



EVIDENCE WATCH

A review and assessment of recent clinical trial data

Oncology Exchange provides overviews of important clinical trial data presented at the 28th Annual San Antonio Breast Cancer Symposium (SABCS), held December 8–11, 2005 in San Antonio, Texas and at the 47th American Society of Hematology (ASH) Annual Meeting, held December 10–23, 2005 in Atlanta, Georgia. Leading Canadian experts offer commentary and clinical interpretations.

Contributors were selected by Joseph Ragaz, MD, FRCPC, Director, Oncology Program, McGill University Health Centre, Montréal, QC and by Isabelle Bence-Bruckler, MD, FRCPC, Hematologist and Associate Professor of Medicine, the Ottawa Hospital, Ottawa, ON.

Breast cancer

THE BENEFITS OF SEQUENCING ADJUVANT TAMOXIFEN AND ANASTROZOLE IN POSTMENOPAUSAL WOMEN WITH HORMONE-RESPONSIVE EARLY BREAST CANCER: 5 YEAR-ANALYSIS OF ABCSG TRIAL 8. SABCS 2005 ABSTRACT 13.

Investigators: R. Jakesz et al.

TRIAL SUMMARY: The Austrian Breast Cancer Study Group (ABCSG) Trial 8 randomized postmenopausal women newly diagnosed with hormone-sensitive early breast cancer to receive either 5 years of tamoxifen or 2 years of tamoxifen followed by 3 years of anastrozole. At median followup of 31 months, 227 events comprising local or distant recurrences or contralateral breast cancer had been reported. In 2529 patients eligible for analysis, the hazard ratio (HR) for event-free survival (EFS) was 0.61 (95% CI 0.42–0.89, $p = 0.01$) in favour of tamoxifen followed by anastrozole, a 39% relative reduction in risk of disease recurrence. This

translates into an absolute improvement of 3.9% EFS at 5 years if women switch to anastrozole. If events from the initial tamoxifen treatment period are included ($n = 2926$, with median followup of 54.6 months), the HR for EFS is 0.76 ($p = 0.068$). Overall survival (OS) was the same for both treatment groups. Regarding toxicities, no differences were seen in myocardial infarction rates (both $< 1\%$) or in the incidence of pulmonary emboli or thromboses. Fracture rates were significantly different, with a 1% incidence in women receiving tamoxifen only compared to 2% in those who switched to anastrozole ($p = 0.015$).

SWITCHING FROM ADJUVANT TAMOXIFEN TO ANASTROZOLE IN POSTMENOPAUSAL WOMEN WITH HORMONE-RESPONSIVE EARLY BREAST CANCER: A META-ANALYSIS OF THE ARNO 95 TRIAL, ABCSG TRIAL 8, AND THE ITA TRIAL. SABCS 2005 ABSTRACT 18.

Investigators: W. Jonat et al.

TRIAL SUMMARY: The 3 trials ABCSG trial 8, Arimidex-Nolvadex (ARNO) 95 and Italian Tamoxifen Arimidex (ITA) trials all examined the outcomes of switching postmenopausal women with hormone receptor-sensitive early breast cancer to anastrozole after 2–3 years on tamoxifen. This meta-analysis assessed whether the improved EFS in the 4006 eligible patients in the individual trials (2579 from ABCSG trial, 8979 from ARNO 95 and 448 from

ITA) translated into improved long-term outcomes including OS. After median followup of 30 months, 4.6% of the women switching to anastrozole had breast cancer recurrences vs 8% of those remaining on tamoxifen. The HR for disease-free survival (DFS) was 0.59 (95% CI 0.48–0.74, $p < 0.0001$) favouring the switch to anastrozole. HR for death was 0.71 (95% CI 0.52–0.98, $p = 0.038$). The safety profiles for anastrozole and tamoxifen were consistent with

those previously reported in the individual trials. The authors concluded that switching to anastrozole results in

an OS benefit and that postmenopausal women currently receiving adjuvant tamoxifen should switch to anastrozole.

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

Aromatase inhibitors (AIs) continue to challenge tamoxifen's stronghold as the mainstay of endocrine therapy for postmenopausal women with early breast cancer. So far, 7 Phase III randomized controlled clinical trials including more than 30,000 women have reported results favouring the use of adjuvant AIs either upfront or after some years of tamoxifen.¹⁻⁶

At the 2005 SABCS, Jakesz et al updated the results of the Austrian Breast and Colorectal Cancer Study Group (ABCSG) trial 8, in which 2926 postmenopausal women received either 5 years of tamoxifen or 2 years of tamoxifen followed by 3 years of anastrozole. Unlike all the other AI switching trials, the participants were randomized immediately after surgery rather than after completing 2 years of tamoxifen. At median followup of approximately 31 months, an absolute improvement of 3.8% in EFS favoured the switch to anastrozole following the initial 2 years of tamoxifen. Using data from this trial as well as the 2 other anastrozole-switching trials, ARNO 95 and ITA,^{4,5} Jonat et al performed a meta-analysis to assess whether the benefits in EFS observed in the individual studies translated into benefits in long-term outcomes, specifically OS. At median followup of 30 months, women switching to anastrozole had 3.4% fewer breast cancer recurrences and a 29% relative reduction in the risk of death.

Both these presentations confirm the efficacy of switching from tamoxifen to an AI, at least in terms of DFS. Professor Jonat's meta-analysis also suggests an OS benefit with this strategy, although several points need to be considered. Ideally, all trials on the question under study should be included in a meta-analysis. The results of the IES trial, which studied the use of 2-3 years of the steroidal AI exemestane after 2-3 years of tamoxifen,³ were notably absent from this meta-analysis. Further, the 3 study populations differed with respect to stage of disease: in the ARNO 95 and ABCSG-8 trials, one quarter of the women had lymph node-positive breast cancers vs almost all in the ITA trial having lymph node-positive disease. The trials also differed in the use of adjuvant chemotherapy: none in the

ARNO 95 and ABCSG trial 8 vs two-thirds in ITA. In addition, the ABCSG trial 8 and ARNO 95 trials were open label studies so treatment allocation was known to the patient and the physician. Overall, the median followup of approximately 2.5 years in the meta-analysis is quite short, and the statistical significance for OS is borderline with confidence intervals approaching one.

Despite these issues, a wealth of information provides evidence of benefit for switching to an AI after 2-3 years of tamoxifen in terms of significantly reducing breast cancer recurrences. Further results of the IES study — the trial with the longest median followup of all the switching trials, last reported at 37.4 months⁷ — may determine if switching to an AI also extends OS. Information on long-term toxicities such as osteoporosis and cardiovascular events is also expected. Which strategy is optimal remains unknown: upfront AI or switching to an AI after some years of tamoxifen. Results from the BIG I-98 trial are expected to answer this in 2008. This trial compares results from 4 treatment arms: 5 years of letrozole, 5 years of tamoxifen, 2-3 years of tamoxifen followed by 2-3 years of letrozole, and 2-3 years of letrozole followed by 2-3 years of tamoxifen.

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UPDATED ANALYSIS OF NCIC CTG MA.17 (LETROZOLE VS. PLACEBO TO LETROZOLE VS PLACEBO) POST UNBLINDING. SABCS 2005 ABSTRACT 16.

Investigators: P.E. Goss et al.

TRIAL SUMMARY: The National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) MA.17 trial randomized postmenopausal women to receive either letrozole or placebo after taking tamoxifen for 5 years. At a median

followup of 30 months, the HR for DFS in favour of letrozole was 0.58 (p = 0.00004). After the first interim analysis the trial was unblinded and the women taking placebo were offered letrozole. The current presentation summarizes the

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efficacy results for 3 groups: those originally randomized to letrozole, those randomized to placebo but who crossed to letrozole and those who stayed on placebo. Of 2594 women originally assigned to placebo who were alive and had no disease recurrence at the time of unblinding, 1655 elected to begin taking letrozole. In multivariate analysis, factors that predicted for choosing to switch to letrozole were age, nodal status, endocrine symptomatology and being in the US as

opposed to Canada. At median followup of 49 months, 342 recurrence events with 211 deaths have occurred. The adjusted hazard ratios were 0.31 for DFS (95% CI 0.18–0.55, $p < 0.0001$), 0.28 for distant DFS (95% CI 0.13–0.62) and 0.53 for OS (CI 0.28–1.00, $p = 0.05$). Women switching to letrozole had a nonsignificant numeric increase in bone fractures and in self-reported new diagnoses of osteoporosis. No differences in cardiovascular events were seen.

ANALYSIS OF DURATION OF LETROZOLE EXTENDED ADJUVANT THERAPY AS MEASURED BY HAZARD RATIOS OF DISEASE RECURRENCE OVER TIME FOR PATIENTS ON NCIC CTG MA.17. SABCS 2005 ABSTRACT 17.

Investigators: J.N. Ingle et al.

TRIAL SUMMARY: This analysis of the MA.17 trial examined the relationship between duration of letrozole therapy and hazard for recurrence using a nonparametric kernel method to estimate the hazard rates and HRs each year following randomization (Table 1). Only events up to time of treatment unblinding were included. Patients taking placebo had a higher risk of disease recurrence that increased with time after discontinuing tamoxifen. For patients taking letrozole the risk of recurrence peaked at about 2 years and then decreased. The HR for cancer recurrence with

letrozole vs placebo increased ($p = 0.02$) over the 4 years analyzed, indicating that the benefit of letrozole increases over time. A similar pattern was observed for distant DFS with HR 0.43 at 12 months and 0.21 at 48 months. HR for OS was less than 1.0 at all time points but was not statistically significant. In women with lymph node-positive breast cancer, HR for DFS, distant DFS and OS decreased significantly over time. In those with lymph node-negative disease, although the HR for DFS decreased significantly with time, for distant DFS and OS it did not.

TABLE 1. Hazard rates and hazard ratios (HRs) for breast cancer recurrence in patients taking letrozole vs placebo in the MA.17 trial

Months post-randomization	hazard rate (n) letrozole group	hazard rate (n) placebo group	HR, letrozole vs placebo (95% CI)
12	0.00093 (2425)	0.00180 (2409)	0.52 (0.40–0.64)
24	0.00105 (1555)	0.00236 (1530)	0.45(0.33–0.56)
36	0.00090 (768)	0.00261 (723)	0.35 0.21–0.48)
48	0.00059 (244)	0.00306 (231)	0.19 (0.04–0.34)

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

The results from the NCIC MA.17 trial evaluating outcomes after unblinding of therapy support the use of letrozole in postmenopausal women after 4.5–6 years of tamoxifen. They imply that women with endocrine-sensitive breast cancers may benefit from letrozole at any time 1–5 years after discontinuing tamoxifen.

No information was provided, however, on whether there was a differential benefit for those women who started the AI shortly after completing tamoxifen compared to those starting several years after finishing tamoxifen. Also, at the time of trial unblinding, few women were in their fourth or fifth year of trial therapy. The patient characteris-

tics of those who opt to take letrozole after placebo differ from those who decide on no endocrine therapy: women on placebo who subsequently chose letrozole were younger, had worse performance status, had lymph node-positive breast cancer and had received adjuvant chemotherapy. Whether these varying characteristics or other undiscovered differences account for the outcomes is unknown. Nevertheless, women who chose letrozole had several risk factors for breast cancer recurrence and would be expected to have poorer outcomes than those who remained on placebo and had lower-risk disease, and the multivariate analysis was undertaken because of the

imbalance in prognostic factors. The issue of how long after discontinuing tamoxifen letrozole can be started is still unresolved. Based on the current data, there may be benefit to initiating letrozole up to 2.5–3 years after completing tamoxifen.

The updated MA.17 results prior to unblinding, presented by Ingle et al at the 2005 SABCS, suggest that the treatment benefits persist and actually improve over time. Even longer therapy with letrozole is currently being studied in the MA.17 extended trial where women previously on MA.17 are given 5 years of letrozole or placebo after completing the original 5 years of letrozole. One may therefore conclude that women remain at risk of breast cancer relapse after completing 5 years of tamoxifen and that they may benefit from up to 5 years of letrozole, and that this benefit is particularly evident in women with lymph node-positive breast cancer.

Although the results of MA.17 are extremely important, currently 5 years of upfront tamoxifen is a declining strategy given the earlier incorporation of AIs into a postmenopausal woman’s therapy. This brings up the issue of the optimum duration of AIs. Once a woman completes 5 years of endocrine adjuvant therapy that included an AI, it is completely unknown whether further extended treatment is of benefit. While these women presumably remain at risk of relapse in the ensuing years, trials exploring this question are only in the planning stages. For now, the data compel us to recommend the use of an AI at some point in the adjuvant endocrine therapy of a postmenopausal woman with hormone-positive breast cancer. All treatment options and toxicities need to be discussed with the individual, who will then choose which therapy is best for her. The previous gold standard of 5 years of tamoxifen alone is clearly now no longer adequate for postmenopausal women with early breast cancer.

Myeloproliferative syndromes

QUANTITATIVE ANALYSIS OF WILD TYPE AND V617F JAK-2 EXPRESSION IN NEUTROPHILS OF POLYCYTHEMIA VERA AND ESSENTIAL THROMBOCYTHEMIA PATIENTS AT DIAGNOSIS. ASH 2005 ABSTRACT 257.

Investigators: E. Lippert et al.

TRIAL SUMMARY: This study aimed to determine the frequency of the V617F JAK2 mutation at the time of diagnosis in patients with the myeloproliferative syndromes polycythemia rubra vera (PRV) and essential thrombocythemia, and to quantify V617F JAK2 expression at the mRNA level. Neutrophil cDNA was available for 56 patients with PRV, 57 with essential thrombocythemia and 47 controls (26 controls had secondary erythrocytosis and 21 had reactive thrombocytosis). The diagnoses were made according to WHO criteria. All patient marrow samples were tested for endogenous colony formation to evaluate presence of erythropoietin-independent growth in vitro (diagnostic of PRV) and a polycythemia rubra vera receptor-1 (PRV-1) mRNA assay.

The researchers performed duplicate reverse transcription followed by quantitative real-time PCRs specific for wild type (normal) JAK2 or V617F JAK2 and reported these as a function of the ABL expression (a tyrosine kinase oncogene associated with chronic myelogenous leukemia) to normalize expression measurements. One of the only 2 PRV patients that did not have elevated PRV-1 levels also did not express V617F JAK2. Elevated PRV-1 expression was seen in 15 of the 57 patients with essential thrombocythemia and all but 1 of these also expressed V617F JAK2 (Table 2). In the patients with secondary erythrocytosis or reactive thrombocytosis, V617F JAK2 incidence was absent. PRV-1 and mutant JAK2 expression levels correlated in both PRV ($r = 0.450$, $p = 0.0006$) and essential thrombocythemia ($r = 0.540$, $p = 0.0005$). Measured as a ratio per 100 copies of ABL, on average, essen-

TABLE 2. Incidence of characteristics reported in patients with polycythemia vera vs essential thrombocythemia

	polycythemia vera	essential thrombocythemia
V617F JAK2	96.6%	70.2%
endogenous colony formation	84.3%	78.6%
elevated PRV-1	96.4%	26.3%

tial thrombocythemia neutrophils expressed 144 V617F JAK2/100 ABL and 462 wild type JAK2/100 ABL, while reactive thrombocytosis neutrophils expressed 496 wild type JAK2/100 ABL; the V617F/wild type ratio in essential thrombocythemia neutrophils was always < 0.7.

This data delineates 2 groups of polycythemia vera patients (Table 3, page 20). The majority, 60.8%, expressed an average of 975 wild type JAK2/100 ABL and 733 V617F JAK2/100 ABL — double the total expression of JAK2 compared to that seen in secondary erythrocytosis, which had an average of 821 wild type JAK2/100 ABL. The V617F/wild type ratio of these patients was always < 3. The minority, 39.2%, expressed low levels of wild type JAK2 (average 247 copies/100 ABL) and high levels of V617F

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TABLE 3. Polycythemia vera groups based on type of JAK2 expression per 100 ABL

	average number of copies per 100 copies of ABL	
	majority group (60.8%)	minority group (39.2%)
wild type JAK2	975	247
V617F JAK2	733	1515
wild type/mutation ratio	< 3	> 3

JAK2 (average 1515 copies/100 ABL) — also doubling the amount of JAK2 mRNA but with a V617F/wild type ratio > 3. In the patients with a V617F/wild type ratio < 3, analysis of the cDNA showed both wild type and mutated sequences, whereas patients with a V617F/wild type ratio > 3 showed only the mutated sequence.

COMMENTARY: Brent Zanke, MD, PhD, FRCPC, Vice President, Ontario Cancer Research Network, Associate Professor, University of Toronto.

JAK2 AND HEMATOPOIETIC RECEPTOR SIGNALLING

Wilks et al first discovered the Janus group of kinases in 1989 using a degenerate PCR approach based on knowledge of common features of protein tyrosine kinases.¹ These kinases, named after a Roman god with 2 heads, have 2 tandem kinase-like domains. The amino-terminal domain has catalytic activity, while the second domain does not and is called a pseudokinase domain. Since their discovery, hundreds of papers have described the important role they play in hematopoietic receptor signalling, particularly Janus kinase 2 (JAK2).

Hematopoietic ligand receptors such as IL3 and erythropoietin have no intrinsic kinase activity. Upon ligand binding, JAK2 becomes activated through tyrosine phosphorylation and then activates signalling molecules such as the signal transducers and activators of transcription STAT3, STAT5a and STAT5b. The hematopoietic ligand receptors also become phosphorylated by JAK2 and recruit other linking signalling molecules such as GRB2 and SOS. These ultimately result in the activation of powerful mitogenic kinases such as PI3Kinase, AKT and p42MAPK, controlling cell division and apoptosis through molecules such as BclXL.

It has long been appreciated that growth of red cell precursors in patients with PRV is erythropoietin-independent. Marrow erythroid progenitors can be identified in vitro by the development of erythroid burst-forming units (BFU-E) when marrow cells are cultured in a semi-solid medium like methylcellulose. Normal BFU-Es need the support of erythropoietin included in the culture medium. BFU-Es from patients with PRV, however, develop in an erythropoietin-independent fashion, suggesting molecular pathology permitting growth factor-independent growth. Erythropoietin signal transduction occurs through JAK2 activation. Conceivably, the independence of erythropoietin in PRV may be induced through a constitutively activating mutation in this tyrosine kinase.

MYELOPROLIFERATIVE DISEASES AND THE JAK2 V617F MUTATION

During the plenary session of the December 2005 ASH Annual Meeting, Josef Prchal (Baylor College of Medicine,

Houston, Texas) presented an overview of evidence implicating the 9p chromosomal region, which contains JAK2, in the pathophysiology of myeloproliferative diseases such as PRV, essential thrombocythemia and myelofibrosis.² Through a genome-wide PCR-based screen for loss of heterozygosity, an area containing approximately 20 genes including JAK2 was identified on chromosome 9p in a large proportion of patients with erythropoietin-independent erythroid hyperplasia.³ Radek Skoda (Basel University Hospital, Switzerland) described a somatic mutation in JAK2 in which valine at position 617 changes to phenylalanine (V617F) in malignant cells with PRV, essential thrombocythemia and idiopathic myelofibrosis.⁴ Occurring in the pseudokinase domain of JAK2, this amino acid substitution prevents the naturally-occurring inhibition of the active kinase domain by its inactive counterpart, resulting in constitutive (constant) kinase activation.

This mutation has been identified in about 76% of patients with PRV, 50% of those with idiopathic myelofibrosis and 29% of those with essential thrombocythemia.⁶ Compared to patients with these diseases who have only wild type JAK2, those with the V617F JAK2 mutation have more marrow fibrosis, bleeding complications and thrombotic events. It appears that this mutation may be acquired after initiation of malignant growth since cells with the V617F JAK2 mutation are observed alongside malignant cells without it. This suggests that the mutation may be a secondary event, producing growth factor-independent outgrowth of a malignant subclone subsequent to a primary tumour-initiating mutation.

William Vainchenker presented a murine model of conditional V617F JAK2 expression in marrow cells. Mice expressing this mutated kinase have rapid polycythemia with massive erythroid hypercellularity of the marrow and increases in liver and spleen volumes.⁷ BFU-E from these mice grow independent of erythropoietin, displaying constitutively phosphorylated STAT5a and p42MAPK activation. After 3 months of erythroid hyperplasia, the hyperplasia remits and marrow fibrosis, dysmorphic red cells, high neutrophil counts and thrombocytopenia develop. These secondary features are likely due to an acquired second mutation,

suggesting that more than one genetic lesion causes the full phenotype.

Lippert et al reported a survey of expression of the JAK2 V617F mutation in PRV and essential thrombocythemia at the time of diagnosis and in controls with nonmalignant increase in erythrocyte or platelet counts. Astonishingly, V617F JAK2 was almost universally found in PRV and over 70% of patients with essential thrombocythemia, although expression levels differed. Patient samples from those with PRV had high expression of both the wild type and mutant forms of JAK2, while expression was lower in patients with essential thrombocythemia, suggesting related but distinct pathophysiology among these 2 groups of patients.

The information reviewed at the ASH meeting suggests that aberrant erythropoietin signalling through a mutated JAK2 molecule contributes to the pathogenesis of myeloproliferative syndromes. Such specific knowledge has diagnostic value, with JAK2 V617F assays now becoming available to distinguish physiological erythroid hyperplasia from PRV. Specific therapy can't be far behind. The therapy of CML with an inhibitor of activated kinase is well advanced: the drug imatinib specifically inhibits the kinase activity of the BCR-ABL gene mutation that results in CML. The

current JAK2 mutation research suggests that myeloproliferative syndromes may one day be similarly treatable. Specific inhibitors of JAK2, while perhaps producing considerable collateral damage of cytokine-dependent immune cells, could become valuable therapies, hopefully to prevent bone marrow fibrosis and failure and progression to acute myeloid leukemia.

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Multiple myeloma

DOUBLE AUTOLOGOUS TRANSPLANT VERSUS TANDEM AUTOLOGUS – NON MYELOABLATIVE ALLOGENEIC TRANSPLANT FOR NEWLY DIAGNOSED MULTIPLE MYELOMA. ASH 2005 ABSTRACT 46.

Investigators: B. Bruno et al.

TRIAL SUMMARY: This study included 241 consecutive patients younger than 65 years old who were diagnosed with multiple myeloma at 5 Italian centres between 1999 and 2004. Among the enrolled patients, 194 had siblings of whom 158 underwent HLA typing. Reasons for not proceeding with HLA typing included ineligibility of patients for high-dose chemotherapy (14), donors ineli-

ble (12) and patient refusal or unknown reasons (11). Of those who underwent HLA typing, 76 had a matched sibling donor and were offered a tandem autologous–nonmyeloablative allogeneic transplant (auto-allo) approach. Eventually, 56/76 (74%) of patients in the auto-allo group completed both transplants. Of the 102 patients who had no sibling donor or who did not proceed to allografting,

TABLE 4. Auto-allo* vs double-auto† transplant: outcomes at median followup of 3 years

	auto-allo*	double-auto†	p-value
transplant-related mortality	11%	4%	p = 0.09 (NS)
complete remission‡	46%	16%	p = 0.00008
overall survival	84%	62%	p = 0.003
progression-free survival	75%	41%	p = 0.00008
event-free survival	61%	38%	p = 0.006

* autografting using melphalan (200 mg/m²); after 2–4 months, low-dose (2.0 Gy) TBI, allogeneic peripheral hematopoietic cell infusion, then mycophenolate mofetil and cyclosporine

† autografting using melphalan (200 mg/m²); repeated after 2-4 months

‡ defined as disappearance of monoclonal paraprotein by immunofixation

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73 (72%) underwent double autologous transplant (double-auto). The remainder received less intensive therapies because of their clinical condition or treatment preference.

Patients in both allo-auto and double-auto groups had induction chemotherapy followed by autografting using high-dose melphalan (200 mg/m²) and mobilized peripheral blood stem cells. After 2–4 months, those in the auto-allo

group had low-dose (2.0 Gy) total body irradiation (TBI), allogeneic peripheral hematopoietic stem cell infusion from the sibling donor and posttransplant immunosuppressive therapy with mycophenolate mofetil and cyclosporine. Those in the double-auto group had a second autologous hematopoietic cell transplant. **Table 4** (page 21) shows results at median followup of 3 years (range 11–80 months).

NONMYELOABLATIVE UNRELATED DONOR (URD) HEMATOPOIETIC CELL TRANSPLANTATION (HCT) FOR THE TREATMENT OF PATIENTS (PTS) WITH POOR-RISK, RELAPSED OR REFRACTORY MULTIPLE MYELOMA. ASH 2005 ABSTRACT 2893.

Investigators: G.E. Georges et al.

TRIAL SUMMARY: This study reported on 24 patients with poor-risk myeloma who underwent nonmyeloablative peripheral blood stem cell allogeneic transplantation using HLA-matched unrelated donors (URDs). Study participants received fludarabine 90 mg/m² and 2 Gy TBI followed by postgraft immunosuppression using mycophenolate mofetil and cyclosporine. At the time of transplantation, 17 patients (71%) had chemotherapy-refractory disease and 14 (58%) had failed autologous transplantation. Thirteen underwent planned autologous-URD tandem transplants and 11 received

URD transplants only. After median followup of 2.5 years, 1 patient had nonfatal graft rejection and nonrelapse mortality was 22%. Complete response was seen in 11 patients (46%) and best response was observed in the recipients of tandem auto-allo transplants (among whom 8 [62%] had complete response). Patients receiving tandem autologous nonmyeloablative URD transplant had superior progression-free survival compared to those who went directly to unrelated donor transplant (63% vs 14%, $p = 0.03$) and a trend towards improved overall survival (76% vs 52%, $p = NS$).

COMMENTARY: David Allan, MD, FRCPC, Hematologist, University of Ottawa and Associate Scientist, The Ottawa Health Research Institute, Ottawa, ON.

Allogeneic transplantation using reduced-intensity conditioning has demonstrated marked reductions in transplant-related mortality compared with conventional myeloablative regimens in patients with newly-diagnosed, relapsed and/or refractory multiple myeloma. The role of allogeneic transplantation in comparison with autografting for multiple myeloma continues to evolve and the standard treatment approach for newly-diagnosed myeloma patients usually involves single or tandem autologous transplantation. The study by B. Bruno et al, presented at an oral session at the 2005 ASH in Atlanta, described a retrospective comparison of double autologous vs autologous followed by nonmyeloablative matched related allogeneic transplantation for newly-diagnosed patients with multiple myeloma. G.E. Georges et al's study, presented as a poster, reported a favourable experience of allografting with unrelated HLA-matched donors for relapsed/refractory myeloma. Together, these abstracts provide insight into the emerging role of reduced-intensity allogeneic transplantation for myeloma.

DOUBLE-AUTO VS TANDEM AUTO NONMYELOABLATIVE RELATED-ALLO TRANSPLANT

Bruno et al's study is the largest reported series combining the cytoreduction of autologous transplantation with the graft-versus myeloma effect of allogeneic transplantation. At the time of analysis, data at a median of 3 years followup was

available on all 56 auto-allo transplants and 55 of the 73 double-auto transplants. The results (**Table 4**, page 21) are intriguing and suggest that the auto-allo combination is beneficial. Patients were similar in both groups with respect to age and percentage with Stage III disease, although a greater number of patients in the auto-allo group had elevated $\beta 2$ -microglobulin levels (75% vs 59%, $p = 0.005$). While a trend towards increased transplant-related mortality was observed for the auto-allo group (11% vs 4%, $p = 0.09$), complete remission rates (46% vs 16%, $p = 0.0001$), overall survival (84% vs 62%, $p = 0.003$) and progression-free survival (75% vs 41%, $p = 0.00008$) were superior for the auto-allo patients.

These results are encouraging and may provide a standard approach to the treatment of newly-diagnosed myeloma in patients younger than age 65 who have HLA-matched siblings. Both groups appeared similar with regard to disease status and equal numbers of patients in both groups actually underwent the intended treatment. More information is needed on the patients receiving transplants, however, as well as longer followup. Possible patient-selection bias cannot be ignored. By including all patients who did not have a HLA-matched sibling and those who were ineligible or who deferred allografting in the double-auto group, the authors have included all patients in their analysis but have discarded an intention-to-treat approach. Corroboration of the findings

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LANDMARKS

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by other groups will be needed to address the issue of wide-spread applicability.

REDUCED-INTENSITY ALLOGENEIC TRANSPLANT USING MATCHED UNRELATED DONORS

Excessive transplant-related mortality has been noted with the use of allografting with conventional preparative regimens for patients with poor-risk or refractory disease or at the time of relapse following autologous transplant. Reduced-intensity conditioning regimens may reduce transplant-related mortality but carry a risk of myeloma progression given the omission of cytoreductive treatment, and the use of unrelated donors has been reserved mostly for younger patients. The report by G.E. Georges et al suggests that the use of unrelated donors does not appear to increase nonrelapse mortality in the treatment of multiple myeloma. The benefits of tandem autologous nonmyeloablative allo-

genic transplantation may be applicable to both HLA-matched related and unrelated donors. Cytoreductive therapy prior to allografting may be important for optimal disease control by the graft-versus-myeloma effect but is less applicable in cases of relapsed myeloma after a prior autologous transplant. Prospective biologically randomized studies where enrollment occurs prior to HLA typing are needed to provide unbiased studies on the value of nonmyeloablative allografting in myeloma and to demonstrate the safety and efficacy of using unrelated donors.

Taken together, these studies on the use of nonmyeloablative transplants for myeloma provide some optimism, both for newly-diagnosed patients and for those with relapsed and/or refractory disease. The use of unrelated donors in a nonmyeloablative setting appears to yield encouraging results and supports the increasing use of unrelated and alternative donors in the treatment of myeloma.

Diffuse large B cell lymphoma

SIX, NOT EIGHT CYCLES OF BI-WEEKLY CHOP WITH RITUXIMAB (R-CHOP-14) IS THE PREFERRED TREATMENT FOR ELDERLY PATIENTS WITH DLBCL: RESULTS OF THE RICOVER-60 TRIAL OF THE GERMAN HIGH-GRADE NON-HODGKIN LYMPHOMA STUDY GROUP (DSHNHL). ASH 2005 ABSTRACT 13.

Investigators: M. Pfreundschuh et al.

TRIAL SUMMARY: The RICOVER-60 trial randomized elderly patients with diffuse large B cell lymphoma (DLBCL) ages 61 to 80 years old to 6 vs 8 cycles of CHOP-14 (cyclophosphamide, doxorubicin, vincristine and prednisone every 14 days) with or without 8 cycles of rituximab (375 mg/m² given on Days 1, 15, 29, 43, 57, 71, 85 and 99). Patients received radiation therapy of 36 Gy to sites of initial bulk and/or extranodal involvement. The primary endpoint was freedom from treatment failure (FFTF) defined as additional therapy, failure to achieve complete remission, progressive disease, relapse or death. The trial was stopped in June 2005 due to a difference in the primary endpoint at the second interim efficacy analysis.

Of 1330 patients enrolled between July 2000 and June 2005, data was presented at the 2005 ASH Annual Meeting on 828 evaluable patients with diffuse large B cell lymphoma (DLBCL). The median age was 68 years. Fifty-four

percent of patients had Ann Arbor Stage I–II disease and 60% had an International Prognostic Index (IPI) of 1–2. Prognostic factors were similar among all treatment groups. With strict adherence to granulocyte colony stimulating factor (G-CSF) given Days 4 through 13, the relative dose intensity of cyclophosphamide was 96% in the 8-cycle arms and 99% in the 6-cycle arms.

Complete response (CR) was higher in the patients receiving CHOP-14 + rituximab (R-CHOP-14) (81%) compared to those receiving only CHOP-14 (73%, $p = 0.008$) (Table 5). At median followup of 26 months, more of the R-CHOP-14 patients (70%) reached the primary endpoint of FFTF, compared to the CHOP-14 patients (57%, $p = 0.00025$). The difference in OS was not statistically significant: 78% vs 74% ($p = 0.13$). The 2.5-year survival of poor-prognosis patients (those with IPI of 3–5) was 64% in the R-CHOP-14 arm. No added benefit was apparent for 8 cycles vs 6 cycles for CR rates (78% vs 76%, $p = 0.432$) or FFTF (64% vs 62%,

TABLE 5. Efficacy outcomes in the RICOVER-60 trial for R-CHOP-14 vs CHOP-14

	R-CHOP-14	CHOP-14	p-value
CR	81%	73%	$p = 0.008$
FFTF* at 26 months	70%	57%	$p = 0.00025$
OS at 26 months	78%	74%	$p = 0.13$ (NS)

*FFTF = freedom from treatment failure

$p = 0.23$). Any trend in favour of 8 vs 6 cycles appeared to be neutralized after the addition of rituximab. Grade 3–4

hematologic toxicity in all arms was around 40% and the risk of Grade 3–4 infections was 27%.

COMMENTARY: Carolyn Fought, MD, FRCPC, Hematologist, Assistant Professor of Medicine, The Ottawa Hospital, Ottawa, ON.

The German RICOVER-60 (rituximab with CHOP over 60) trial has potentially important clinical application, as the majority of all patients with DLBCL are over 60 years of age and the average age in this large randomized trial was 68 years. The rationale was based on the favourable results shown by Bertrand Coiffier et al with the addition of rituximab to CHOP-21 in the Groupe d'Etude des Lymphomes de l'Adulte (GELA)² and the improved outcome shown by Michael Pfreundschuh et al in the NHL-B2 trial of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL),³ with an interval reduction of 21 days to 14 days between CHOP cycles in elderly patients with DLBCL. The respective authors have attempted to compare these 2 trials. At 5 years, 43.5% of patients receiving CHOP-14 were event-free vs 32.3% of those receiving CHOP-21 ($p = 0.003$) and rates of OS were 53% vs 40.6% ($p < 0.001$). The 5-year outcomes in the GELA trial favouring R-CHOP-21 over CHOP-21 were 47.5% vs 28% ($p = 0.00002$) for EFS and 58% vs 45% ($p < 0.0073$) for OS.⁴ While the results appear similar, some important differences in these 2 trials complicate comparisons. The median age and IPI score was higher in the GELA trial. More than 40% of the patients in the NHL-B2 trial received radiation, not part of the planned treatment in the GELA trial. Finally, only 71% of the patients in the NHL-B2 trial actually had DLBCL.


The accrual for the RICOVER-60 trial began just after accrual in NHL-B2 closed.³ CHOP-14 was presumably considered the new treatment standard based on the findings of NHL-B2. RICOVER-60 was designed to answer 2 important questions: whether rituximab would improve CHOP-14 and whether 8 cycles are better than 6. Regarding the optimal number of cycles of CHOP, up until the 2005 ASH meeting no randomized trial had compared the efficacy and toxicity of 6 vs 8 cycles. Common practice is to give 2 further cycles of CHOP after documentation of CR with a minimum of 6 cycles, as most patients achieve CR after 4. Most clinical trials to date, however, have favoured the use of 8 cycles of CHOP, but the recently completed Mabthera International Trial (MINT) in younger patients with low-risk disease⁵ and the NHL-B2 trial² used only 6 cycles. RICOVER-60 showed only a trend for better FTF after 8 cycles of CHOP-14 compared to 6 cycles (58% vs 53%, $p = 0.13$). The addition of rituximab yielded 70% FTF for both 6 and 8 cycles of R-CHOP-14, neutralizing this trend, so the authors concluded that only 6 cycles were necessary. While this conclusion may hold up in general, patients with high-risk disease may derive some benefit from 8 cycles — but information to support this is not yet available.

In considering whether CHOP-14 is improved by adding rituximab, the finding of benefit in RICOVER-60 is consistent with results in the 3 major randomized trials to date in patients with DLBCL.^{2,6,7} So far, however, the benefit was only in FTF, not overall survival — in contrast to the GELA trial which showed a statistically significant EFS and OS benefit at both 2 and 5 years. Detailed subgroup analysis is not yet available for the RICOVER-60 trial but over half the patients had low-risk disease. In the GELA trial, 5-year OS of low-risk patients was 80% vs 62% ($p = 0.062$) in favour of R-CHOP-21 over CHOP-21.⁴ This will likely be a difficult number to improve upon. In contrast, high-risk patients had only a trend in 5-year OS favouring rituximab (48% vs 39%, $p = 0.062$) in the GELA trial. Pfreundschuh suggested that in RICOVER-60 the largest benefit was seen in patients with high-risk disease (IPI 3–5) with an estimated 2.5-year survival of 74% in the R-CHOP-14 arm, while results for the CHOP-14 arm were not reported. The benefit according to IPI may prove to be a fundamental difference in these 2 trials.

PRACTICAL CONSIDERATIONS FOR CHOP-14

A concern for physicians will be the feasibility of administering CHOP every 2 weeks. Other groups besides Pfreundschuh et al have shown that CHOP-14 is feasible when given with growth factor support.^{8,9} Despite the success in maintaining dose intensity with G-CSF in RICOVER-60, (96% to 99% dose intensity of cyclophosphamide), Grade 3–4 hematologic and infectious toxicities with CHOP-14 were considerably higher than with R-CHOP-21 (12% rate of Grade 3–4 infections in the GELA trial). This implies significant morbidity and cost to the individual patient — many of our elderly patients would likely be excluded from such a clinical trial based on comorbidities, cytopenias or bone marrow involvement.

Returning to Pfreundschuh's original question of whether rituximab improves upon CHOP-14, a better question to ask would have been whether R-CHOP-14 is better than R-CHOP-21. To definitively answer this the GELA are currently enrolling elderly DLBCL patients aged 66 to 80 years in such a study, LNH03-6B, which began recruitment in December 2003. Until results are available physicians will continue to mull over how best to deliver R-CHOP and will make individual decisions based on their current comfort and experience with both regimens. Clearly R-CHOP-14 is feasible in this elderly population but does result in at least a 2-fold risk of Grade 3–4 infections compared to R-CHOP-21. The cost and availability of G-CSF also may play a role in the treatment decision. At present, the followup for the RICOVER-60 trial is too short and important data

on outcomes with respect to subgroup analysis according to the IPI are missing. Although R-CHOP-14 may eventually turn out to be a superior regimen in patients with high-risk disease, as the RICOVER-60 trial's principle investigator suggests, it is premature to adopt R-CHOP-14 as the new standard in elderly patients with DLBCL. 

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