



EVIDENCE WATCH

A review and assessment of recent clinical trial data

Oncology Exchange provides overviews of important clinical trial data presented at the 48th Annual Meeting of the American Society of Hematology (ASH), held December 8–11, 2006 in Atlanta, Georgia and the 29th San Antonio Breast Cancer Symposium (SABCS), held December 14–17, 2006. Leading Canadian experts offer commentary and clinical interpretations. Reporting on both conferences will continue in the next issue of *Oncology Exchange*.

Presentations from the 48th Annual Meeting of the American Society of Hematology

Contributors were selected by Douglas A. Stewart, MD, FRCPC, Tom Baker Cancer Centre

Acute lymphoblastic leukemia

TOWARDS A PEDIATRIC APPROACH IN ADULTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL): THE GRAALL-2003 STUDY. ASH 2006, ABSTRACT 147.

Investigators: F. Huguet et al.

TRIAL SUMMARY: The GRAALL-2003 study offered a pediatric-style treatment approach to adults ≤ 60 years old with Philadelphia chromosome-negative acute lymphoblastic leukemia (ALL). Called FRALLE, the treatment used 8.6 times more steroids, 3.7 times more vincristine and 16 times more L-asparaginase, cumulatively, compared to the standard LALA-94 treatment, and included 5 induction drugs, high dose-intensity consolidation blocks, delayed intensification, and 2 years of maintenance. Allogeneic stem cell transplant during the first complete remission was offered to all high-risk patients who had suitable donors (unlike in pediatric therapy). Patients with poor early response received additional induction therapy with high-dose cyclophosphamide sequence (HyperC). This report compares 212 GRAALL-2003 patients with median followup of 18 months to 712 patients previously treated in the LALA-94 trial.

The treatment given in GRAALL-2003 was associated with significantly higher complete response and 2-year event-free and overall survival (Table 1). The survival differences persisted in analysis of non-stem cell transplant patients. Older patients had lower tolerance to induction and post-remission therapy, such that the benefit of the pediatric approach was not statistically significant in those

over 40 years of age. Analysis by T vs B cell lineage showed greater outcome improvement in T cell disease. The T-ALL poor early-responders allocated to HyperC induction, however, had a non-statistically significant tendency towards better event-free survival than did the T-ALL good early-responders, suggesting that HyperC is particularly beneficial for this subset of patients.

TABLE 1. Outcomes for adult ALL patients treated with a pediatric approach in GRAALL-2003 compared to those receiving conventional treatment in LALA-94

	GRAALL-2003	LALA-94	p-value
complete response	93%	88%	p = 0.02
2-year event-free survival	56%	41%	p = 0.0002
2-year overall survival	66%	54%	p = 0.02
T-ALL subgroup	75%	51%	p = 0.016
B-ALL subgroup	61%	56%	p = 0.25

COMMENTARY: A. Robert Turner MD, FRCPC, Professor of Medicine, University of Alberta, and Cross Cancer Institute, Edmonton, AB.

ALL in adults is a curable malignancy! This was the theme that reverberated at ASH 2006 in education sessions, plenary and simultaneous oral abstracts and posters. “Young” patients with ALL — those under about 40 or 50 years old — need to be treated aggressively. Pediatricians cure twice as many of their patients as do internists. Adult physicians should emulate their pediatric colleagues and become much more compulsive about elevating dose intensity and maintaining dose schedule. This is not new: Charles Schiffer brought ALL-treaters to task in a 2003 editorial in the *Journal of Clinical Oncology*, saying essentially that conservative treatment of adult ALL patients was no longer justifiable.¹

This research from the French ALL Cooperative Group points to the need to intensify the dose of asparaginase, vincristine, corticosteroid and cyclophosphamide. Cyclophosphamide in high doses ameliorated the poor prognosis of T-ALL. All of this dose-intensity was given with very little morbidity. Overall survival at 2 years was 66% for patients receiving the intense protocol. Surprisingly, the T-ALL subgroup had better 2-year survival than the B-ALL group. The French group also use allogeneic BMT for high-risk patients who have a donor, an approach validated by Jacob Rowe’s presentation at the plenary session.² This MRC/ECOG study, using 1993 chemotherapy, reported that allogeneic BMT in first complete remission of standard-risk adult ALL produced the best long-term survival. One wonders if a more intense chemotherapy protocol might reduce the need for transplantation.

Two posters presenting a Canadian experience with a pediatric regimen for adult ALL were also presented. Abstract 1858 reviewed the early results of the NCIC-CTG study

AL4, a Phase II study of the Dana Farber dose-intensified pediatric regimen in adults.³ Abstract 1875 reported Princess Margaret Hospital’s experience with the Dana Farber protocol.⁴ Both determined that dose modification of L-asparaginase appears to be the key to producing improved efficacy, providing better event-free and overall survival rates in both studies. Both found the Dana Farber protocol to be safe and feasible up to the age of 50.

ASH PEARL: MILK THISTLE AND LIVER FUNCTION

It also appears that complementary medicine advocates have something important to contribute to conventional medicine: pediatric oncologists from Columbia University in New York and Children’s Hospital, Philadelphia, reported a placebo-controlled trial showing that milk thistle extract, given for 28 days with hepatotoxic chemotherapy, was beneficial in allowing greater dose intensity of hepatotoxic chemotherapy. Liver dysfunction is a common cause of dose reductions in ALL treatment.

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Acute myeloid leukemia

GENE MUTATIONS AS PREDICTIVE MARKERS FOR POSTREMISSION THERAPY IN YOUNGER ADULTS WITH NORMAL KARYOTYPE AML. ASH 2006, ABSTRACT 4.

Investigators: R.F. Schlenk et al.

TRIAL SUMMARY: This study evaluated the prognostic impact of several genes previously identified as molecular markers for response to induction therapy, relapse-free and overall survival, and efficacy of selected postremission therapies in patients with normal karyotype acute myeloid leukemia (AML). Study subjects (16–60 years old) had been enrolled in 4 German treatment trials (AML-2/95, AML-1/99, AML HD93 and AML HD98A) between 1993 and 2004. Genetic randomization assigned all patients with an HLA-matched family donor and a first complete remission to allogeneic stem cell transplantation. **Table 2** shows mutations identified in 872 patients with normal karyo-

TABLE 2. Mutations identified in analysis of 872 adults with normal karyotype AML

mutation	percent identified	number of samples analyzed
NPM1	53%	526
FLT3-ITD	31%	531
FLT3-TKD	11%	717
CEBPA	14%	509
MLL-PTD	8%	640
NRAS	13%	641

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types, with median age of 48 years and median followup of 49 months. Logistic regression showed the genotypes NPM1+/FLT3-ITD- ($p < 0.0001$) and CEBPA+ ($p = 0.05$) to be associated with induction success. Of 666 patients achieving complete response after induction therapy, 171 had a HLA-matched family donor and 143 (84%) of these received an allogeneic stem cell transplant during their first complete remission. Cox proportional hazard models for relapse-free and overall survival revealed prognostic factors to be age < 48 years, availability of a HLA-matched family donor, CEBPA+ genotype and NPM1+/FLT3-ITD- genotype (Table 3). Further, as shown in Table 4, subgroup

TABLE 3. Factors shown to be prognostic factors for relapse-free and overall survival in 872 adults with normal karyotype AML

	hazard ratio for relapse-free survival	hazard ratio for overall survival
age < 48 years	0.72	0.62
availability of a HLA-matched family donor	0.62	0.75
CEBPA+ genotype	0.42	0.36
NPM1+/FLT3-ITD- genotype	0.34	0.43

TABLE 4. Outcomes according to genotype of leukemic cells

	NPM1+/FLT3-ITD- subgroup	other genotype combinations
relapse-free survival (hazard ratio, 95% CI)	HR 0.89 (95% CI 0.49-1.64)	HR 0.56 (95% CI 0.39-0.81)
overall survival (hazard ratio, 95% CI)	HR 0.93 (95% CI 0.51-1.67)	HR 0.69 (95% CI 0.48-0.98)
4-year relapse-free survival rate with donor and transplant	61%	47%
4-year relapse-free survival rate without donor and transplant	57%	23%

analyses showed that patients without the combined NPM1+/FLT3-ITD- mutations had twice the 4-year relapse-free survival, if transplanted.

The authors concluded that the NPM1+/FLT3-ITD- and CEBPA+ genotypes are highly significant prognostic factors for response to induction therapy and for survival, and that absence of the genotypic marker constellation NPM1+/FLT3-ITD- predicts a strong beneficial effect of allogeneic stem cell transplant during first complete remission.

COMMENTARY: A. Robert Turner MD, FRCPC, Professor of Medicine, University of Alberta, and Cross Cancer Institute, Edmonton, AB.

Choice of postremission therapy in younger patients with intermediate-risk AML has been problematic. A significant number are considered cured by several courses of chemotherapy¹ and there is a small but appreciable mortality risk with allogeneic bone marrow transplantation (BMT). Some long-term survivors of BMT have significant morbidity, reducing their quality of life. This has led to the practice of reserving non-sibling donor BMT to AML patients in second complete remission, even though there may be losses due to re-induction failure and increased morbidity due to the BMT in second complete remission.

This study points out the usefulness of several gene mutations in prognostication. Some of them would prompt a conservative approach to alternative donor BMT while others portend a poor prognosis and should accelerate the search for an appropriate donor in first complete remission. It is no longer sufficient to include only cytogenetics, age and comorbidity in the analysis of prognosis. Gene mutation analysis will be essential in making informed treatment decisions and will be mandatory in AML clinical trials. Providing the expertise in mutation analysis at all sites treating AML may be difficult, however, and collaborative use of centralized laboratories may be a practical solution.

The National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) has recently opened ALC1, a randomized trial of gemtuzumab ozogamicin added to AML induction chemotherapy. Alan Burnett et al presented pre-

liminary results from the MRC AML 15 trial, reporting that gemtuzumab ozogamicin significantly improved disease-free survival, compared to historical controls, although no difference has yet been seen in overall survival (approximately 50% at 3 years). Gemtuzumab ozogamicin-treated patients had more mucositis, antibiotic use and platelet transfusions; the rate of induction deaths was the same. This agent appears to be an important addition to the armamentarium for AML and the NCIC-CTG trial will provide useful information in addition to giving access to a novel therapy for Canadian patients.

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Multiple myeloma

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF THALIDOMIDE PLUS DEXAMETHASONE VERSUS DEXAMETHASONE ALONE AS PRIMARY THERAPY FOR NEWLY DIAGNOSED MULTIPLE MYELOMA. ASH 2006, ABSTRACT 795.

Investigators: S.V. Rajkumar et al.

TRIAL SUMMARY: This double-blind, placebo controlled study randomized 470 symptomatic, previously untreated multiple myeloma patients to receive either thalidomide + dexamethasone or placebo + dexamethasone. The escalating target doses of thalidomide were 50 mg orally for the first 15 days of the first 28-day cycle, 100 mg daily during the second half of the cycle and 200 mg daily from cycle 2 thereafter. Dexamethasone was given at doses of 40 mg orally on days 1–4, 9–12 and 17–20, throughout the cycles. Analyses were on an intention to treat basis and the study completion rate was 82%. Median time to progression, the primary end-

point, was not reached in the thalidomide + dexamethasone arm and was 8.1 months (95% CI 6.5–12.8 months) in the placebo + dexamethasone group ($p < 0.001$). The total response rate (complete response + partial response) in patients receiving thalidomide + dexamethasone was 59% and for those receiving placebo + dexamethasone it was 42% ($p < 0.001$). The most important Grade 3–4 adverse event was deep vein thrombosis, occurring in 17.9% of the patients receiving thalidomide + dexamethasone and 4.3% of those in the placebo + dexamethasone arm. Other Grade 3 events occurred in less than 4% of all cases in both groups.

FIRST ANALYSIS OF THE AUSTRALASIAN LEUKAEMIA AND LYMPHOMA GROUP (ALLG) TRIAL OF THALIDOMIDE AND ALTERNATE DAY PREDNISOLONE FOLLOWING AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) FOR PATIENTS WITH MULTIPLE MYELOMA. ASH 2006, ABSTRACT 58.

Investigators: A. Spencer et al.

TRIAL SUMMARY: This multicentre, stratified and randomized controlled trial evaluated the synergic effect of thalidomide added to alternate-day prednisolone, preceded by autologous stem cell transplantation (ASCT) with melphalan 200 mg/m², in 243 non-progressive multiple myeloma patients. Levels of B2-microglobulin (a marker that reflects neoplastic cell turnover and renal function) before ASCT were employed as criteria for stratification. Six weeks after ASCT, all patients received 50 mg of alternate-day prednisolone. Patients in the thalidomide group received up to a maximum dose of 200 mg daily, for up to 12 months; 65% of patients were able to complete 12 months of thalidomide at a median dose of 100 mg. Patients in both groups also received 4 mg of zoledronic acid intravenously every 28 days to prevent osteolysis. Analyses were conducted on an intention to treat basis.

Estimates of progression-free survival for patients in the thalidomide group were 90% at year 1, compared to 69% in those not receiving thalidomide ($p = 0.0005$), 66% vs 40% at year 2, and 39% vs 25% at year 3 (Table 5). At median followup of 2 years, patients in the thalidomide group showed superior overall survival compared to those not receiving thalidomide ($p = 0.021$), also shown in Table 5.

TABLE 5. Progression-free and overall survival in treatment-naïve multiple myeloma patients receiving thalidomide added to alternate-day prednisolone following autologous stem cell transplant (ASCT) + melphalan vs no thalidomide

	thalidomide	no thalidomide
progression-free survival ($p = 0.0005$)		
year1	90%	69%
year2	66%	40%
year3	39%	25%
overall survival ($p = 0.021$)		
year1	97%	95%
year2	91%	80%
year3	86%	75%

COMMENTARY: Tony Reiman, MD, FRCPC, Medical Oncologist and Assistant Professor, Faculty of Medicine and Dentistry, University of Alberta, Cross Cancer Institute, Edmonton, AB.

There is a growing body of literature on the value of thalidomide as a treatment for multiple myeloma. Since its introduction in the late 1990s, several clinical trials have been initiated or completed evaluating the optimal use of thalidomide in this disease. Initially the drug gained favour as a treatment for relapsed myeloma, in which it was first studied.¹ Remarkably, however, reports of results from randomized trials evaluating thalidomide in the relapse setting have been lacking — perhaps the reason that thalidomide has yet to gain approval as a therapy for multiple myeloma in Canada. This is unfortunate, given its effectiveness and its unique, tolerable side-effect profile that includes only a minimal degree of myelosuppression.

THALIDOMIDE IN FIRST-LINE THERAPY

On the other hand, a proliferation of results from randomized studies of thalidomide used as part of first-line therapy has recently been published. The abstract by Rajkumar et al discusses a multicentre, international, randomized trial evaluating the use of thalidomide in combination with dexamethasone as induction therapy for previously untreated myeloma patients. A prior, similarly designed Eastern Cooperative Oncology Group (ECOG) study by Dr. Rajkumar and colleagues demonstrating improved response rates with thalidomide + dexamethasone in transplant-eligible patients² was considered important in the recent FDA approval of thalidomide for myeloma. This new abstract reported — for the first time — improved time to progression with thalidomide + dexamethasone in comparison to patients treated with placebo + dexamethasone. Although this trial has yet to demonstrate an improvement in overall survival, the results are highly encouraging given the short followup period.

The lead abstract by the Intergroupe Francophone du Myélome (IFM) group at the 2006 ASCO meeting reported on an overall survival advantage when thalidomide was added to standard melphalan and prednisone for elderly patients,³ and an Italian trial is also showing significant improvements in time to progression when thalidomide is added to this old but still standard treatment.⁴ Using thalidomide + dexamethasone without melphalan has the advantage of allowing stem cell collection for subsequent autologous transplantation, making it an attractive regimen for transplant-eligible patients, although it remains to be seen whether incorporation of thalidomide into induction therapy will improve overall survival in the transplant-eligible population.⁵

It is now well understood that thrombosis is a significant complication of thalidomide therapy for myeloma, particularly when used to treat patients with active disease and particularly when used in combination with other drugs. The high rate of venous thrombosis seen in the study by Rajkumar et al reflects the need to consider prophylaxis with antithrombotic agents when using thalidomide therapy. The optimal method of prophylaxis remains undefined but as demonstrated in several presentations at last December's ASH, effective options include aspirin and

prophylactic or full doses of warfarin or low molecular-weight heparin.

The Australian study described above reports on a randomized trial of thalidomide + prednisolone vs prednisolone alone as maintenance therapy following frontline autologous transplant for myeloma patients. This study demonstrated significant improvement in progression-free and overall survival with 12 months of thalidomide maintenance therapy. The results are concordant with the IFM study of indefinite thalidomide monotherapy as maintenance following tandem autologous transplant.⁶ The study also demonstrates that in the setting of maintenance therapy, the rate of thrombotic events with thalidomide (roughly 5% in this study) is much lower than what is seen when given as therapy for active disease. Routine thromboprophylaxis is probably not necessary in the maintenance setting.

CANADIAN TRIAL ENROLLMENT

In Canada, the NCIC-CTG MY.10 study is currently enrolling patients following autologous transplant and is randomizing patients to thalidomide + prednisone vs observation. Maintenance treatment in this trial is scheduled to continue for up to 4 years. The encouraging Australian result makes it all the more important to enroll patients in the Canadian study. Only through the completion of multiple, well-conducted studies can we determine the optimal way to employ thalidomide in the maintenance setting — to determine the best dose, schedule, combination and duration of therapy. These questions remain unanswered but MY.10 should contribute important data in this regard when considered in the context of the French and Australian trials, as well as ongoing trials of other maintenance therapy approaches.

The current bounty of positive, randomized controlled trials should prompt reconsideration of thalidomide as a standard treatment option for myeloma patients in Canada, where the drug is only available at present through a Health Canada Special Access Program, and where most provinces do not routinely fund thalidomide treatment.

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Presentations from the 29th Annual San Antonio Breast Cancer Symposium

Contributors were selected by Joseph Ragaz, MD, FRCPC, Director, Oncology Clinical Research, McGill University Health Centre, Montreal, QC.

Adjuvant chemotherapy for early breast cancer

A RANDOMIZED TRIAL OF CEF VERSUS DOSE DENSE EC FOLLOWED BY PACLITAXEL VERSUS AC FOLLOWED BY PACLITAXEL IN WOMEN WITH NODE POSITIVE OR HIGH RISK NODE NEGATIVE BREAST CANCER, NCIC CTG MA.21: RESULTS OF AN INTERIM ANALYSIS. SABCS 2006, ABSTRACT 53.

Investigators: M. Burnell et al.

TRIAL SUMMARY: This randomized trial compared 3 chemotherapy regimens given to 2104 women age 60 years or younger who had axillary node-positive or high-risk node-negative breast cancer, following lumpectomy or mastectomy. The regimens were:

- CEF: cyclophosphamide 75 mg/m² orally on Days 1–14, epirubicin 60 mg/m² + fluorouracil 500 mg/m² intravenously on Days 1 and 8, with concurrent antibiotic prophylaxis, given for 6 cycles
- EC-T: epirubicin 120 mg/m² + cyclophosphamide 830 mg/m², both intravenously on Day 1, every 14 days for 6 cycles, with filgrastim 5/kg/day subcutaneous on Days 2–13 and epoetin alpha 40,000 units subcutaneous once per week; followed by 4 cycles of paclitaxel 175 mg/m² every 21 days, with filgrastim and epoetin alpha
- AC-T: doxorubicin 60 mg/m² + cyclophosphamide 600 mg/m² intravenously every 21 days for 4 cycles; followed by paclitaxel 175 mg/m² every 21 days, with filgrastim and epoetin alpha

In this planned interim analysis after 227 disease recurrences, with median followup of 30.4 months in participants still alive, recurrences had occurred in 79 of the patients receiving CEF, 70 of those receiving EC-T, and 112 of those receiving AC-T.

COMMENTARY: Sunil Verma, MD, MEd, FRCPC, Medical Oncologist, Toronto Sunnybrook Regional Cancer Centre, Toronto, ON.

A DECADE OF DEVELOPMENT AND UNCERTAINTY

Over the last two decades we have seen a substantial decline in the mortality associated with breast cancer. This is mostly due to significant advances made in treatments including improvement in the adjuvant therapy of early breast cancer,¹ among them using increased doses of epirubicin in adjuvant protocols, delivery of chemotherapy in a dose-dense manner, and the incorporation of taxanes in the adjuvant setting. Despite significant progress, a lot of confusion and uncertainty remains among clinicians as to which of the regimes are superior — is it CEF? FEC100? dose-dense AC-paclitaxel? non-dose-dense AC-paclitaxel? And now, most recently, evidence shows that FEC100 for 3 cycles

TABLE 6. Disease recurrence and recurrence-free survival rates in 2104 women randomized to receive 3 chemotherapy regimens

	CEF	EC-T	AC-T
disease recurrence	79 patients*	70 patients*	112 patients*
recurrence-free survival rate	90.1%	89.5%	85.0%

* global p = 0.0009547

The global test of significance for the 3 arms was p = 0.0009547 (Table 6, also showing corresponding recurrence-free survival rates). Hazard ratios (HR) for recurrence were AC-T vs CEF: 1.49, 95% CI 1.12–1.99, p = 0.005; AC-T vs EC-T: 1.68, 95% CI 1.25–2.27, p = 0.0006; and EC-T vs CEF: 0.89, 95% CI 0.64–1.22, p = 0.46. The authors concluded that in women with high-risk operable breast cancer AC-T given every 3 weeks provides significantly inferior relapse-free survival compared to CEF or EC-T, and called for further investigation of non-dose-dense-based taxane chemotherapy.

followed by 3 cycles of docetaxel is superior to FEC100 alone.² This uncertainty has led to individual, centre, and provincial recommendations based on indirect comparisons among the different trials.

THE LONG-AWAITED RESULTS OF MA.21

As noted above, the patients enrolled in the MA.21 trial were randomized to 1 of 3 arms. Due to the significant differences in outcomes seen at this planned interim analysis, and upon recommendations made by the Data Safety Monitoring Committee, the authors decided to present these results after median followup of 30.4 months. A statistically significantly greater number of recurrence events were seen in

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patients who received AC followed by paclitaxel compared to those in the 2 more dose-intensive treatment arms, leading to an absolute difference of 5% in the primary endpoint of recurrence-free survival. Overall survival and mortality data were not presented.

INCLUSION CRITERIA MATTER

The enrollment criteria for the study included patients who were younger than age 60, node-positive or high-risk node-negative (i.e. tumour ≥ 1 cm, Grade III, estrogen receptor-negative (ER-) or lymphovascular invasion-positive) with chemotherapy initiated within 12 weeks of surgery. About 28% of the patients were node-negative. It is important to keep these inclusion criteria in mind, especially the age restriction, if we are going to make treatment decisions based on this study. We should also evaluate the toxicity associated with these regimens. Primary prophylaxis with growth factor support was given to patients who received dose-dense EC, and routine antibiotic prophylaxis was given to those receiving CEF chemotherapy. The febrile neutropenia rates were 22.9%, 16.7% and 4.8% in CEF, dose-dense EC-T and AC-T arms, respectively. Grade 3-4 CHF rates, thromboembolic and leukemia rates were also higher in the patients randomized to CEF and to dose-dense EC-T as compared to those on AC-T.

Subgroup analysis of data with respect to key factors including lymph node, epidermal growth factor receptor 2 (HER2), and ER status was not presented. Patients were allowed to receive trastuzumab if they completed chemotherapy anytime after January 2005, in accordance with the National Surgical Adjuvant Breast and Bowel Project (NSABP) alert of June 2005.

IMPACT ON CLINICAL PRACTICE

This is a pivotal study that we should be proud of across Canada as many of the Canadian centres participated and contributed data. Despite the substantial difference seen in recurrence-free survival, however, it is important to remem-

ber that this was an interim analysis, albeit planned and significant. The median followup is still short at only 30.4 months. As with all trials of adjuvant therapy, most patients with recurrences are still alive, so more time is needed to generate overall survival data. Further, CEF chemotherapy was associated with significantly higher febrile neutropenia rates and more cardiac and leukemic events.

Should the results of the MA.21 study induce us to change the adjuvant treatment options we present to patients? Despite the short followup on this study and concern about increased toxicity, it may no longer be reasonable and safe to consider AC-paclitaxel as equivalent to other first-choice options for adjuvant treatment of high-risk patients. The top-tier adjuvant therapy choices for high-risk disease now include CEF, dose-dense EC-paclitaxel, FEC-docetaxel, TAC (docetaxel + doxorubicin + cyclophosphamide) and dose-dense AC-paclitaxel. Is CEF or dose dense EC-paclitaxel any better than the other options? The answer is unknown, but we do know that they all have different toxicity profiles which need to be discussed with patients along with efficacy when making treatment decisions.

FUTURE AVENUES OF RESEARCH

A very important area of research is the predictive utility of HER2 and topoisomerase II alpha (topo2a) to determine if the dose-intensive and dose-dense approaches are required for all patient subsets, and if there is a need for anthracyclines in the adjuvant setting. Combined results of at least 4 adjuvant trials with centralized assessment of tumour specimens are expected later this year. Data from this large retrospective analysis will be important to help answer these questions.

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Metastatic breast cancer

A RANDOMIZED PHASE 2 TRIAL OF QW OR Q3W ABI-007 (ABX) VS. Q3W SOLVENT-BASED DOCETAXEL (TXT) AS FIRST-LINE THERAPY IN METASTATIC BREAST CANCER (MBC). SABCS 2006, ABSTRACT 46.

Investigators: W. Gradishar et al.

TRIAL SUMMARY: This study randomized 300 women with metastatic breast cancer to receive 1 of 4 regimens:

- intravenous albumin-bound paclitaxel (ABI-007) 300 mg/m² every 3 weeks
- 100 mg/m² on Days 1, 8 and 15, every 28 days
- 150 mg/m² on Days 1, 8 and 15, every 28 days
- intravenous solvent-based docetaxel 100 mg/m² every 3 weeks.

Patients were enrolled from November 2005 to June 2006 and tumour assessments were done every 8 weeks. At the first planned interim analysis in July 2006, 210 (70%) of patients had had at least one tumour assessment. As shown in **Table 7**, early results show the greatest response in the group receiving ABI-007 at the 150 mg/m² dose. They also show lower rates of tumour progression and/or death and significantly reduced Grade 4 neutropenia for all doses

of ABI-007 vs docetaxel. Further, only 1 case of febrile neutropenia occurred among patients receiving ABI-007 (in the 100 mg/m² group) vs 4 cases in the docetaxel group, 1 being fatal. Preliminary data on Grade 3 peripheral neuropathy reported 2 cases in the ABI-007 300 mg/m² arm, none in the 100 mg/m² arm, 4 in the 150 mg/m² arm and 2 in the docetaxel 100 mg/m² arm.

TABLE 7. Selected efficacy and toxicity results for 300 women with metastatic breast cancer receiving albumin-bound paclitaxel at 3 doses vs docetaxel

Outcome	ABI-007 300 mg/m ² every 3 weeks	ABI-007 100 mg/m ² 3 of 4 weeks	ABI-007 150 mg/m ² 3 of 4 weeks	docetaxel 100 mg/m ² every 3 weeks
confirmed response	20%*	29% [†]	44%	20% [‡]
total response, including unconfirmed	33%	42%	62%	31%
tumour progression and/or death	11%	12%	9%	25%
Grade 4 neutropenia	5%	3%	8%	67% [§]

* for ABI-007 300 mg/m² vs 150 mg/m², p = 0.042
[†] for ABI-007 100 mg/m² vs 150 mg/m², p = 0.004
[‡] for ABI-007 150 mg/m² vs docetaxel 100 mg/m², p = 0.014
[§] for all doses of ABI-007 vs docetaxel 100 mg/m², p < 0.001

COMMENTARY: Sunil Verma, MD, MEd, FRCPC, Medical Oncologist, Toronto Sunnybrook Regional Cancer Centre, Toronto, ON.

A number of systemic treatment options are available to women with metastatic breast cancer (MBC). Clinicians determine the choice of treatment of MBC depending on many treatment-, tumour- and patient-related factors. In general, chemotherapy is reserved for patients after they have exhausted endocrine treatments if they are ER-positive, or in whom symptomatic visceral disease is present. Docetaxel given every 3 weeks has been shown to be superior to paclitaxel given every 3 weeks and is considered the standard first-line treatment, especially as most of these patients will have received anthracyclines in the adjuvant setting.¹ Despite superior efficacy, however, docetaxel is associated with increased toxicity including febrile neutropenia.

Nanoparticle albumin-bound paclitaxel (nab-paclitaxel, ABI-007) has been shown to be superior to solvent-bound paclitaxel, with significantly higher response rates and time to tumour progression, and a favourable safety profile.

NAB-PACLITAXEL VS DOCETAXEL

This was a 4-arm Phase II study evaluating first-line treatment of MBC with nab-paclitaxel given every 3 weeks, 2 different dosage arms of weekly nab-paclitaxel given 3 weeks out of 4, and docetaxel given every 3 weeks. The primary endpoints were response assessment and toxicity. Around 75 patients were randomized to each arm. About a third of patients had liver metastases and approximately 40% had previously received chemotherapy in the adjuvant or neo-adjuvant setting. Results presented at the conference based on the third planned interim analysis indicate a significantly higher response rate for weekly nab-paclitaxel as compared with 3-weekly docetaxel. There was also prolongation of progression-free survival. Further, nab-paclitaxel had a superior toxicity profile with lower rates of neutropenia, febrile neutropenia and mucositis.

CLINICAL IMPACT

The results of this very important study were much anticipated. As noted above, nab-paclitaxel had previously dem-

onstrated superiority to solvent-based paclitaxel but there was speculation on how it compared to standard first-line treatment, i.e. docetaxel. This Phase II study shows that nab-paclitaxel, especially given weekly, offers a superior response rate and favourable toxicity profile compared with 3-weekly docetaxel.

This study is pivotal in many respects. It again shows that nab-paclitaxel has significant activity in MBC, and that it has a favourable toxicity profile — much needed as we strive to maintain a good risk-benefit ratio in the management of MBC. So are we ready to change our standard first-line treatment for MBC? Not quite yet. This was a Phase II study and the results presented are interim; blinded independent radiology review of this data is still pending. Based on this study, a randomized Phase III multinational trial comparing weekly nab-paclitaxel at a dose of 100mg /m² weekly to 3-weekly docetaxel at 100mg /m² is being planned, which will help determine whether standard first-line treatment should change.

A ROLE IN TAXANE-PRETREATED PATIENTS?

An important area of future study is the use of nab-paclitaxel in patients who have previously received taxanes in the adjuvant setting. With increasing use of taxanes for early breast cancer, how best to treat patients when they develop MBC becomes a vital question. Nab-paclitaxel has shown significant activity in taxane-pretreated patients and its evaluation in this setting is underway and much anticipated.

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Breast cancer epidemiology

A SHARP DECREASE IN BREAST CANCER INCIDENCE IN THE UNITED STATES IN 2003. SABCS 2006, ABSTRACT 5.

Investigators: P.M. Ravdin et al.

TRIAL SUMMARY: Researchers conducting this epidemiologic, observational study analyzed records from the SEER (Surveillance Epidemiology and End Results) to examine changes in incidence of breast cancer in the U.S. The data showed a marked age-adjusted decrease overall from 1998 to 2003 of 7% for all cases of invasive and ER+ disease. The decline was 1% in both the first and second halves of 2002, 6% in the first half of 2003, and 9% in the second half of the same year. No significant changes were noted for estrogen receptor-negative (ER-) disease, but the small number of cases diminished the statistical power of this subset. As shown in **Table 8**, women over the age of 50 years showed the steepest decrease in breast cancer incidence. The 8% decline in ER+ tumours was greater than the 4% decline in ER- ones, with women in the 50 to 69 year age group experiencing the most significant decline

TABLE 8. Decline in incidence of breast cancer by age group in SEER observational data 2002-2003

	40 to 49 years	50 to 51 years	60 to 61 years	70 to 71 years
decline	1%	11%	11%	7%

(12% in ER+ vs 4% ER- tumours). The authors estimated that the observed drop in incidence translates to 14,000 fewer diagnoses of invasive cancer in the U.S. for 2003 compared with 2002, and speculated that a possible explanation may be the decrease in use of hormone replacement therapy (HRT) in postmenopausal women.

COMMENTARY: Daniel Rayson, MD, FRCPC, Chair Nova Scotia Provincial Breast Cancer Team, Associate Professor of Medicine, Dalhousie University, Halifax, NS.

Researchers studying the epidemiology of breast cancer used SEER data to analyze increases and decreases in breast cancer incidence. This data set assesses cancer incidence and survival in 9 U.S. jurisdictions: 4 cities (Atlanta, Detroit, Seattle and San Francisco) and 5 states (Utah, Connecticut, New Mexico, Hawaii and Iowa). A gradual increase in incidence averaging 1.7% per year was observed between 1990 and 1998. Data from the same database showed that in 1998 the incidence began to decrease an average of 1% per year through to the year 2002 and fell by 7% between 2002 and 2003. Because the SEER database incorporates a 3-year time lag in the update process, the data presented during this 2006 conference specifically refers to incidence statistics for 2003 compared with those from 2002 and earlier.

CHANGES IN HRT PRESCRIPTIONS

These observations on reduced breast cancer incidence must be regarded as preliminary at this point, and causality has not been determined. A compelling argument exists, however, to examine this change in observed incidence rates in the context of the dramatic decrease in new and refill prescriptions for HRT observed since the findings from the Women's Health Initiative (WHI) were released.¹ The WHI study, which randomized healthy postmenopausal women to combined estrogen-progesterone HRT or placebo, was stopped in July 2002 because of a 1.26 increased relative risk of breast cancer in the treated cohort compared with placebo. Increased occurrence of cardiovascular disease and of other

cancers were subsequently reported. Five to six months following the release of this data, prescriptions for HRT fell by 38% to 50% in the U.S. The authors proposed that this precipitous drop in the prevalence of HRT use may have accounted for the observed decline in incidence of invasive breast cancer. Canadian data for 2002 to 2003 show a similar 6% decline in breast cancer incidence, and it will be interesting to see if there has been a similar decline in prescriptions for HRT.

OTHER POSSIBLE FACTORS

Another factor considered was mammographic screening rates over the same time interval: an absolute decrease of 3.2% was observed for women aged 50 to 64 years, and of 1.6% for those aged 75 years and older. An increase of 0.8% was noted in women aged 65 to 74 years. The investigators concluded, however, that these small changes were unlikely to account for the observed decline in breast cancer incidence. Also considered were changes in breast screening practices and changes in prevalence of raloxifene usage for prevention and therapy of osteoporosis: neither seems to have changed to a degree sufficient to explain the decline in breast cancer incidence.

If there has truly been a shift in carcinogenic potential due to the fall in HRT usage, a persistent downward trend in incidence may be observed. Indeed, if the drop in HRT usage is the only explanation, incidence rates should continue to fall in subsequent years. It is possible, however, that discontinuing HRT simply deprived subclinical disease of a potent growth factor, maintaining microscopic disease

in an undetectable state, and that in the absence of HRT, subclinical disease may yet progress to detectable disease at a later date — in which case the observed decline may be a temporary finding.

MORE FOLLOWUP NEEDED

Ongoing followup of these trends will be needed to confirm these data, establish the robustness of the current observation and shed more light on possible causative factors. The implication that the increased incidence of inva-

sive breast cancer observed in many developed countries may be partly or entirely due to iatrogenic causes is an important area of ongoing investigation and may hold many lessons for both the public health and epidemiologic domains.

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MATURE ANALYSIS FROM THE WOMEN'S INTERVENTION NUTRITION STUDY (WINS) EVALUATING DIETARY FAT REDUCTION AND BREAST CANCER OUTCOME. SABCS 2006, ABSTRACT 32.

Investigators: RT Chlebowski et al.

TRIAL SUMMARY: This prospective, multicentre, randomized Phase III study involved 2437 women with resected early-stage breast cancer whose baseline diet resulted in dietary fat making up 20% or more of their caloric intake. The women, aged 48 to 79 years, were randomized to a dietary adjuvant intervention aiming to reduce fat intake, yet maintain caloric adequacy (40% of study participants) or to continue their normal diet (60%).

Women in the intervention arm reduced their median fat intake by 18 to 19 grams/day ($p < 0.01$) and reduced the percent calories from fat by 8% to 9% ($p < 0.01$). They also experienced a mean weight reduction of 6 pounds and drop in BMI of 1.1 kg/m² ($p < 0.05$ for both). In contrast to the first interim analysis, and with a median followup time of 5.8 years, the difference in

relapse-free survival (i.e. survival without local, regional, distant, ipsi- and contralateral breast cancer recurrences) between the arms was not quite statistically significant (10.8% in the intervention group vs 12.9% in the controls (HR 0.79, 95% CI 0.62–1.00). Further, although disease-free survival events (breast cancer recurrences, second malignancies and deaths without breast cancer relapse) (15.9% vs 18.7%) and overall survival (7.7% vs 10.2%) were numerically superior for the intervention arms, these differences also were not statistically significant. An exploratory analysis showed that the only subset to experience a statistically significant improvement in relapse-free and overall survival were those women with estrogen- and progesterone-negative disease ($n = 147$ in the intervention arm vs 215 controls).

COMMENTARY: Daniel Rayson, MD, FRCPC, Chair Nova Scotia Provincial Breast Cancer Team, Associate Professor of Medicine, Dalhousie University, Halifax, NS.

These authors reported findings from the largest dietary intervention trial in breast cancer thus far completed. The WINS (Women's Intervention Nutrition Study) is a collaborative study that took place in 39 sites across the U.S. between 1997 and 2001. While the sample size is robust, the striking ratio of those eligible ($n = 5466$) compared to those screened ($n = 68,325$) emphasizes the difficulty in undertaking trials of this type, and serves as a cautionary note regarding the generalizability of any results. Of the 5466 women who were eligible, 2437 women consented to participate in the study. Because outcomes of women who discontinued study participation or who were lost to followup ($n = 387$) are not reported, definitive conclusions regarding efficacy outcomes for the primary endpoint of relapse-free survival are less certain.

The women who did participate had a median age of 58.5 years, with a median tumour size of 1.9 cm. Seventy-three percent had node-negative disease. All subjects had completed primary therapy for breast cancer, including chemotherapy for hormone receptor-negative disease, and were on tamoxifen for hormone-sensitive disease. The primary endpoint was relapse-free survival. The only statisti-

cally significant imbalance in baseline characteristics was that more women in the intervention arm had undergone a modified radical mastectomy (35.5% vs 29.9%, $p = 0.004$).

All participants kept a food diary to record their daily food consumption. A nutritionist met with women in the study arm every other week for 16 weeks for one-on-one counselling, followed by meetings every 3 months until study end. The study group diet contained approximately 33 grams of fat/day with the control group following their usual diet, containing approximately 57 grams of fat/day. Most women in both groups had sedentary lifestyles.

FURTHER STUDY DIFFICULT

The finding of numerically superior outcomes for the intervention arm, while not statistically significant, is provocative and probably merits further study — although, as is evident from this trial, design and implementation of large-scale dietary intervention trials are problematic. The finding of a statistically significant result for the small subset with hormone-negative disease must be considered as hypothesis-generating only, as this was not a planned subset analysis and was not powered to demonstrate a difference.

Hormonal therapy for breast cancer

FULVESTRANT VERSUS EXEMESTANE FOLLOWING PRIOR NON-STEROIDAL AI THERAPY: FIRST RESULTS FROM EFECT, A RANDOMIZED, PHASE III TRIAL IN POSTMENOPAUSAL WOMEN WITH ADVANCED BREAST CANCER. SABCS 2006, ABSTRACT 12.

Investigators: W. Gradishar et al.

TRIAL SUMMARY: EFECT is a randomized, multicentre, Phase III double-blind trial conducted in an effort to identify treatment options for postmenopausal women with hormone receptor-positive breast cancer following failure of nonsteroidal aromatase inhibitor (AI) therapy. Women were eligible to participate if they had disease progression or recurrence while on a nonsteroidal AI as adjuvant therapy or within 6 months of treatment discontinuation. The 693 enrolled patients received either exemestane 25 mg once a day orally (plus placebo) or intramuscular injection of fulvestrant with a loading dose of 500 mg on Day 0, followed by 250 mg on Days 14 and 28, followed by 250 mg every 28 days (plus placebo) until progression, death or withdrawal from the trial.

In this analysis, disease progressed in 288 (82.1%) patients receiving fulvestrant vs 299 (87.4%) of those

receiving exemestane. Median time to progression, the primary endpoint, was 3.7 months in both groups, with a HR of 0.96 (95% CI 0.82–1.13, $p = 0.65$). Objective response rates were 7.4% and 6.7% and clinical benefit rates were 32.2% vs 31.5% for fulvestrant vs exemestane, respectively (p -values insignificant). In responding patients, the median durations of response for fulvestrant vs exemestane, respectively, were 13.5 months vs 9.8 months and median durations of clinical benefit were 9.3 months vs 8.3 months. In the 60% of patients with visceral disease, clinical benefit rates were 29.1% and 27.2%. No significant differences were observed in adverse events. The authors concluded that fulvestrant represents another treatment option for women whose disease has progressed or recurred on a nonsteroidal AI.

COMMENTARY: Debjani Grenier, MD, FRCPC, Medical Oncologist, CancerCare Manitoba, St. Boniface General Hospital; Assistant Professor, University of Manitoba, Winnipeg MB.

Metastatic breast cancer remains mostly incurable: the main goals of treatment are to optimize quality of life, extend survival and palliate symptoms. Endocrine therapy remains the preferred option for many patients and several choices are available. In postmenopausal women, first-line endocrine therapy with an AI is the mainstay of therapy, based on several Phase III trials comparing first-line AIs to tamoxifen.¹⁻³ In general these trials showed improved tumour response rates, time to tumour progression and clinical benefit rates with AIs compared to tamoxifen, but no survival differences have yet emerged.

Exemestane is a steroidal AI and has demonstrated a clinical benefit rate of 20% as second- or third-line hormonal treatment after disease progression on a nonsteroidal AI.⁴ Fulvestrant is an estrogen receptor antagonist with no agonistic properties. It is indicated for the treatment of hormone receptor-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. The EFECT trial sought to determine which drug is more effective in postmenopausal women with metastatic breast cancer after disease has progressed or recurred on nonsteroidal AI therapy. Approximately 50% of the women had received at least 2 prior lines of endocrine therapy (usually including tamoxifen) and 56% of those enrolled had visceral metastases. Both drugs showed comparable efficacy in terms of overall response rates, time to progression and clinical benefit rate. Duration of response appeared to be higher in women on fulvestrant (13.5 months) compared to those on exemestane (9.8 months),

although this was determined retrospectively. Overall safety profiles were comparable with 2% of patients withdrawing from both groups due to adverse events.

This Phase III trial confirms the benefits of second- or third-line endocrine therapy after disease progression on a nonsteroidal AI in postmenopausal women. The clinical benefit rate is approximately 30% in patients who take exemestane or fulvestrant in this situation and both therapies are well tolerated. Results of the quality of life subprotocol from this trial are anticipated shortly. Another trial, SOFEA (Study of Faslodex versus Exemestane with/without Arimidex), has a schema similar to EFECT and has yet to report results.

CLINICAL IMPLICATIONS

Postmenopausal women who have progressive disease after letrozole or anastrozole could consider exemestane or fulvestrant therapy. A key issue for women will centre on the route of administration: fulvestrant is a monthly intramuscular injection while exemestane is a daily oral dosage, and there is an ease to oral therapy. As nonsteroidal AIs become the mainstay of adjuvant endocrine therapy for postmenopausal women with breast cancer, drugs such as exemestane, fulvestrant and tamoxifen are viable options for therapy upon relapse. Fulvestrant's exact place in the treatment algorithm needs further study, however, and its role continues to emerge. It may in fact be most effective in combination with an AI (providing complete estrogen blockade) and this strategy is being studied in the first-line metastatic

setting (SWOG [Southwest Oncology Group]/NCIC-CTG [National Cancer Institute of Canada–Clinical Trial Group] MAC.7 trial) as well as adjuvantly.

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Breast cancer prevention

LONG TERM EFFICACY OF TAMOXIFEN FOR CHEMOPREVENTION RESULTS OF THE IBIS-I STUDY. SABCS 2006, ABSTRACT 34.

Investigators: J. Cuzick et al.

TRIAL SUMMARY: This was an updated analysis of the International Breast Cancer Intervention Study (IBIS)-I study, which previously showed a reduction in risk of ER+ disease in women at high risk for breast cancer.¹ Study participants (n = 7154) were randomized to receive either tamoxifen 20 mg/day or placebo for 5 years. At a median followup of almost 96 months, 142 cancers in the tamoxifen group vs 195 in the placebo group were detected (odds ratio 0.73, 95% CI 0.58–0.91, p = 0.005). ER+ breast cancers were reduced by one third in women receiving tamoxifen but no difference was seen in the incidence of ER– can-

cers in the two groups. This effect of tamoxifen has remained fairly constant, and was similar in most subgroups examined except that women who also took hormone-replacement therapy (HRT) experienced no benefit. More women receiving tamoxifen (65) had died compared to the 55 in the placebo group, but the difference was not statistically significant (p = 0.36) and the difference between the 2 groups was less than in the earlier-reported analysis at 50 months followup (25 vs 11 deaths). Breast cancer-specific deaths were similar, with 13 in the tamoxifen arm vs 11 in the placebo arm.

20 YEAR FOLLOW-UP OF THE ROYAL MARSDEN TAMOXIFEN BREAST CANCER PREVENTION TRIAL. SABCS 2006, ABSTRACT 51.

Investigators: T.J. Powles et al.

TRIAL SUMMARY: This was the second planned analysis of this trial investigating the effect of tamoxifen on breast cancer incidence. Starting in 1986, 2494 healthy pre- and postmenopausal women were randomized to receive tamoxifen 20 mg/day or placebo for up to 8 years. The first analysis after 70 deaths in 1998 showed no difference between treatment groups.

At median followup of 13 years, 96 women receiving tamoxifen vs 113 receiving placebo have been diagnosed with breast cancer (HR 0.85, 95% CI 0.65–1.11, p = 0.2). In the tamoxifen vs placebo groups, respectively, 65% vs 83% of these cancers were ER-positive (HR 0.62, 95% CI 0.44–0.87, p = 0.005). As shown in **Table 9**, analysis of the 8-year treatment period vs the post-treatment period showed that the benefit was only for ER-positive cancer and that most of the benefit occurred in the followup period. The death rates were similar in both groups, and the toxicity profile was similar to that reported previously.

TABLE 9. Incidence of breast cancer on-treatment vs post-treatment effects of tamoxifen in the Royal Marsden tamoxifen breast cancer prevention trial

Time period	tamoxifen	placebo	hazard ratio (95% CI)	p-value
all breast cancers				
8 years on treatment	44	48	0.92 (0.61–1.38)	p = 0.7
post-treatment	38	56	0.68 (0.45–1.02)	p = 0.6
ER+ cancers				
8 years on treatment	30	39	0.77 (0.48–1.24)	p = 0.3
post-treatment	23	47	0.49 (0.30–0.80)	p = 0.005

LANDMARKS

COMMENTARY: Debjani Grenier, MD, FRCPC, Medical Oncologist, CancerCare Manitoba, St. Boniface General Hospital; Assistant Professor, University of Manitoba, Winnipeg, MB.

Four randomized controlled trials involving 28,000 women have reported potential benefit of tamoxifen compared to placebo in reducing the incidence of breast cancers in women at high risk for developing the disease. A meta-analysis of those trials showed a reduction in ER+ breast cancer incidence by approximately one half following 5 years of tamoxifen adjuvant therapy.¹

BENEFIT CONTINUES WITH LONGER FOLLOWUP

The IBIS-I study initially reported at a median followup of 5 years;² this current analysis is now at almost 8 years (95.6 months). Of the women enrolled, 26% were current or previous users of HRT. Notably, women on this trial remain blinded to their therapy assignment. A significant reduction in the incidence of ER+ invasive and in situ breast cancers was seen in women who received tamoxifen (3.9%) compared to a 5.5% rate in those on placebo. The odds ratio for developing breast cancer was 0.73 during the tamoxifen treatment phase compared to 0.57 after completing treatment, indicating the continuing benefit of tamoxifen even after its discontinuation. The mortality rate was 4.7% in women on placebo vs 6.4% in women who took tamoxifen, a non-statistically significant difference. Although the benefit of tamoxifen treatment appeared greater if women had no current or prior HRT use compared to if currently taking HRT, this difference was also not significant. Not surprisingly, most treatment-related side effects occurred during active therapy and the authors concluded that the risk-benefit ratio improves with longer followup. Eleven women on placebo developed uterine cancer vs 17 on tamoxifen with an odds ratio of 1.54 ($p = 0.25$); there were no deaths from uterine cancer in those who received tamoxifen.

The Royal Marsden Tamoxifen Breast Cancer Prevention Trial also explores the role of tamoxifen vs placebo in preventing breast cancers and is now at a median followup of 13 years. This is a smaller trial than the IBIS-I study, and tamoxifen was given for 5–8 years, but it also showed that tamoxifen significantly reduced the incidence of ER+ breast cancers — primarily in the post-treatment period — by approximately one-half (HR 0.49, 95% CI 0.30–0.80, $p = 0.005$).

These 2 trials have the longest followup of all the prevention trials. The continued blinded nature of therapy makes determination of an accurate risk-benefit ratio possible. This is not the situation with the similarly-designed but larger NSABP P-1 trial where treatments were unblinded once results were released.³ Ongoing trials exploring the role of AIs in breast cancer prevention in postmenopausal women include IBIS-II, the NSABP P-4 STELLAR (Study to Evaluate Letrozole and Raloxifene) trial and the NCIC-CTG MAP.3 trial.

CLINICAL IMPLICATIONS

These trials thus confirm the efficacy of 5 years of tamoxifen in reducing the incidence of ER+ breast cancers. Reassuringly, this benefit continues up to at least 5 years after discontinuing therapy. Survival, however, has thus far not improved using this therapy. A woman at high risk of developing breast cancer can consider that tamoxifen may reduce her chances of developing this disease, balanced with known toxicities that occur primarily during active therapy. The risk-benefit ratio fortunately appears to improve over time. Postmenopausal women also have the option of taking the selective estrogen receptor antagonist raloxifene, based on the results of the NSABP STAR (A Study of Tamoxifen and Raloxifene) trial.⁴ Efficacy of raloxifene in premenopausal women is unfortunately unknown.

Both the IBIS-I and Royal Marsden trials show that breast cancers can develop after completing 5 years of tamoxifen and that the benefits of therapy appear more pronounced after this time. A future strategy may be 5 years of tamoxifen in premenopausal patients followed by an AI in those women who subsequently become postmenopausal; this will be the basis of a future study.

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Breast cancer in premenopausal women

THE IMPACT OF TREATMENT-INDUCED AMENORRHEA ON SURVIVAL OF PREMENOPAUSAL PATIENTS WITH ENDOCRINE-RESPONSIVE BREAST CANCER: 10-YEAR RESULTS OF ABCSG-05 (CMF VS. GOSERELIN+TAMOXIFEN). SABCS 2006, ABSTRACT 17.

Investigators: M. Gnant et al.

TRIAL SUMMARY: This prospective randomized trial randomized 1099 premenopausal women with endocrine-responsive Stage I–II breast cancer to receive either 6 cycles of chemotherapy using cyclophosphamide, methotrexate

and fluorouracil (CMF) or 3 years of the luteinizing hormone-releasing hormone agonist (LHRHA) goserelin plus 5 years of tamoxifen (GosTam). At a median followup of almost 11 years, 10-year recurrence-free survival and

overall survival in all patients were equivalent at 82.7% and 84%, respectively. Treatment-induced amenorrhea was defined as no more menstrual periods from treatment month 3 to 6 and occurred in 53% of CMF patients and in all patients on GosTam. Recurrence-free survival significantly improved if there was treatment-induced amenorrhea (HR 0.58, 95% CI 0.40–0.83, $p = 0.003$) but overall survival did not improve significantly (HR 0.82, 95% CI

0.59–1.14, $p = 0.23$). Similarly, in the CMF group, treatment-induced amenorrhea predicted improved recurrence-free survival (HR 0.56, 95% CI 0.35–0.90, $p = 0.02$) but not overall survival (HR 0.79, 95% CI 0.53–1.16, $p = 0.23$). The prognostic impact of treatment-induced amenorrhea was primarily seen in women less than 40 years of age and in those with HER2-negative tumours.

COMMENTARY: Debjani Grenier, MD, FRCPC, Medical Oncologist, CancerCare Manitoba, St. Boniface General Hospital; Assistant Professor, University of Manitoba, Winnipeg MB.

Several retrospective studies have suggested that outcomes are poorer in young women with early breast cancer¹ and that the prognosis of women who develop amenorrhea during chemotherapy may be better than for those who continue to menstruate.^{2,3} Gnant et al report results of the ABCSG-05 (Austrian Breast & Colorectal Cancer Study Group) trial that compares outcomes of premenopausal women with breast cancer treated with 6 cycles of adjuvant CMF chemotherapy to those treated with 3 years of the LHRHA goserelin plus 5 years of tamoxifen.

At a median followup of almost 11 years there is no difference in recurrence-free survival between the 2 groups. 53% of women who received CMF became amenorrheic and experienced improved recurrence-free survival compared to those continuing menses, but there was no difference in overall survival between the 2 groups. Not surprisingly, the frequency of amenorrhea after CMF treatment increased with age, such that 30% of women under 40 years of age became menopausal vs 57% of those aged 41 to 50 years. Further, the prognostic impact of treatment-induced amenorrhea was seen mostly in women below the age of 40. Although these results need to be interpreted cautiously as the analysis is retrospective, the findings add to the growing body of evidence of poorer outcome in young women who continue to menstruate after adjuvant chemotherapy for breast cancer.

The 15-year update from the EBCTCG (Early Breast Cancer Trialists' Collaborative Group) confirms a reduction in breast cancer recurrences and mortality with ovarian function suppression (OFS) compared to no systemic therapy but the effects are smaller in the presence of chemotherapy.⁴ Cuzick et al also reported at this year's SABCS on the impact of LHRHAs on breast cancer recurrence and mortality, from an overview of 13 randomized clinical trials in women with hormone receptor-positive early breast cancer.⁵ They concluded that LHRHAs provided a small additional benefit after chemotherapy or after tamoxifen, at least in terms of less recurrences, but no differences in survival. LHRHAs were as effective as adjuvant chemotherapy but CMF was the primary regimen used in the trials.

The Suppression of Ovarian Function Trial (SOFT) is an international Phase III randomized-controlled trial exploring the potential benefit of OFS in premenopausal women with ER-positive breast cancers who have received either no chemotherapy or who remain premenopausal following completion of adjuvant and/or neoadjuvant chemotherapy.

They are randomized to 1 of 3 arms: 5 years of adjuvant tamoxifen alone, 5 years of tamoxifen + OFS or 5 years of the steroidal AI exemestane + OFS. It is anticipated that the results of this important trial will clarify the role of OFS added to standard adjuvant systemic therapy in premenopausal women.

CLINICAL IMPLICATIONS

Women with hormone-sensitive breast cancers who remain premenopausal after chemotherapy should be encouraged to participate in clinical trials of OFS, such as the SOFT study. Outside of clinical trials, however, such women should have a discussion about OFS — especially those under 40 years of age who are considered at high risk for breast cancer recurrence. They need to be informed that while Level 1 evidence for benefit of OFS in addition to standard systemic therapy is still lacking, younger women appear to have a poorer outcome if they remain premenopausal. The decision to have OFS needs to be balanced with known side effects due to rapid onset of menopause. Certain women with endocrine-sensitive breast cancers may also choose LHRHAs and tamoxifen instead of adjuvant chemotherapy but they should be aware that there is less data supporting this treatment strategy. Further, only a few trials comparing these modalities included an anthracycline-based regimen, and none included taxanes — the mainstays of current treatment.

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Biological markers and chemotherapy in breast cancer

TOPOISOMERASE II ALPHA PROTEIN OVEREXPRESSION HAS PREDICTIVE UTILITY IN A RANDOMIZED TRIAL COMPARING CMF TO CEF IN PREMENOPAUSAL WOMEN WITH NODE POSITIVE BREAST CANCER (NCIC CTG MA.5). SABCS 2006, ABSTRACT 38.

Investigators: F. O'Malley et al.

TRIAL SUMMARY: These authors assessed the prognostic and predictive utility of topoisomerase II alpha protein (topo2) overexpression in the NCIC-CTG MA.5 trial, which compared outcomes of an anthracycline vs a non-anthracycline regimen in 710 premenopausal women with node-positive breast cancer. Enrolled patients were randomized to receive adjuvant CEF (epirubicin 60 mg/m² + fluorouracil 500 mg/m², both intravenously, on Days 1 and 8, and cyclophosphamide 75 mg/m² orally on Days 1 through 14) vs CMF (methotrexate 40 mg/m² + fluorouracil 600 mg/m², both intravenously, on Days 1 and 8 and cyclophosphamide 100 mg/m² orally on Days 1 through 14), all for six 28-day cycles. Paraffin-embedded specimens from 480 (67%) of these patients were used to assemble tissue microarrays. The researchers assessed topo2 by immunohistochemistry (IHC) using the Ki-S1 antibody, counting the number of IHC-positive cells per 500 tumour cells and expressed this as a percentage; IHC results were available on 478 of 480 patients (99.6%). Cox models adjusting for other covariates were employed to assess interaction between treatment and topo2-overexpression.

With a threshold of 13%, 136 (28.5%) tumours exhibited topo2-overexpression. Differences in Nottingham tumour

grade ($p < 0.0001$) and estrogen receptor status ($p = 0.04$) were statistically significant between the samples with topo2-overexpression and those with no overexpression, with the 5-year relapse-free survival (adjusted $p = 0.18$) and overall survival ($p = 0.39$) not statistically different between the 2 groups. However, the differences seen between patients with topo2-overexpressing tumours according to whether they received CEF vs CMF were statistically significant for both disease-free survival (adjusted HR 0.49, 95% CI 0.28–0.85, $p = 0.01$) and overall survival (adjusted HR 0.51, 95% CI 0.28–0.93, $p = 0.03$). In patients lacking topo2-overexpression the differences were not statistically significant (relapse-free survival: adjusted HR 0.9, $p = 0.5$; overall survival: adjusted HR 0.98, $p = 0.91$). A statistically significant interaction was seen between topo2-overexpression and treatment for relapse-free survival (adjusted $p = 0.04$) and overall survival (adjusted $p = 0.03$). Thus, the authors concluded, topo2-overexpression is not a prognostic factor in previously untreated premenopausal women with node-positive breast cancer, but it does predict for improved disease-free and overall survival with CEF treatment.

A POOLED ANALYSIS ON THE INTERACTION BETWEEN HER-2 EXPRESSION AND RESPONSIVENESS OF BREAST CANCER TO ADJUVANT CHEMOTHERAPY. SABCS 2006, ABSTRACT 41.

Investigators: A. Gennari et al.

TRIAL SUMMARY: This group conducted a systematic review to evaluate the interaction between HER2 expression and responsiveness of breast cancer to adjuvant chemotherapy, specifically comparing anthracycline-based with non-anthracycline-based regimens, in studies that reported subset analyses according to HER2 expression. They followed standard meta-analysis procedures to obtain pooled estimates of the published disease-free and overall survival HRs. The rate of HER2-overexpression was 27.8% in 5099 patients with adequate data in 7 eligible studies.¹⁻⁷

As shown in **Table 10**, in the HER2-positive patients the HR for disease-free survival in anthracycline-receiving vs non-anthracycline-receiving groups was 0.71 (95% CI 0.61–0.83, $p = 0.0001$). For HER2-negative patients the HR difference between treatment groups was 0.98 (95% CI 0.88–1.09, $p = 0.75$). For overall survival, the HR pooled estimate was 0.73 (95% CI 0.62–0.85, $p = 0.0001$) in HER2-positive and 1.03 (95% CI 0.92–1.16, $p = 0.59$) in HER2-negative patients. The tests for interaction of treatment and HER2

TABLE 10. Pooled estimates for recurrence and mortality hazards ratios in patients receiving anthracycline vs non-anthracycline-based chemotherapy

	HER2-positive (HR, 95% CI, p-value)	HER2-negative (HR, 95% CI, p-value)
disease-free survival	0.71 95% CI 0.61–0.83 $p = 0.0001$	0.98 95% CI 0.88–1.09 $p = 0.75$
overall survival	0.73 95% CI 0.62–0.85 $p = 0.0001$	1.03 95% CI 0.92–1.16 $p = 0.59$

expression, both for disease-free and overall survival, yielded highly significant results (disease-free survival $\chi^2 = 10.9$, $p < 0.001$, overall survival $\chi^2 = 12.0$, $p < 0.001$), confirming

that the difference of anthracycline impact between HER2-positive and HER2-negative cases was indeed significant. The authors concluded that patients with HER2-overex-

pressing tumours appear to derive a greater advantage from anthracycline-based over non-anthracycline-based regimens compared to those with non-HER2-overexpressing tumours.

COMMENTARY: Joseph Ragaz, MD, FRCPC, Director, Clinical Research, McGill University Hospital, Royal Victoria Hospital, Montreal; Clinical Professor, Medicine & Oncology, McGill University, Montreal, Quebec.

In the late 1960s and 1970s, starting with the work of Edward Jensen, discovery of estrogen receptors (ERs) to predict outcomes and select breast cancer patients for endocrine treatment revolutionized approaches to the management of breast cancer. This inaugurated the concept of targeted therapy for breast cancer, permitting more sophisticated options in selecting and administering therapeutic agents. Therapies would be given according to a target — an identified molecule with a distinct association between the tumour and therapy — rather than blindly across the whole population. In the case of endocrine therapy, the target is associated with the agent's mode of action, as the estrogen receptors are related to the mechanism of hormonal membrane binding and transport to the nucleus.

In the case of the new class of biological therapeutics generally termed “targeted therapies” (e.g. trastuzumab, bevacizumab and imatinib), the targets are genetic markers including HER2, the VEGF receptor and c-KIT. These are all well known molecules with signalling pathways clearly associated with basic mechanisms of cancer biology. They are also implicated in the synthesis of biological agents via modern bioengineering processes: the target is identified first (e.g. the HER2/*Neu* molecule), then an agent is created to match the target (e.g. trastuzumab). Importantly, only the patients whose tumours express the target are treated. For example, in the case of trastuzumab, only the approximately 20% who are HER2-positive are treated.

TARGETING CHEMOTHERAPY

Until recently, this was not the case for chemotherapy, the most toxic oncology treatment. Chemotherapy is still given according to risk stratification, such as positive nodal status, rather than according to expression of molecular targets. Recent evidence, however, is causing chemotherapy to also undergo a shift towards treatment selection according to predictive targets for ER and HER2. Specifically, both Berry⁸ and Albain⁹ independently reported benefit of dose-dense or dose-intensive chemotherapy over conventional chemotherapy to be restricted to the ER-negative⁸ or HER2-positive cohorts,^{8,9} with ER-positive and/or HER2-negative cohorts deriving similar benefit from the conventionally dosed regimens. Thus, tumour markers such as ER or HER2, although not clearly related to the chemotherapy's mode of action, do have a potential to select for chemotherapy-treatment impact.

NEW EVIDENCE

The 2 excellent studies presented at SABCs 2006 summarized above epitomize this approach. The extension of the Canadian MA.5 trial determined with solid evidence, albeit in only 478 cases, that the benefit of the much more toxic

CEF regimen over the standard, relatively non-toxic CMF regimen is restricted to cohorts with overexpression of topo2, representing 30% or less of all high-risk patients. Pritchard et al recently reported a similar observation from the same trial regarding the value of HER2 status for predicting chemotherapy effect:¹⁰ CEF was superior to CMF in terms of disease-free and overall survival only among HER2-overexpressors (i.e. 20% to 25% of cases), while for the rest of the patients, CMF achieved similar results.

The meta-analysis by Gennari et al provides an almost identical conclusion. It encompasses a much larger number of cases with known HER2 status — over 5000 patients — and includes 7 large randomized adjuvant trials assessing anthracyclines vs non-anthracycline chemotherapy. The results confirm the MA.5 observations: the benefit of anthracyclines over non-anthracyclines is restricted to cohorts with HER2-positive status, with a highly significant test for interaction.

STRENGTH OF THE ARGUMENTS

What is the significance of these results, and do they provide a sufficient level of evidence to lead to change in practice? There is less doubt that in the case of topo2, a direct association between a drug and its target is clearly observed: absence of target (the topo2) = absence of benefit (of anthracyclines). While the sample size of the MA.5 topo2 trial is small, and it is only a retrospective analysis of one trial, the conclusion is backed by strong statistics. It is one of the first studies to implicate topo2 as a possible predictive target for selecting anthracycline adjuvant regimens for breast cancer. The first such observation was made by the Breast Cancer International Research Group (BCIRG) 006 trial, as presented by Slamon et al at the 2005 SABCs,¹¹ In that study, topo2-overexpression was significantly associated with greater benefit (but also more cardiotoxicity) of an anthracycline regimen, AC-docetaxel + trastuzumab, over a non-anthracycline regimen, carboplatin-docetaxel + trastuzumab.

While the interpretation of HER2 as a chemotherapy predictor is more difficult to explain than topo2, as HER2 is not a known direct chemotherapy target, the co-expression of HER2 and topo2 is a recognized phenomenon: both occupy the same amplicon, implicating common signalling pathways.¹² Another possible explanation for the strength of HER2 as a predictive chemotherapy selection marker is its association with other prognostic factors indicating high risk for relapse and a greater sensitivity to chemotherapy, e.g. negative estrogen receptors, high growth fraction (e.g. percentage of tumour cells that are actively dividing and giving rise to more cancer cells) and high proportion S-phase (the part of the cell division cycle during which DNA is duplicated).

LANDMARKS

SHOULD PRACTICE CHANGE?

Are we ready to introduce guideline-driven approaches towards selecting adjuvant chemotherapy regimens for breast cancer based on topo2 and HER2 markers? Without question, the MA.5 topo2 re-analysis and last year's BCIRG B-06 trial data provide strong evidence in favour of retesting samples from other dose-dense and dose-intensive adjuvant chemotherapy trials, or even starting prospective randomized trials. Similar conclusions surely apply to the HER2 reviews.

For individual community patients and their oncologists, however, the current topo2 and HER2 data may already be solid enough to guide chemotherapy selection — particularly when in doubt about the worth of chemotherapy for cases with high ER-positivity, good grade and low HER2 expression, despite otherwise seeming high-risk due to positive nodes or large tumour size. In such situations, the new data imply that obtaining additional information about topo2 and HER2 status may be helpful: for those patients in whom topo2 and HER2-expression are absent, the high-intensity anthracycline-based therapies may not be warranted.

The stakes are high as, in general, the dose-dense or dose-intensive anthracycline-containing regimens have become known as superior over the conventionally dosed regimens. For most high-risk breast cancer patients, these regimens presently constitute increasingly accepted guideline-based practice across North America and most of the western world. In view of the data presented above, however, their cost and toxicity could be prohibitive for large subsets of patients who derive only marginal benefit.

TOWARDS A NEW ERA

These important developments emphasize the advent of an era when fewer patients will be treated with cancer therapeutics and

therapy selection will be based on more refined tumour biology-related mechanisms, with much greater benefit. Thus, overall societal cost and patients' toxicities will be reduced significantly, while maintaining a similar population survival impact. This is an important message, and the speed with which these conclusions are incorporated into daily practice will affect the management of thousands of breast cancer cases across Canada.

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Combined hormonal and targeted therapy

TRASTUZUMAB PROLONGS PROGRESSION-FREE SURVIVAL IN HORMONE-DEPENDENT AND HER2-POSITIVE METASTATIC BREAST CANCER. SABCS 2006, ABSTRACT 3.

Investigators: J.R. Mackey et al.

TRIAL SUMMARY: The randomized, controlled, open-label, multicentre, Phase III TAnDEM (TrAstuzumab in Dual HER2 ER-positive Metastatic breast cancer) study explored the effect of combining treatments that target both HER2 and estrogen receptor (ER) signalling pathways in postmenopausal women with HER2-positive and ER-positive and/or progesterone receptor-positive metastatic breast cancer. Enrolled patients received either anastrozole only (1 mg/day orally) (n = 104) or anastrozole + trastuzumab (4 mg/kg by intravenous infusion on Day 1, then 2 mg/kg every week) until disease progression (n = 103). Progression-free survival — the primary endpoint — was significantly better in the patients receiving both trastuzumab and anastrozole (4.8 vs 2.4 months, p = 0.0016), as shown along with other endpoints in **Table 11**. The difference in overall survival was not statistically significant, but more

TABLE 11. Selected outcomes in patients receiving trastuzumab + anastrozole vs anastrozole alone in the TAnDEM study in postmenopausal women with HER2+, hormone receptor-positive metastatic breast cancer

	trastuzumab + anastrozole	anastrozole	p-value
Progression-free survival	4.8 months	2.4 months	p = 0.0016
Overall survival	28.5 months	23.9 months	p = 0.325
Clinical benefit rate	42.7%	29.9%	p = 0.026
Time to progression	4.8 months	2.4 months	p = 0.0007

than half of patients in the anastrozole-only arm chose to also receive trastuzumab upon disease progression. Among the subgroup of patients without liver metastases, those who received both trastuzumab and anastrozole (n = 77)

had significantly longer overall survival (41.3 vs 32.1 months, p = 0.04) and progression-free survival (7.7 vs 3.8 months, p = 0.0006) compared to those receiving anastrozole only (n = 73).

COMMENTARY: Hagen Kenneke, MD, MHA, FRCPC, Medical Oncologist, British Columbia Cancer Agency, Vancouver, BC.

Many posters and oral presentations at SABCS 2006 were dedicated to understanding the crosstalk between cell signalling pathways and to evaluating therapeutic interventions targeting multiple pathways. Dr. Richard J Santen was the 2006 William L. McGuire Lecturer and reviewed potential mechanisms of resistance to AI therapy including PI3K/AKT/mTOR and IGFR/EGF/MAPK pathways. Sabnis and Brodie reported results of in vitro studies of letrozole-resistant MCF-7Ca breast cancer cells treated with trastuzumab.¹ Therapy with trastuzumab in these ER+ breast cancer cells inhibited growth, reduced cell viability and reduced phosphorylated HER2 and MAPK levels. Combination therapy with trastuzumab and letrozole (as well as other AIs) reduced cell viability even further compared to trastuzumab alone (p < 0.001). The authors suggested that combined therapy with trastuzumab and AIs may be an attractive means to restore hormonal sensitivity and/or to prevent resistance.

TANDEM'S UNEXPECTED RESULTS

Dr. John Mackey presented the results of the TAnDEM study, a trial evaluating dual ER- and HER2 receptor-targeted therapy (summarized above). A relatively short duration of trial therapy was notable in both treatment arms: progression-free survival was 2.4 months among anastrozole-treated patients and 4.8 months in the trastuzumab + anastrozole group. While cross-trial comparison should be done with caution, trials of first-line AI vs tamoxifen therapy have demonstrated progression-free survival time of 8–11 months with AI therapy.^{2,3} Herceptin + chemotherapy combinations used in first-line treatment of metastatic breast cancer have yielded progression-free survival times of 7–11 months.^{4,5}

Thus, while the shorter than expected time to progression in both study arms makes the interpretation of the TAnDEM

trial more difficult, the trial results do suggest that hormonal therapy alone may be less effective than endocrine therapy plus trastuzumab in combined HER2+/ER+ metastatic breast cancer. A possible exception to the shorter than expected time to progression in TAnDEM may be the subset of patients without liver metastases, who had significantly longer progression-free survival with anastrozole, with and without trastuzumab. In this group, trastuzumab also significantly increased overall survival. This subset analysis was unplanned, however, and should be interpreted with caution.

The TAnDEM trial results confirm the benefit of trastuzumab therapy for HER2+/ER+ breast cancer. This study seems to bear out preclinical results pointing to increased efficacy and preservation of sensitivity to hormonal therapy by adding trastuzumab. Oncologists will likely continue to offer trastuzumab preferentially with chemotherapy to patients with HER2+/ER+ breast cancer, either after or before single-agent hormonal therapy. Future trials of combination trastuzumab + hormonal therapy without chemotherapy seem warranted, particularly for patients with more indolent, non-visceral metastases.

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Risk in T1a–bN0, HER2+ breast cancer

RECURRENCE RISK IN T1A-B, NODE NEGATIVE, HER2 POSITIVE BREAST CANCER. SABCS 2006, ABSTRACT 2037.

Investigators: D. Black et al.

TRIAL SUMMARY: This study examined recurrence risk in T1a–b (i.e. primary tumour ≤ 1 cm) breast cancer compared to that in T1c (1.1–2 cm) and T2 (2.1–5 cm), node-negative HER2+ breast cancer. Investigators reviewed the records of 164 patients with node-negative breast cancers ≤ 5 cm who

had HER2 testing at the time of diagnosis. The average age was 54 years, 27 patients had T1a tumours, 47 had T1b, 60 had T1c and 30 had T2; 48% of tumours were Grade 3, 24% had lymph vessel invasion and 76% were ER+. Among patients with tumours <1 cm, 34% received chemotherapy

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and 54% received hormonal therapy. Those who received chemotherapy experienced fewer recurrences (4%) than those without (17%), but the difference was not statistically significant. Disease-free survival at 5 years was higher among patients with T1a-b (90.5%) and T1c (89.5%) compared with T2 (79.5%) tumours, as shown along with other endpoints in **Table 12**. The authors concluded that these findings indicate moderate risk for locoregional and distant recurrence of breast cancer in patients with HER2+ breast cancers ≤ 1 cm, and that further studies are needed to assess the impact on recurrence following treatment with chemotherapy, hormonal therapy and HER2-targeted therapy.

TABLE 12. Recurrence events in node-negative HER2+ breast cancer at 5-year median followup

Stage (n)	Any event	distant metastasis (%)	locoregional events (%)	contralateral events (%)
T1 a-b (74)	14 (19%)	6 (8)	4 (5.4)	4 (5.4)
T1c (60)	9 (15%)	3 (5)	3 (5)	3 (5)
T2 (30)	7 (23%)	4 (13)	2 (6.7)	1 (3.3)

POOR 10 YR BREAST CANCER SPECIFIC SURVIVAL AND REPLAPSE FREE SURVIVAL FOR HER2 POSITIVE T1N0 TUMORS. SABCS 2006, ABSTRACT 2031.

Investigators: B. Norris et al.

TRIAL SUMMARY: These investigators accessed a 4444-case tumour tissue array of patients diagnosed with breast cancer in British Columbia between 1986 and 1992 and referred to the British Columbia Cancer Agency (BCCA). Out of 3836 cases identified who were female with invasive disease and in whom both ER and HER2 could be determined, 1245 had T1N0 stage breast cancer. Median followup was 12.5 years. HER2 was scored positive if IHC3+ or FISH-amplified. Relapse-free survival and breast cancer-specific mortality were determined. The overall HER2+ rate was 16%, 62% of HER2+ cases were Grade 3 and 41% were ER+. Among the 1245 T1N0 cases, 90.6% were HER2- and 9.4% were HER2+. Seventy-five percent of the T1N0 cases received no adjuvant systemic therapy. Breast cancer-specific mortality was significantly worse in HER2+ cases (18.7%) than in those that were HER2- (9.9%) ($p = 0.031$) (**Table 13**). Only 21 patients had T1a-b, HER2+ disease, of whom 5 (24%) received adjuvant systemic therapy. Breast cancer-specific

TABLE 13. Outcomes of BCCA database patients with T1N0 disease according to HER2 status

T1N0 n = 1245	HER2- n = 1128 (90.6%)	HER2+ n = 117 (9.4%)
10 year breast cancer specific mortality	9.9%	18.7%
10 year relapse free survival	78.7%	71.6%

mortality was 9.8% and relapse-free survival was 75.6%. The authors concluded that HER2-overexpression correlates with a poorer outcome both in the entire population and the T1N0 subset, and they suggest considering adjuvant systemic therapy including trastuzumab for these women.

COMMENTARY: Hagen Kennecke, MD, MHA, FRCPC, Medical Oncologist, British Columbia Cancer Agency, Vancouver, BC.

Previous studies have established that high-risk, ≥ 1 cm, HER2+ breast cancers, both node-positive and node-negative, experience significant reductions in recurrence when treated with adjuvant trastuzumab. However, patients with node-negative tumours < 1 cm are excluded from adjuvant trastuzumab trials as well as from most guidelines for adjuvant therapy of HER2+ breast cancer. Norris et al have convincingly demonstrated that HER2 positivity significantly increases the risk of relapse and mortality in patients with T1N0 breast cancer. For T1a-bN0, HER2+ disease, both studies have contributed significantly by adding to the very limited information about risk of relapse in this cohort.

In a Finnish population-based study, Joensuu et al¹ previously reported on amplification of *erbB2* as a risk factor for distant recurrence. This study included 852

patients with unilateral T1 node-negative breast cancer and had a median followup time of 9.5 years. Only 5% of participants received systemic adjuvant therapy. Among 12 patients with 1-10 mm tumours and HER2+ amplification as defined by immunohistochemistry 3+ or chromogenic in situ hybridization, distant disease-free survival was 67%.

Table 14 summarizes results of all 3 studies.

CLINICAL IMPLICATIONS

When interpreting these results, it should be kept in mind that the studies are limited by small subgroup size, potential referral bias and retrospective biases. The proportion of patients receiving adjuvant systemic therapy was also variable. Nevertheless, it is notable that the risk of distant relapse or death described in the current abstracts is lower than that described by Joensuu et al. Risk of distant recur-

rence was 33% in the Finnish study in comparison to the current studies, which reported distant relapse and mortality risks of 8% and 9.8%, respectively. This may be due to shorter followup time in the case of the Dana Farber cohort, although recent trials of adjuvant trastuzumab therapy imply that HER2+ disease tends to relapse early. There was also variability in the rate of adjuvant systemic therapy given, with a higher rate in the BCCA and Dana Farber cohorts than in the Finnish group.

Overall, the studies indicate that the risk of distant metastasis and breast cancer specific-death is moderate in patients with T1a-bN0, HER2+ breast cancer. With earlier detection due to mammography and breast self-examination, such patients may represent an increasing proportion of patients today

TABLE 14. Outcomes of patients with T1a–b, N0 tumours overexpressing HER2 in 3 retrospective cohorts

Cohort	% receiving other therapies	median followup	Risk
Dana Farber Cancer Institute (n = 74)	34% chemotherapy 54% hormone therapy	5 years	distant relapse risk: 8% breast cancer event risk: 19%
British Columbia Cancer Agency (n = 21)	24% adjuvant systemic therapy	10 years	breast cancer-specific mortality: 9.8% relapse-free survival: 75.6%
Finnish Cancer Registry (n = 12)	5% adjuvant systemic therapy	9.5 years	distant disease-free survival: 67%

compared to the past. Decisions surrounding benefit of adjuvant systemic therapy are challenging for physicians and patients alike for this subgroup and studies of adjuvant systemic therapy seem warranted.

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Cancer stem cells and resistance to treatment

BREAST CANCER STEM CELLS ARE RESPONSIBLE FOR THERAPEUTIC RESISTANCE AND RESIDUAL DISEASE. SABCS 2006, ABSTRACT 205.

Investigators: J.C. Chang et al.

TRIAL SUMMARY: These researchers obtained paired breast cancer core biopsies from patients before and 12 weeks after treatment with neoadjuvant chemotherapy to test the hypothesis that breast tumours contain a subpopulation of cancer stem cells that is resistant to conventional therapy, so that after conventional therapy residual tumours contain a higher level of cancer stem cells with increased tumourigenic ability. They performed gene expression array analyses using hybridization to Affymetrix U133 chips, compared mammosphere formation (i.e. spherical colonies of cells of mammary origin grown in suspension) in culture, and performed xenotransplantation (i.e. human tumour cells implanted in immunocompromised mice to overcome cellular rejection between species) assays in SCID/Beige mice

before and after treatment. They found that the molecular pattern in residual cancer cells showed decreases in patterns associated with cell proliferation and apoptosis, and increases in putative stem cell markers. Specifically, gene expression of stem cell self-renewal pathways CD44, CD133 (PROM1), cell cycle inhibitors (cdk), integrins (α6, β1), polycomb, and members of IGF and Wnt pathways were increased after neoadjuvant chemotherapy. The researchers also observed a positive correlation between the number of CD44+/CD24-/lineage-negative (Lin-) cells and mammosphere-forming ability (r = 0.8, p < 0.05). Furthermore, xenograft tumours were successfully established in SCID/Beige mice from 3 out of 4 post-chemotherapy biopsies, compared to 1 out of 5 pre-chemotherapy biopsies.

BREAST CANCER STEM CELLS AND TAMOXIFEN RESISTANCE. SABCS 2006, ABSTRACT 206.

Investigators: J. Selever et al.

TRIAL SUMMARY: In this study, the researchers hypothesized that a key component of resistance to hormonal therapy in breast cancer may be the stem cell growth regulator

Dicer, a RNase III-family nuclease that initiates microRNA interference, and that Dicer overexpression modulates breast cancer stem cells, increasing their resistance to the growth

LANDMARKS

inhibitory effects of hormonal agents. They grew mammospheres using 4 human breast adenocarcinoma cell lines:

- MCF-7 parental (i.e. original cell line of human adenocarcinoma)
- MCF-7 vector control-transfected (i.e. cells transfected with an inactive substance)
- MCF-7-Dicer-transfected cells
- MCF-7 tamoxifen resistant (MCF-7-TR) cells.

The researchers analyzed protein lysates from the mammospheres for estrogen receptor alpha (ER α) and breast cancer resistance protein 1 (BCRP1) expression. They also studied these cells using flow cytometry for Hoechst 33342 dye efflux (a substance which stem cells and chemotherapy-resistant cancer cells exclude) and the putative stem cell

markers CD44+/CD24-. They found that primary and secondary mammosphere formation was enhanced in MCF-7-TR cells, as compared with MCF-7 parental cells. In addition, the MCF-7-TR cells contained an increased CD44+/CD24- population. Finally, the MCF-7-Dicer-overexpressing cells treated with tamoxifen exhibited both increased mammosphere formation and a greater efflux of the Hoechst 33342 dye, suggestive of an enhanced "side population" (cellular staining with the Hoechst 33342 dye followed by the simultaneous detection using flow cytometry of Hoechst fluorescence at 2 well-defined emission wavelengths plotted against each other, resolves this small and distinct cellular population, enriched in stem cells and chemotherapy-resistant cancer cells).

STEM/PROGENITOR PHENOTYPES IN MCF-7 CELLS ARE ASSOCIATED WITH RADIATION RESISTANCE. SABCS 2006, ABSTRACT 207.

Investigators: J. Li et al.

TRIAL SUMMARY: This group studied the hypothesis that a subpopulation of MCF-7 cells with selected stem/progenitor cell phenotypes is resistant to radiation. They had previously shown that the side population of normal mouse mammary glands are resistant to radiation. They used flow cytometry to examine putative stem/progenitor phenotypes in MCF-7 cells before and after radiation. The side population of MCF-7 cells

was found to contain larger quantities of stem/progenitor cell phenotypes after radiation, suggesting that the non-stem/progenitor population had been selectively killed. Finally, selection for MCF-7 cells using mammosphere passage (serial isolation of cells from growing cell clusters in suspension which subsequently grow to produce new mammospheres) identified a subpopulation of cells resistant to radiation.

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A PARADIGM SHIFT

As the San Antonio Breast Cancer Symposium highlights the principal advances in breast cancer research, a section of this symposium was dedicated to breast stem cells. The current focus on breast stem cells represents a paradigm shift in oncology.^{1,3} In the traditional stochastic model, most cancer cells can proliferate extensively to form new tumours. In the cancer stem cell model, only rare cancer stem cells have the intrinsic ability to proliferate extensively to form new tumours.^{1,4}

In this context, effective therapies should target cancer stem cells, while sparing normal cells. Therapies that kill cancer cells but not cancer stem cells may lead to tumour regression, but disease will subsequently recur as the cancer stem cells act as lethal seeds to repopulate the tumour.⁴ Thus, tumour regression in itself may represent an incomplete clinical endpoint. In the presence of therapies that kill cancer stem cells, tumours lose their ability to generate new cells, and subsequently degenerate, leading to complete tumour eradication.

CANCER STEM CELLS AS A THERAPEUTIC TARGET

Stem cells are multipotent cells with high proliferative capacities and the concomitant properties of self-renewal and differentiation into multilineage cells. Recent findings suggest that stem cell properties are integral to the formation and

perpetuation of human cancers, including breast cancer.⁵ The current hypothesis suggests that the most primitive human breast stem cell does not express the estrogen receptor while more mature progenitors may or may not express estrogen receptor depending on their location in the differentiation pathway.⁶ The highly proliferative capacities of stem cells may drive the continued expansion of malignant cells. As cellular proliferation decreases with differentiation, the long-lived and slowly dividing stem and progenitor cells (cells which can replicate themselves and differentiate but lack the self-renewal capacity of stem cells) are likely candidates for the accumulation of mutations associated with carcinogenesis.^{2,6}

Tumour-initiating cells with stem cell properties are termed "cancer stem cells." Given the parallels between normal and cancer stem cells, it has been suggested that cancer stem cells arise from mutations in normal stem cells, and are responsible for the proliferative capacity of cancers.⁵ Mutated progenitor cells that acquire self-renewal properties may also become cancer stem cells.^{5,7} The accumulation of mutations in cancer stem cells may disrupt the tight control of normal stem cells, leading to deregulation of self-renewal and tumourigenesis, loss of asymmetric division, and aberrant differentiation resulting in tumour heterogeneity.^{6,8} The fate of stem cells, including self-renewal and differentiation, may be determined by the stem

cell niche (i.e. the cellular microenvironment providing necessary support and stimuli to sustain self-renewal) and other environmental factors.^{2,6,7,9-12} Cancer stem cells may also acquire features associated with tumour progression, metastases and therapeutic failure, including genetic instability and drug resistance.² Mechanisms of therapeutic resistance include cellular quiescence and the acquisition of protein expression responsible for the cellular efflux of chemotherapeutic agents, as described in the 3 trial summaries above.

The elimination of the cancer stem cell compartment of a tumour may be essential to achieve stable, long-lasting remission of cancer. Therapeutic strategies designed to eradicate the cancer stem compartment should selectively, or at least preferentially, target the self-renewal, survival and proliferative pathways specific to cancer stem cells. Thus, advances in our knowledge of stem cell properties are pivotal to the specific and effective targeting of these cells in therapeutic strategies, including cancer therapies.

MAMMARY CELL PROGENITORS

The human mammary gland is organized during development as a hierarchy of stem and progenitor cells that are progressively limited in their multilineage potential and proliferative capacity. The transplantation of mammary cells into cleared (epithelium-free) murine fat pads is a functional assay used to identify mammary epithelial cells with stem cell properties.^{13,14} The existence of a stem cell origin of murine mammary development was established using studies of transplants of cells at limiting dilutions (i.e. dilution of a cell suspension to yield a single cell per well, which will then proliferate as an isolated clone of cells derived from a single cell). This allowed confirmation of the clonal nature of the regenerated alveolar, ductal and more complex structures.¹⁴⁻¹⁷ The unequivocal demonstration of the existence of a murine mammary stem cell occurred with the reconstitution of a complete and functional mammary gland from a single Lin⁻/CD24⁺/CD29⁺ cell.¹⁸

Three types of murine mammary epithelial cell progenitors have been identified.^{14,16,17} The first is a bipotent progenitor with features of both luminal and myoepithelial characteristics, the second type has luminal features and the third has myoepithelial features. Analogous human studies of stem and progenitor cells have been limited by the challenges associated with the development of suitable *in vivo* xenotransplant assays. Thus, numerous efforts have been undertaken to optimize conditions that support the *in vitro* growth and differentiation of primitive human epithelial cells seeded at clonal densities. These include the proliferation of non-adherent mammospheres in suspension from samples of human breast cancer tissues^{10,19} and murine mammary fat pads.²⁰ These mammospheres contain an enhanced quantity of stem and progenitor cells as illustrated by their ability to differentiate along all 3 mammary epithelial lineages and to clonally generate complex functional structures in reconstituted 3-dimensional culture systems.¹⁰ Additional studies used to characterize stem and progenitor cells include the identification of side populations (i.e. low Hoechst dye 33342-retaining populations) using flow cytometry.^{21,22} This side population is enriched 30-fold in mammospheres from human tissues.¹⁰

The use of this *in vitro* assay subsequently led to the discovery that the Notch signalling pathway plays a pivotal role in normal human mammary development by acting on both stem and progenitor cells, concurrently affecting self-renewal and lineage-specific differentiation. As a result, it was proposed that abnormal Notch signalling may contribute to mammary carcinogenesis by deregulating the self-renewal of normal mammary stem cells.¹⁹ Additional pathways involved in stem cell self-renewal include Hedgehog, Bmi-1, Wnt, and PTEN.^{2,23,24}

Further studies in human breast stem and/or progenitor cells include the identification of a subset of human breast cancer cells, isolated using flow cytometry with the phenotype CD44⁺/CD24⁻/Lin⁻, that possessed highly tumourigenic properties in a NOD/SCID (an immunodeficient mouse) xenograft model.¹³ As few as 200 cells with the ESA⁺ (epithelial-specific antigen), CD44⁺/CD24⁻/Lin⁻ phenotype consistently generated tumours in mice, whereas even 20,000 cells with alternative phenotypes did not. After this tumourigenic cell population was isolated and serially passaged in NOD/SCID mice, CD44⁺/CD24⁻/Lin⁻ cells gave rise to additional tumourigenic CD44⁺/CD24⁻/Lin⁻ cells, as well as phenotypically diverse non-tumourigenic cells that composed the bulk of the tumours. While the unequivocal demonstration of human stem cell characteristics necessitates the development of model systems capable of tumour generation from a single cell, CD44⁺/CD24⁻/Lin⁻ cells appear to exhibit properties of human breast stem/progenitor cells in NOD/SCID mice.


INVESTIGATIONS OF THERAPEUTIC RESISTANCE

J.C. Chang et al presented data at the 2006 SABCS suggesting that treatment with neoadjuvant chemotherapy resulted in an enrichment of therapy-resistant cancer stem cells. Breast cancer core samples taken from women 12 weeks after chemotherapy showed increased gene expression patterns associated with putative stem cell properties and their associated self-renewal pathways, numbers of cells bearing putative cancer stem cell markers (CD44⁺/CD24⁻/Lin⁻) and tumourigenicity of residual tumours compared to samples taken prior to chemotherapy administration, albeit with a limited number of samples. Similarly, another recent study suggests that human breast cancer cell lines that express CD44⁺/CD24⁻ also express higher levels of proinvasive genes and have highly metastatic properties.²⁵

The results presented by Selever et al suggested that tamoxifen treatment of MCF-7-TR and MCF-7-Dicer-overexpressing cells enriches their content of putative stem cells, specifically those with the markers CD44⁺/CD24⁻. This cellular population may be involved in the emergence of tamoxifen-resistant growth and the recurrence and metastasis of breast cancer. Similar studies that include Lin⁻ as a putative cancer stem cell marker and clinical samples pre- and post-tamoxifen therapy would be of interest, as well as an assessment of the corresponding tumourigenicity using xenotransplantation. In addition, a better understanding of the effect of current therapies on the cancer stem cell population is pivotal. Current therapies may yield tumour regression principally based on the destruction of differentiating cells, while sparing cancer stem cells.

These cancer stem cells may subsequently self-renew and proliferate to yield a relapse of the tumour. Thus, further studies to accurately identify the stem cell population are critical, so that an assessment of the residual tumour burden and therapeutic response may be accurately performed with high levels of sensitivity. Also critical, with regard to hormonal therapy, is determining the hormonal responsiveness of the most primitive human breast stem cell, which is currently thought not to express the estrogen receptor.^{2,6}

Li et al found that radiation appears to increase the population of stem cells in a line of breast cancer cells. This group's data concurs with a recently published report demonstrating in human cells that the CD44+, CD24-/low, subpopulation of MCF-7 and MDA-MB-231 cells is relatively radiation-resistant, and increases in numbers after short courses of fractionated radiation.²⁶ Future studies using clinical samples pre- and post-radiotherapy will be of interest, as well as an assessment of the corresponding tumorigenicity using xenotransplantation. Determination of the effectiveness of radiotherapy on cancer stem cell eradication will require the definition and sensitive detection of markers of these cells.

Additional challenges in the design of effective therapeutic strategies which selectively eliminate cancer stem cells include overcoming the slow cell cycle kinetics and active DNA repair, and the anti-apoptotic mechanisms associated with these cells.² 

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Disclosure

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