



EVIDENCE WATCH

A review and assessment of recent clinical trial data

Oncology Exchange provides overviews of important clinical trial data presented at the 30th San Antonio Breast Cancer Symposium (SABCS), held December 13–16, 2007, and the 49th Annual Meeting of the American Society of Hematology (ASH), held December 8–11, 2007 in Atlanta, Georgia. Leading Canadian experts offer commentary and clinical interpretations. Reporting on both conferences will continue in the next issue of *Oncology Exchange*.

PRESENTATIONS FROM THE 30TH SAN ANTONIO BREAST CANCER SYMPOSIUM

Contributors were selected by Joseph Ragaz, MD, FRCPC, McGill University, Montreal, QC.

Neoadjuvant lapatinib

Joseph Ragaz, MD, FRCPC

DECREASE IN TUMORIGENIC BREAST CANCER STEM CELLS IN PRIMARY BREAST CANCERS WITH NEOADJUVANT LAPATINIB. SABCS 2007, ABSTRACT 82.

Investigators: X. Li et al.

TRIAL SUMMARY: This group had previously shown that breast cancer stem cells that overexpress CD44 and express little or no CD24 (CD44+/CD24-/low cells) are resistant to conventional chemotherapy; that following conventional chemotherapy, more of these cells are present; that they are tumorigenic in vitro (as assessed by mammosphere formation) and in animal studies (as assessed by xenograft transplantation assay); and that they have abnormal molecular pathways including epidermal growth factor receptor (EGFR, also known as HER1) and HER2. In this prospective, Phase I–II trial, 30 women with locally advanced HER2-overexpressing breast cancer received the tyrosine kinase inhibitor lapatinib as monotherapy for 6 weeks, and then 12 weeks of weekly trastu-

zumab plus 3-weekly docetaxel, followed by surgery. Assessment of biopsies taken at diagnosis and after week 6 of the lapatinib treatment showed that median tumour response was 60.8% (range 0 to 86.5%, $p = 0.001$) and that levels of CD44+/CD24-/low breast cancer stem cells decreased from 10.6% to 4.7%. Mammosphere assays showed reduced self-renewal capacity from 30 to 15 mammospheres/10,000 cells ($p = 0.01$). The pathologic complete response rate was 63% (16 out of 25). The authors note that this is the first time neoadjuvant therapy has been shown to reduce tumorigenic breast cancer stem cells in primary breast cancers. These results suggest that therapies targeting the pathways responsible for stem cell renewal may achieve long-term cure of breast cancer.

COMMENTARY: Joseph Ragaz, MD, FRCPC, Medical Oncologist; Clinical Professor and Senior Oncology Researcher, McGill University Departments of Medicine and Oncology, Montreal, QC.

This study from Li et al's group at Baylor College of Medicine (Houston, TX) on lapatinib's role in neoadjuvant treatment for breast cancer was unique for the unexpected finding of stem cell reduction — the first time such a benefit has been reported for a therapeutic agent in human breast cancer. This was in addition to showing that the

preoperative regimen of lapatinib + trastuzumab + docetaxel provided an unusually high pathologic complete response rate (pCR) of 63%. The same research group previously reported < 35% pCR using taxane-containing chemotherapy without biologic agents.¹

LAPATINIB BACKGROUND

Lapatinib is the only available oral agent for breast cancer that targets and effectively blocks both EGFR (HER1) and HER2 receptors. Its documented clinical effects in patients who have relapsed on trastuzumab^{2,3} implicate the HER1/EGFR receptor pathway as an important mechanism in breast cancer biology. Prior analysis of the Baylor College database on over 2500 patients showed in 2006 that HER1 status, while positive in just over 18% of cases, is significantly associated with a high-risk breast cancer phenotype that includes estrogen receptor negativity, high S-phase fraction, HER2 positivity and poor differentiation. Compared to HER1 non-expressers, women with HER1-positive tumours have significantly higher rates of relapse (hazard ratio [HR] 1.6, $p = 0.001$) and death (HR 1.7, $p = 0.001$).⁴

Confirming the significance of HER1 in breast cancer, recent Phase II and III trials have shown a beneficial impact of lapatinib in advanced metastatic and inflammatory disease that has relapsed on treatment with trastuzumab + chemotherapy combinations. In the largest of these, Geyer et al randomized 321 patients with HER2-positive Stage IV breast cancer, who had relapsed on past chemotherapy including trastuzumab, to capecitabine + lapatinib vs capecitabine alone.³ The overall response rate (complete [CR] + partial [PR]) and time to progression (TTP) were significantly prolonged in the group receiving the lapatinib + capecitabine combination compared to those receiving capecitabine alone, with CR + PR rates of 22% vs 14% and median TTP of 8.4 months vs 4.4 months (HR 0.491, 95% CI 0.34 to 0.71, $p < 0.01$).

Lapatinib is given orally and is relatively safe compared to other agents. In Geyer et al's randomized study, the main adverse events in the combination-therapy group were diarrhea, hand-foot syndrome and nausea. Adverse events led to discontinuation of treatment in 22 women in the combination capecitabine + lapatinib group (13%) vs 18 in the capecitabine monotherapy group (12%).

EFFECT ON CANCER STEM CELLS

Li et al's study showed the provocative finding of significant cancer stem cell reduction after lapatinib neoadjuvant monotherapy. The CD 44+/CD24-/low cell count, considered a marker for stem cells, dropped from 10.6% at baseline to 4.7% after 6 weeks of lapatinib monotherapy. Mammosphere assays measuring the self-renewing stem cell population (also using CD44+/CD24-/low marker stem cells) showed a 50% reduction from 30 to 15 mammospheres/10,000 cells. Last year, using the same stem cell assay, this group showed that conventional state-of-the-art taxane-containing chemotherapy without biologics had no

impact on the stem cell population, despite objective responses by tumour volume measurements.¹ On the contrary, their work documented that post-treatment resistance to chemotherapy, tamoxifen and radiation without biologics is followed by a surge in CD 44+/CD24-/low stem cell count. The seminal question of causality vs effect — specifically, does the increase in stem cell count associated with conventional cancer therapy represent a cause or a consequence of therapeutic resistance — has not yet been addressed or tested prospectively. Li et al's study lends credence to the concept of stem cells' importance in propagating cancer and to the idea that systemic therapy must be capable of selectively eradicating the stem cells. The results indicate that biologics may have the potential to affect stem cells — a point particularly important in view of the increasingly accepted hypothesis that cure requires the complete abolition of cancer stem cells.

NEXT STEPS

Several North American and European controlled trials of lapatinib are underway or in the planning stages, with at least 3 adjuvant therapy trials recently initiated. Of these, Canadian oncologists have the opportunity to participate in the Phase III Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO) study (BIG 2-06/N063D, NCT00490139), which will randomize patients with HER2-overexpressing and/or -amplified breast cancer to any chemotherapy plus 4 targeted therapy options: lapatinib alone, trastuzumab alone, lapatinib given concomitantly with trastuzumab (these 3 all for 1 year) and trastuzumab for 6 months followed by lapatinib for 6 months.

As of January, 2008, individual U.S.-based institutions can offer lapatinib for Stage IV disease, but it is not available in Canada. While there is intense lobbying to release lapatinib for routine use after trastuzumab, particularly for high-risk cases, neither the Canadian or U.S. regulatory bodies have officially approved lapatinib for early breast cancer outside controlled trials. No doubt, the present study will facilitate acceptance of lapatinib and will stimulate additional neoadjuvant and adjuvant trials of this promising agent.

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Adjuvant chemotherapy in high-risk breast cancer

Sunil Verma, MD, MEd, FRCP and Danny Robson, MD, FRCPC

HIGH-DOSE CHEMOTHERAPY WITH AUTOLOGOUS STEM-CELL SUPPORT VERSUS STANDARD-DOSE CHEMOTHERAPY: META-ANALYSIS OF INDIVIDUAL PATIENT DATA FROM 15 RANDOMIZED ADJUVANT BREAST CANCER TRIALS. SABCS 2007, ABSTRACT 11.

Investigators: D.A. Berry et al.

TRIAL SUMMARY: Some women with breast cancer who have 4 or more positive lymph nodes, and thus are at high risk of recurrence, have been treated with adjuvant high-dose chemotherapy with autologous hematopoietic stem-cell transplant (HDC), but the number of patients in each trial for which data is available has been too limited to determine the benefit of this treatment. Berry et al's group conducted a meta-analysis on 6210 individual patient records from 15 randomized trials; 3118 of the women received HDC and 3092 received standard-dose chemotherapy (SDC). Median followup was 6 years, ranging from 0 to 15.3 years; median age was 46 years, ranging from 20 to 67 years; and 46.8% of tumours were hormone receptor-positive, 23.7% were negative and 29.5% had unknown hormone receptor status. By Cox proportional hazards regression adjusted for age and trial, women receiving

HDC had statistically significantly longer disease-free survival (DFS), with a HR of 0.87 (95% CI 0.81 to 0.940, $p = 0.0001$). Breast cancer-specific survival (BCSS) was not improved, however (HR 0.93, CI 0.85 to 1.02, $p = 0.10$), nor was overall survival (OS) (HR 0.95, CI 0.87 to 1.02, $p = 0.16$). After adjusting for hormone receptor status in patients for whom it was known, a greater benefit of HDC on DFS was seen (HR 0.83, CI 0.77 to 0.90, $p < 0.0001$), with some benefit on BCSS and OS, with HR for BCSS of 0.88 (CI 0.79 to 0.97, $p = 0.013$) and HR for OS of 0.89 (CI 0.82 to 0.98, $p = 0.016$). The authors concluded that HDC prolongs DFS overall and provides modest benefit on BCSS and OS in women with hormone receptor-positive disease. Importantly, they noted, the regimens used in the SDC arms did not involve modern adjuvant therapies including taxanes and targeted therapies.

EXTENDED FOLLOW-UP AND ANALYSIS BY AGE OF THE US ONCOLOGY ADJUVANT TRIAL 9735: DOCETAXEL/CYCLOPHOSPHAMIDE IS ASSOCIATED WITH AN OVERALL SURVIVAL BENEFIT COMPARED TO DOXORUBICIN/CYCLOPHOSPHAMIDE AND IS WELL-TOLERATED IN WOMEN 65 OR OLDER. SABCS 2007, ABSTRACT 12.

Investigators: S. Jones et al.

TRIAL SUMMARY: The US Oncology Adjuvant Trial 9735 enrolled 1016 women with both node-negative and node-positive Stage I–III invasive breast cancer after complete surgical removal of the primary tumour. Participants were randomized to receive either 4 cycles every 3 weeks of standard-dose doxorubicin 60 mg/m² + cyclophosphamide 600 mg/m² (AC, n = 510) or docetaxel 75 mg/m² + cyclophosphamide 600 mg/m² (TC, n = 506). Patients received radiotherapy as appropriate, and those with hormone-positive disease received tamoxifen. As shown in **Table 1**, at median followup of 6.9 years, docetaxel + cyclophosphamide provided statistically significant improvements in both DFS and OS compared to doxorubicin + cyclophosphamide. Women older than age 65 years in both treatment groups had more febrile neutropenia than younger women, but other toxicities did not differ significantly by age. The authors concluded that docetaxel + cyclophosphamide should now be considered a standard non-anthracycline combination for treating early breast cancer, and that this regimen may be preferable in older women since it is not cardiotoxic.

TABLE 1. US Oncology trial 9735 of doxorubicin 60 mg/m² + cyclophosphamide 600 mg/m² (AC) vs docetaxel 75 mg/m² + cyclophosphamide 600 mg/m² (TC), 6.9-year results

	AC (n)	TC (n)	p-value	hazard ratio
disease-free survival	79% (n = 510)	85% (n = 506)	p = 0.018	0.69
< 65 years old	82% (n = 428)	88% (n = 428)		
≥ 65 years old	75% (n = 82)	82% (n = 78)		
overall survival	84% (n = 510)	88% (n = 506)	p = 0.045	0.73

COMMENTARY: Sunil Verma, MD, MEd, FRCPC, Medical Oncologist and Danny Robson, MD, FRCPC, Breast Oncology Fellow, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON.

Two key studies on different chemotherapy strategies presented at the December 2007 SABCS addressed important issues about optimal adjuvant chemotherapy regimens.

HIGH-DOSE CHEMOTHERAPY

Dr. Donald Berry of MD Anderson Cancer Center (Houston, TX) presented a meta-analysis of 15 randomized trials investigating high-dose chemotherapy requiring bone marrow transplant, when given as adjuvant therapy for women with breast cancer at high risk of recurrence. Results of this methodologically sound meta-analysis were largely disappointing. Despite the power of data from 6210 patients, DFS was the only statistically significant endpoint (HR 0.87). Several of the individual clinical trials had found similar DFS benefits. Moreover, the meta-analysis found no significant differences in breast cancer-specific survival or overall survival, suggesting a lack of benefit with high-dose chemotherapy — notwithstanding the toxicity of autologous stem cell transplantation.

Better overall survival was seen only in a subgroup analysis of women with hormone receptor-positive tumours. This group may have further benefited from the ovarian ablation induced by high-dose chemotherapy, since tamoxifen was not mandated in every trial protocol. Further, as today's standard regimens for these high-risk individuals would most certainly incorporate taxanes or dose-dense regimens that do not require bone marrow transplantation, any marginal benefit of high-dose chemotherapy seen in this meta-analysis is likely mitigated by recent advances in non-myeloablative chemotherapy.

While it summarizes the failures of an already antiquated practice, this meta-analysis has scientific merit. It emphasizes the unacceptably high relapse rates for N2 breast cancer: only 40% to 50% of patients remain disease free at 10 years. It also suggests that modern-day chemotherapy may achieve a plateau of benefit, and that alternative strategies for adjuvant care such as biologics may be needed to break this stalemate, especially in women at high risk for relapse.

ADVANTAGES OF DOCETAXEL + CYCLOPHOSPHAMIDE

The second study addressed adjuvant breast cancer care at the other end of the spectrum of chemotherapeutics, in a randomized clinical trial comparing the “new generation,” less toxic chemotherapy agent docetaxel to a more conventional regimen containing cyclophosphamide and the anthracycline doxorubicin. With evidence first published in 2006, docetaxel + cyclophosphamide (TC) was shown to be superior to doxorubicin + cyclophosphamide (AC) chemotherapy, with improved DFS.¹ Interest in TC was fueled by a growing body of literature uncovering unacceptable rates of anthracycline-associated toxicity, both cardiac and leukemogenic.

At the December SABCS, Dr. Stephen Jones, medical director of US Oncology, presented data from 6.9 years of

followup of this study, revealing not only a more robust DFS (HR 0.69) but also a significant OS benefit (HR 0.73), seen regardless of age, hormone-receptor and HER2-receptor status. The toxicity profile favoured the non-anthracycline arm, even in the cohort of women over 65 years of age.

This landmark trial has helped catalyze 2 important trends in adjuvant breast cancer care. First, the efficacy of TC marks a shift towards less toxic, non-anthracycline adjuvant regimens, particularly in regard to cardiotoxicity. The BCIRG 006 trial has already reported on the efficacy of adjuvant docetaxel + carboplatin + trastuzumab vs a standard anthracycline regimen + docetaxel, with and without trastuzumab, in a cohort of HER2-positive women.² With similar efficacy endpoints in the 2 trastuzumab-containing arms, the toxicity profile significantly favoured those who did not receive an anthracycline.

Second, as a result of improved toxicity and efficacy, and with physicians' willingness to treat older women more aggressively, patients over age 65 are now being included in adjuvant clinical trials. Nearly 16% of enrollees in the US Oncology Adjuvant Trial 9735 were women over 65. In contrast, previous adjuvant trials excluded older women: early trials of cyclophosphamide + methotrexate + fluorouracil vs anthracycline-containing regimens limited enrollment to premenopausal women,^{3,4} and the median age of most taxane trials was 50.^{5,6}

IMPACT ON PRACTICE

Many U.S. oncologists have already adopted TC as a standard adjuvant regimen, although the departure from using anthracyclines has not been universal. In Canada, use of the more expensive chemotherapeutic agent docetaxel in combination with cyclophosphamide is not a publicly funded option in most parts of the country for adjuvant treatment of early-stage disease, even when high-risk. At the time of this trial's inception, AC was a standard treatment for node-positive breast cancer. Since then, a number of third-generation chemotherapy regimens have come into routine use for early-stage breast cancer — including dose-dense or weekly taxane-containing regimens — all with favourable efficacy profiles compared to AC. However, half the patients included in Jones' trial were node-positive, making it difficult to identify how 4 cycles of TC compares to the new-generation protocols, particularly in the higher-risk setting. To address this issue, US Oncology is leading a Phase III trial (Trial 06090) comparing TC with docetaxel + doxorubicin + cyclophosphamide (TAC), although 6 cycles of TC will be tested, rather than 4 cycles as studied in trial 9735.

One conclusion to be drawn from this study is that TC may be an option for patients considered candidates for AC or cyclophosphamide + methotrexate + fluorouracil (CMF). TC may now also be considered for those with node-positive disease for whom the safety of anthracyclines is a con-

cern. Of particular interest is the group over age 65 with high risk of breast cancer recurrence.

We are at an important time in our fight against this cancer. Increasingly the focus is on less toxic treatments and on identifying those patients who truly need the therapy and may benefit from it. These 2 trials help support this way of thinking and confirm that “more” is not necessarily better.

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Prognostic molecular testing in breast cancer

Debjani Grenier, MD, FRCPC

PROGNOSTIC AND PREDICTIVE VALUE OF THE 21-GENE RECURRENCE SCORE ASSAY IN POSTMENOPAUSAL, NODE-POSITIVE, ER-POSITIVE BREAST CANCER (S8814, INT0100). SABCS 2007, ABSTRACT 10.

Investigators: K. Albain et al.

TRIAL SUMMARY: The 21-gene Recurrence Score assay (RS) has previously been shown to predict prognosis for postmenopausal women with lymph node-negative, estrogen receptor-positive breast cancer who are treated with tamoxifen alone, with high RS predicting a large benefit from additional CMF chemotherapy. The present analysis used data from the Phase III Southwest Oncology Group (SWOG) 8814 trial to determine whether the RS also prognosticates DFS in node-positive women treated with tamoxifen alone, and whether it can identify a group who do not benefit from anthracycline-containing chemotherapy despite having cancer in their lymph nodes.

The trial randomized 1477 postmenopausal women with node-positive, estrogen receptor-positive breast cancer to receive either tamoxifen alone or chemotherapy with cyclophosphamide, doxorubicin and fluorouracil plus tamoxifen either concurrently (CAFT) or sequentially (CAF-T). At 10 years’ followup, patients receiving CAF had improved DFS and OS, especially those who received tamoxifen sequentially. Paraffin-embedded tumour blocks for reverse-transcription polymerase chain reaction (RT-PCR) analysis by the 21-gene RS were collected from 45% of participants. Sufficient RNA for RT-PCR was obtained on 367 patients: 148 in the tamoxifen-only arm and 219 in the CAF-T arm (the CAFT arm showed inferior results and was excluded from this analysis). The RS assessed 40% of patients as low-risk, 28% as intermediate-risk and 32% as high-risk for disease recurrence.

In patients receiving tamoxifen alone, the RS was prognostic for DFS and OS at 10 years: 10-year DFS rates for

TABLE 2. Ten-year Kaplan-Meier disease-free survival (DFS) estimates for women in the S8814 trial receiving tamoxifen alone vs CAF followed by tamoxifen (CAF-T)

RS risk group	tamoxifen (95% CI)	CAF-T (95% CI)	p-value
low-risk	60% (40% to 76%)	64% (50% to 75%)	p = 0.97
intermediate-risk	49% (32% to 63%)	63% (48% to 74%)	p = 0.48
high-risk	43% (28% to 57%)	55% (40% to 67%)	p = 0.03

low-, intermediate- or high-risk patients were 60%, 49% and 43% respectively (p = 0.017), including those with 1–4 positive nodes, and OS rates were 77%, 68% and 51% respectively (p = 0.003). Patients determined to be at high risk for recurrence by RS showed a large benefit from the addition of CAF, but those at low risk did not. **Table 2** shows 10-year Kaplan-Meier DFS estimates. The authors concluded that the RS predicts prognosis for node-positive patients treated with tamoxifen, that it predicts the benefit of CAF chemotherapy in patients with high-RS tumours, and that low RS may define a group of node-positive women who apparently do not benefit from anthracycline-based adjuvant chemotherapy.

LANDMARKS

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

Oncotype DX, also known as the 21-gene recurrence score assay, measures the expression of 21 genes using RT-PCR in fixed, paraffin-embedded tumour tissue.¹ Of these genes, 16 are cancer-related and the other 5 are reference genes. Based on their levels of expression, a mathematic algorithm calculates a recurrence score (RS) that defines a risk group (low, intermediate or high). The RS quantifies the likelihood of distant recurrence and was validated in a population-based study.² It also predicts the benefit of CMF chemotherapy in this patient group, and may correlate more strongly with outcome than the widely used Adjuvant! Online program (www.adjuvantonline.com).^{3,4} Based on these data, the American Society of Clinical Oncology recently endorsed the clinical utility of the Oncotype DX assay in patients with node-negative, estrogen receptor-positive breast cancers.⁵

Oncotype DX, offered by Genomic Health Inc. since January 2004, is the first commercially available diagnostic multigene expression test. To date, approximately 70,000 physicians have ordered more than 40,000 tests and many healthcare plans in the U.S. provide reimbursement. This contrasts sharply with the situation in Canada, where this assay is not funded by the public system and private health insurance rarely covers it, leaving patients accountable for the US\$ 3600 per-test charge. Similarly, cancer agencies do not currently provide funding. However, patients with lymph node-negative, estrogen receptor-positive breast cancers do have access to the assay by participating in the Trial Assigning Individualized Options for Treatment (TAILORx, NCIC-MAC12, NCT00310180) study, endorsed by numerous cooperative trial groups including the National Cancer Institute of Canada Clinical Trials Group (NCI-CTG). Each patient's RS is determined by the Oncotype DX assay, and based on this result they are categorized into low-, intermediate- or high-risk groups. Those with low RS receive endocrine hormonal treatment alone (HT) and those with high RS receive adjuvant chemotherapy and HT. The main study group is patients with intermediate-risk scores who are randomized to HT alone or HT plus chemotherapy. The trial is powered to show non-inferiority. Of note, this is one of the first trials to subtract treatment rather than add treatment or substitute one treatment for another. It was launched in 2006 and thus far has accrued 2670 patients out of a planned 11,000, and at least 10 Canadian centres are actively participating.

GUIDES TREATMENT SELECTION, BUT MORE STUDY NEEDED

Albain and colleagues now present the first data showing the prognostic and predictive value of the RS assay in patients with lymph node-positive breast cancer. The study population included women who participated in the SWOG 8814 trial of CAF chemotherapy with tamoxifen vs tamoxifen alone.⁶ Low, intermediate and high RS were associated with 10-year DFS of 60%, 49% and 43%, respec-

tively, and with 10-year OS of 77%, 68% and 51%, respectively. Importantly, adding chemotherapy provided a significant improvement in DFS in women with high RS but not in those with low RS. A benefit of chemotherapy in patients with intermediate RS could not be ruled out, but differences in outcomes were not statistically significant. The authors concluded that women with high RS derive a benefit from CAF chemotherapy and that those with low RS may not, even in the presence of lymph node-positive cancer. A separate study by Goldstein et al presented at the 2007 SABCS showed that the RS was significantly predictive of recurrence in both lymph node-negative and lymph node-positive disease.⁷

While these results are encouraging for an emerging role of the Oncotype DX in women with lymph node-positive breast cancers, more evidence is needed before recommending widespread use in this population. The SWOG correlative science study was retrospective, with a small sample size of 367 patients (40% of the parent trial), and confidence intervals were wide. More confirmatory studies are required. Of uppermost importance is a prospective, randomized trial of adjuvant chemotherapy plus HT vs HT alone in lymph node-positive, estrogen receptor-positive patients with low RS. Of note, the chemotherapy in this trial was CAF, considered a second-generation regimen, and this may not be the optimal chemotherapy in women with lymph node-positive disease. Thus it is not known whether CAF has efficacy similar to a third-generation taxane-based combination, as third-generation adjuvant chemotherapy may provide incremental benefit in all risk groups.

The clinical utility of other gene assays such as the MammaPrint (Amsterdam 70-gene signature assay) remain under investigation.⁸ The MammaPrint test, also commercially available in the U.S., requires fresh tissue containing at least 30% malignant cells. It may predict patient prognosis, and is currently being prospectively studied in the Microarray in Node-Negative Disease may Avoid Chemotherapy trial (MINDACT, EORTC Trial 10041, BIG 3-04, NCT004433589), which has a similar design to the TAILORx trial.

CURRENT IMPLICATIONS

For now, women should be informed of the evolving role of the Oncotype DX assay and have the opportunity to access the test if they have lymph node-negative, hormone receptor-positive breast cancers, and centres should be encouraged to participate in the TAILORx trial. In addition to the chemotherapy consideration above, women and their physicians should also be aware that in terms of hormonal therapy, trials exploring the utility of the assay included only patients treated with tamoxifen. Whether the same results apply to women taking aromatase inhibitors is unclear, but estimated recurrence rates would likely be lower with their use. While there are currently insufficient data to

fully endorse and fund use of the Oncotype DX assay in Canada to help select adjuvant chemotherapy in women with lymph node-positive breast cancers, the results of this study are compatible with recent trials of single-marker predictors such as HER2, estrogen receptors, and topoisomerase II, which also identify breast cancer patients who derive little or no benefit from dose-intensive chemotherapy on the basis of tumour biology.⁹⁻¹²

We are certainly entering an exciting time in breast cancer management with improved tailoring of therapies — thereby avoiding treatments in those individuals least likely to benefit and offering therapies to those who benefit substantially more. As knowledge continues to evolve, these developments will no doubt lead to increased patient confidence in treatment selection.

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PRESENTATIONS FROM THE 49TH ANNUAL MEETING OF THE AMERICAN SOCIETY OF HEMATOLOGY

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Multiple myeloma

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MELPHALAN-PREDNISONE-THALIDOMIDE (MP-T) DEMONSTRATES A SIGNIFICANT SURVIVAL ADVANTAGE IN ELDERLY PATIENTS ≥75 YEARS WITH MULTIPLE MYELOMA COMPARED WITH MELPHALAN-PREDNISONE (MP) IN A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL, IFM 01/01. ASH 2007, ABSTRACT 795.

Investigators: C. Hulin et al.

TRIAL SUMMARY: The IFM 01-01 randomized controlled trial examined the safety and efficacy in 229 elderly patients (≥ 75 years old) of melphalan 0.2 mg/kg/day + prednisone 2 mg/kg/day on Days 1-4 plus daily placebo, for 12 cycles every 6 weeks (MP-placebo, n = 116) compared to the same melphalan and prednisone combination plus thalidomide 100 mg/day (MPT, n = 113). At median followup of 24 months, median overall survival was 45.3 months (standard equivalent [SE] 1.6 months) for patients receiving MPT vs 27.7 months (SE 2.1 months) for those taking MP-placebo (p = 0.03). **Table 3** shows this and other results. However, 42% of

TABLE 3. Benefit of adding thalidomide to melphalan + prednisone in multiple myeloma patients ≥ 75 years old

endpoint	MPT* (standard equivalent)	MT-placebo† (standard equivalent)	p-value
overall survival	45.3 (1.6) months	27.7 (2.1) months	p = 0.03
progression-free survival	19 (1.4) months	24.1 (2) months	p = 0.001
complete response	7%	1%	p < 0.001
very good partial response	22%	7%	p < 0.001
partial response	62%	31%	p < 0.001

* melphalan 0.2 mg/kg/day + prednisone 2 mg/kg/day + thalidomide 100 mg/day
 † melphalan 0.2 mg/kg/day + prednisone 2 mg/kg/day + placebo

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patients in the MPT group stopped treatment because of toxicity vs 11% in the MP-placebo group, mainly due to peripheral neuropathy (12 of 48), neutropenia (7 of 48) and deep vein thrombosis (DVT) (7 of 48). Peripheral neuropathy, neutropenia and depression occurred more often in the MPT group while differences in rates of DVT and

somnolence were not significant. Patients in the MP-placebo arm had the option of receiving thalidomide after relapse. The authors concluded that these results show that MPT provides superior survival with acceptable toxicity in newly diagnosed elderly multiple myeloma patients.

COMMENTARY: Kevin W. Song, MD, FRCPC, Hematologist, Vancouver General Hospital, British Columbia Cancer Agency.

Until recently, therapeutic advances in treatment of myeloma had been in the younger population, particularly using stem cell transplantation. Now, however, evidence is strengthening in support of the use of novel drugs alone and in combination to allow non-transplant eligible adult patients to also enjoy improved survival and quality of life.

The combination of melphalan and prednisone (MP) has long been standard initial treatment for myeloma patients not eligible for stem cell transplantation. With this study conducted by Hulin et al, at least 3 trials have demonstrated the superiority of the combination of melphalan and prednisone plus thalidomide (MPT) compared MP alone.^{1,2} Remarkably, this trial was limited to patients 75 years of age or older, an elderly population that has not been well studied in spite of the fact that they account for a significant number of patients diagnosed with this malignancy. This study demonstrated superior overall survival for those receiving MPT compared to the control group, providing further support for the use of MPT as a standard treatment for non-transplant eligible patients, irrespective of age.

A great advantage of the MPT regimen is that it can be given orally without significant inconvenience, and when problems with toxicity arise it can be stopped immediately. Toxicity is a concern, but although 42% of the patients on the MPT arm discontinued treatment due to toxicity, overall survival increased by more than 18 months in the patients assigned to MPT. This improvement occurred even though 77% of those in the standard MP arm eventually received thalidomide, implying that the benefit of thalidomide is greatest when used in initial treatment.

Another clinical trial for newly diagnosed patients not eligible for stem cell transplantation presented at the ASH 2007 meeting used a combination of bortezomib, melphalan and prednisone (VMP) compared to melphalan and

prednisone (MP) alone,³ and demonstrated the superiority of VMP compared to MP alone.

A PARADIGM SHIFT

After several decades of relative stagnation, suddenly there are several options using novel drugs with different modes of action to treat newly diagnosed patients with multiple myeloma who are not eligible for stem cell transplantation. While survival improvements are being seen, the most effective combinations and preferred settings have yet to be determined. Although initial development of newer drugs has occurred in the relapsed and /or refractory setting, the biggest benefit may be realized in upfront treatment. Many more trials are expected to explore initial treatment of newly diagnosed myeloma patients. Given the increasing evidence of the superiority of novel regimens, MPT, VMP or other such regimens may become the standard arm rather than MP.

Does the evidence for improved overall survival with these newer upfront regimens establish a new standard of care outside the clinical trial setting? This will likely depend upon a number of factors including drug availability, cost of the therapies and different side effect profiles. Specifically for MPT, in Canada availability of thalidomide remains limited. But with mounting evidence supporting its use, there will be increasing pressure for wider access.

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Acute lymphoblastic leukemia

Stephen Couban, MD, FRCPC

IMPROVED EARLY EVENT FREE SURVIVAL (EFS) IN CHILDREN WITH PHILADELPHIA CHROMOSOME-POSITIVE (PH+) ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) WITH INTENSIVE IMATINIB IN COMBINATION WITH HIGH DOSE CHEMOTHERAPY: CHILDREN'S ONCOLOGY GROUP (COG) STUDY AALL0031. ASH 2007, ABSTRACT 4.

Investigators: K.R. Schultz et al.

TRIAL SUMMARY: Children enrolled in this trial received induction therapy followed by 2 sequential intensive chemotherapy regimens (Consolidation Blocks 1 and 2), followed by a series of reinduction, intensification and maintenance therapy regimens. The regimens included imatinib 340 mg/m² for 1 of 5 durations: 42 days (Cohort 1, n = 8), 63 days (Cohort 2, n = 12), 84 days (Cohort 3, n = 11), 126 days (Cohort 4, n = 12) or 280 days (Cohort 5, n = 50). Bone marrow transplant (BMT) was done after the first 2 cycles of post-induction chemotherapy in 21 patients with an HLA-identical sibling donor (8 of 43 in Cohorts 1–4 and 13 of 44 in Cohort 5). Out of 93 patients treated with induction therapy, 83 (89%) obtained a remission. Eleven of the 83 were removed from the trial to receive alternative donor BMT, and the others continued chemotherapy. BMT patients began to receive imatinib 4–6 months after BMT and continued it for 6 months. Among the 83 patients with response to induction, minimal residual disease positivity (< 0.01%) was significantly lower in Cohorts 3–5, in which imatinib was given post-induction,

compared to Cohorts 1 and 2 combined, in which no imatinib was given post-induction ($p = 0.0002$ for Consolidation Block 1 and $p = 0.007$ for Consolidation Block 2).

Patients had increasingly longer early event-free survival (EFS) with longer imatinib exposure: those in Cohorts 1 and 2 had 1-year EFS of $70.6 \pm 11.1\%$, those in Cohorts 3 and 4 had EFS of $90.9 \pm 6.4\%$, and those in Cohort 5 had EFS of $95.3 \pm 3.6\%$ ($p = 0.02$). Historical controls receiving intensive chemotherapy without imatinib in previous Children's Oncology Group (COG) studies had 1-year EFS of $65.7 \pm 6.4\%$, and recipients of sibling donor BMT had EFS of 78%. No statistically significant difference was seen in Cohort 5 patients (who received 240 days of imatinib) between those with or without sibling donor BMT ($p = 0.26$). The authors concluded that imatinib added to intensive chemotherapy significantly improves early EFS and reduces minimal residual disease, and that imatinib given after sibling donor BMT also improves early outcome compared to results in historical controls.

COMMENTARY: Stephen Couban, MD, FRCPC, Director of the Blood and Marrow Transplant Programs, Queen Elizabeth II Health Sciences Centre; Associate Professor of Medicine, Dalhousie University, Halifax, NS.

Acute lymphoblastic leukemia (ALL) remains both fascinating and challenging for most hematologists and oncologists in 2008. Despite our increasing knowledge about the molecular pathophysiology of this disease, most therapeutic advances in ALL have derived from empiric changes in treatment tested in successive cohort studies and randomized trials. Philadelphia chromosome-positive (Ph⁺) ALL has always represented a particular challenge because of very poor results with chemotherapy, particularly in adults but also in children. Allogeneic hematopoietic stem cell transplantation has been the recommended treatment for patients for whom a donor can be found.

Ph⁺ ALL is associated with the BCR-ABL translocation also found in chronic myeloid leukemia (CML), but usually with a different breakpoint (m-bcr) in the BCR gene, resulting most commonly in overexpression of the P190 tyrosine kinase. The observation that the tyrosine kinase associated with Ph⁺ ALL is inhibited by imatinib, a specific inhibitor of the bcr-abl tyrosine kinase, has opened a potential novel therapeutic window. Imatinib revolutionized the

therapy of CML in the last decade, transforming it from a disease for which allogeneic transplantation was commonplace to one where transplantation is now only rarely undertaken. Since imatinib also inhibits the Ph⁺ ALL bcr-abl tyrosine kinase, various centres and cooperative groups have studied it as a single agent, in combination with chemotherapy, and in the pre- and post-transplant period for this subtype of ALL. This presentation by Schultz et al at the 207 ASH Annual Meeting on behalf of the Children's Oncology Group, describing a cohort study examining the efficacy of imatinib in children with Ph⁺ ALL, highlights several important and emerging issues in this disease.

NOTABLE FINDINGS

First, with increasing length of exposure to imatinib after the start of induction therapy, there was a progressive improvement in 1-year EFS, with a concomitant reduction in minimal residual disease positivity at the end of the first and second blocks of consolidation therapy. Ph⁺ ALL is a disease with a high proliferative index, but transient expo-

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sure to imatinib during induction and consolidation therapy ranging from 42 to 280 days improved EFS at 1 year. Similarly, the EFS of children in Cohort 5 who received 280 days of imatinib therapy was significantly better than in historical controls from previous COG studies who had not received imatinib. This finding confirms earlier reports about the benefit of adding imatinib to chemotherapy in Ph⁺ ALL, although it does not address the best dose of imatinib or the best schedule of administration.

The second notable finding relates to the relative outcomes of patients with Ph⁺ ALL treated with chemotherapy and imatinib compared to those treated with allogeneic hematopoietic cell transplantation. It was recommended in this study that patients with Ph⁺ ALL who had sibling matches proceed to allogeneic transplantation. While alternative donor transplants were not part of the study protocol, patients could be withdrawn to receive alternative donor transplants. Out of 93 patients in the study, 83 achieved remission; 21 of those achieving remission underwent sibling allogeneic transplantation and 11 were removed from the protocol for alternative donor transplantation. The 1-year EFS of patients in Cohort 5 who were treated with chemotherapy and the longest duration of imatinib (280 days) but without transplantation was similar to patients who had undergone sibling allogeneic BMT (95.8% vs 95%). The 1-year EFS of patients who had undergone sibling allogeneic transplantation and who

received 6 months of imatinib therapy post-transplant was better than a group of historical control patients with Ph⁺ ALL from previous COG studies who had undergone sibling allogeneic transplantation without post-transplant imatinib (95% vs 78%). Most importantly, the outcome of patients who had been removed from the protocol to undergo alternative donor transplantation was substantially inferior (81.5% 1-year EFS) to those who had not received transplants (95.8%) or who had received a sibling allogeneic transplantation (95% 1-year EFS),

Third, combining imatinib with chemotherapy or giving it post-transplantation did not appear to incur significant toxicity, at least in the manner in which it was used in this study.

LIMITATIONS AND FURTHER QUESTIONS

The study population was relatively small, with limited followup so far — it will be important to see whether the excellent EFS of patients treated with chemotherapy and imatinib is maintained with longer followup. This was not a randomized study, so the inferior outcomes of patients undergoing sibling allogeneic transplantation and alternative donor transplantation may be confounded by selection of patients for these treatments. Further study of the use of imatinib and other tyrosine kinase inhibitors and of the dose and schedule with which they should be administered in this disease is needed. 

Disclosure

Dr. Couban reports having no potential conflicts of interest pertaining to this article. Dr. Grenier reports being on advisory boards of AstraZeneca, GlaxoSmithKline and Schering. Dr. Ragaz reports serving on advisory boards of GlaxoSmithKline, Novartis, Roche and Sanofi-Aventis. Dr. Robson reports having no conflicts of interest pertaining to this article. Dr. Sehn reports receiving research support from Roche, serving as a consultant to Roche and Biogen Idec, serving on the advisory board of Roche, and on the speaker's bureau for Genentech. Dr. Song reports receiving research support from Celgene and being on advisory boards of Celgene and Ortho-Biotech. Dr. Verma reports receiving research support from, and being a consultant and on advisory boards and speakers' bureaus for Abraxis, BMS, Roche, Pfizer and Sanofi Aventis.