) over the lifetime versus continuing tamoxifen therapy.

Similarly, researchers Skedgel et al. found both anastrazole and tamoxifen followed by exemestane were associated with QALY gains relative to tamoxifen alone.[12] The cost-effectiveness of anastrazole relative to tamoxifen alone was $21,098 per QALY gained, while tamoxifen followed by exemestane relative to tamoxifen alone was $10,305 CDN per QALY gained. The cost-effectiveness of anastrazole relative to tamoxifen followed by exemestane was $138,838 CDN per QALY gained. Based on the unfavourable results of the cost-effectiveness of anastrazole relative to tamoxifen followed by exemestane, the group concluded that tamoxifen followed by exemestane be considered the preferred option.

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Dr. Verma's perspective:

Advances in adjuvant endocrine therapy of early-stage breast cancer continue to accrue. Although survival advantages have yet to be demonstrated in the ATAC, IES, and BIG I-98 trials, it is clear that most other outcomes are favourably influenced by the addition of an AI in this setting, as data presented at SABCS 2005 confirm. Yet specific questions remain unanswered, such as: Which model of care should be adopted (using an AI instead of tamoxifen, switching to an AI after two to three years or after five years of tamoxifen) and which AI should be chosen? From a clinical perspective, the AIs appear to be equivalent. However, data from McCloskey et al. suggest that there might be important pharmacological differences that merit further inquiry.

Perhaps the most interesting news from SABCS 2005 was the post-unblinding data of the MA. 17 trial presented by Goss and colleagues, wherein patients who had switched from placebo (i.e., had been off therapy for a variable period of time) to letrozole demonstrated significant benefits compared to those who remained on placebo. This has potential immediate and significant implications for practice in Canada.

Finally, the cost of new therapies, in particular AIs, has continued to trouble many in the healthcare sector. It is important that studies such as those presented by our Canadian colleagues are conducted rigorously and methodically. Although individual drug acquisition costs are higher, they are offset by increased benefits and reduced risks. The conclusion from all of the study data collected thus far is that AIs in the adjuvant setting are associated with acceptable cost effectiveness.

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