

Your article (# 03-2035) from Journal of the National Cancer Institute is available for download

=====

Dear author:

This site contains a PDF file of the page proofs of your article, scheduled for publication in the Journal of the National Cancer Institute, along with an offprint order form.

CORRECTIONS TO PAGE PROOFS ARE DUE 48 HOURS AFTER THIS MESSAGE WAS SENT; they should be sent to the production editor by fax or at the e-mail address given below.

THE OFFPRINT ORDER FORM IS DUE AT 5:00 P.M. EASTERN TIME ON July 7, 2004.

To access the site you will need to know:

URL address:

<http://rapidproof.cadmus.com/RapidProof/retrieval/index.jsp>

Your user ID, which is your e-mail address

Your password: ----

You will need Adobe Acrobat Reader software to read the PDF file (<http://www.adobe.com/products/acrobat/readstep.html>).

PAGE PROOFS

Please print out the PDF. Read the proofs carefully but confine your corrections to errors only. Avoid making non-essential changes that could have been made to the edited manuscript; the Journal reserves the right to refuse to make such changes or to require you to pay for them. Check all your data thoroughly to ensure that all numbers are cited correctly and consistently in the abstract and text and in any figures or tables. It is imperative that you return the proofs to your production editor within 48 hours of their being sent to you. **FAX ALL PAGES OF YOUR CORRECTED PAGE PROOF TO 301-841-1297.** If you have any questions or concerns, please contact the production editor to whom you sent your latest revision: Laurie Cullen, phone, 301-841-1282 (cullenl@oupjournals.org); Gabe Waggoner, 301-841-1283 (gabe.waggoner@oupjournals.org); or Maggie Meitzler, 301-841-1281 (meitzlem@oupjournals.org).

OFFPRINT ORDERS

If you would like offprints of your paper, please print out the PDF and return the completed form with payment by the date given above. Offprints (copies printed at the time of publication of an issue) must be scheduled in advance; reprints (copies printed after the time of publication) will cost **TWICE** the amounts listed on the enclosed form. Please note:

- 1) Offprints containing any color reproduction will cost twice the amount for black-and-white (see order form); offprints must be made with color if the actual published paper contains color.
- 2) Payment **MUST** accompany the offprint order form. Please express mail the form with credit card payment, check, or money order to: Journal of the National Cancer Institute, Offprint Coordinator, Suite 500, 8120 Woodmont Ave., Bethesda, MD 20814 (phone: 301-841-1270). Also, to guarantee your order if express mail delivery is delayed, **PLEASE FAX THE FORM (WITH CREDIT CARD PAYMENT OR PHOTOCOPY OF CHECK OR MONEY ORDER) TO: 301-841-1299.**
- 3) Offprints will not be made if we do not receive the offprint order form and payment by the deadline. It is the author's responsibility to make sure the check or other form of payment reaches us by the due date. Please call the Journal office at 301-841-1270 with any questions or to confirm receipt of your payment.

Thank you,

The Production Department

Journal of the National Cancer Institute

Journal of the National Cancer Institute
OFFPRINT ORDER FORM

To order offprints (copies made at time of publication) of your paper, please complete this form and return it with payment to the address below on or before the date indicated. Using the price schedule below, determine the amount due. Payment may be made by check or money order payable to Oxford University Press or by VISA, MasterCard, or American Express. (We cannot accept institutional purchase orders.) Rates include shipping (be sure to verify the shipping address below). Only prepaid orders can be processed, and cancellations cannot be accepted. **Allow 8 weeks after publication for delivery within the United States; allow 12-16 weeks for delivery outside the United States.** Your order must be received before the issue goes to press; copies ordered after publication will cost more and will require an extra 6 weeks to process. Only one shipping address may be used for an order, but multiple orders for a single paper may be made. (Note: The federal taxpayer ID number for Oxford University Press is 23-7398718.)

MS No.: 03-2035

Title: _____

Authors: _____

COMPLETED FORM AND PAYMENT ARE DUE: July 7, 2004

(OFFPRINTS WILL NOT BE MADE unless form and payment are received by this date.)

Quantity (in increments of 100): _____ Amount due: _____

Payment method (circle one): *Check enclosed / Money order enclosed /*
VISA / MasterCard / American Express

Credit card No.: _____ Exp. date: _____

Signature: _____

PRICE SCHEDULE*	No. of offprints	1-8 pages, no color	1-8 pages, with color†	9-16 pages, no color	9-16 pages, with color†	17-24 pages, no color	17-24 pages, with color†
	100	\$275	\$550	\$340	\$680	\$400	\$800
	200	460	920	535	1070	600	1200
	300	580	1160	660	1320	740	1480
	400	690	1380	800	1600	900	1800
	500‡	820	1640	930	1860	1030	2060

*Residents of North Carolina and California and of Canada please add the appropriate sales tax.

†If the original contains any color, color charges apply to offprints.

‡For orders over 500, please contact Julie Gribben at 44 1865 267827, fax: 44 1865 267774.

Ship my offprints to the following address:

PLEASE EXPRESS MAIL this form (with payment) to: Offprint Coordinator, *Journal of the National Cancer Institute*, Suite 500, 8120 Woodmont Ave., Bethesda, MD 20814-2743 (telephone 301-841-1270). **ALSO, PLEASE FAX** the form (with credit card payment or copy of check or money order) to: 301-841-1299.

NOTE: The corresponding author of this paper will receive one free copy of the complete issue in which the paper appears. Authors of the paper may purchase additional copies now for UK£12 (in Europe) or US\$18.75 (in the U.S., Canada, and rest of the world) per copy. Names, addresses, and payment for the additional copies must accompany this form.

ARTICLES

Conventional Adjuvant Chemotherapy Versus Single-Cycle, Autograft-Supported, High-Dose, Late-Intensification Chemotherapy in High-Risk Breast Cancer Patients: A Randomized Trial

Robert C. F. Leonard, Michael Lind, Christopher Twelves, Robert Coleman, Simon van Belle, Charles Wilson, Jonathan Ledermann, Ian Kennedy, Peter Barrett-Lee, Timothy Perren, Mark Verrill, David Cameron, Elizabeth Foster, Ann Yellowlees, John Crown

For the Anglo-Celtic Cooperative Oncology Group

Background: Breast cancer patients with four or more positive axillary lymph nodes who are treated with conventional adjuvant therapy have a poor prognosis. In uncontrolled studies, high-dose chemotherapy produced much better results than conventional therapy. We compared the benefits of a single cycle of high-dose chemotherapy and the benefits of conventional chemotherapy in patients with high-risk breast cancer in a prospective, unblinded, randomized trial. **Methods:** Between February 23, 1995, and June 29, 1999, 605 patients with breast cancer who had four or more positive lymph nodes were randomly assigned to treatment (307 to high-dose therapy and 298 to conventional therapy). The conventional chemotherapy regimen was four cycles of doxorubicin (75 mg/m² of body surface area) followed by eight cycles of CMF (cyclophosphamide [600 mg/m²], methotrexate [50 mg/m²], and 5-fluorouracil [600 mg/m²]), all given intravenously on day 1 of a 21-day cycle. The high-dose regimen was four cycles of doxorubicin (75 mg/m²), followed by a single cycle of intermediate-dose cyclophosphamide (4000 mg/m²) supported by filgrastim (300 µg/day) for up to 10 days followed by high-dose cyclophosphamide (6000 mg/m²) and thiotepa (800 mg/m²). Peripheral blood progenitor cells were harvested by leukapheresis after treatment with cyclophosphamide and filgrastim and then re-infused after the high-dose cycle. Log-rank tests were used to compare survival rates. All statistical analyses were two-sided. **Results:** At a median follow-up of 6 years, no statistically significant differences were detected between the arms in 5-year relapse-free survival (high-dose arm = 57%, 95% confidence interval [CI] = 51% to 63%; conventional-dose arm = 54%, 95% CI = 48% to 61% (*P* = .73) or in 5-year overall survival (high-dose arm = 62%, 95% CI = 56% to 68%; conventional-dose arm = 64%, 95% CI = 57% to 70%) (*P* = .38). **Conclusion:** Autograft-supported, high-dose therapy is not superior to conventional chemotherapy in patients with breast cancer who have multiple involved lymph nodes. This conclusion should be viewed in the context of improving the success of conventional chemotherapy. [J Natl Cancer Inst 2004;96:000-000]

Many patients with apparently localized breast carcinoma already harbor micrometastases, which can lead to relapse. The probability of such occult dissemination before definitive surgery is influenced by a number of factors, including tumor size, overexpression of the HER2/neu oncogene, and axillary lymph node status. Approximately two-thirds of patients with four or more lymph nodes that contain cancer cells (i.e., positive lymph nodes) at surgery will develop fatal metastases (1). These patients require systemic adjuvant chemotherapy in addition to surgery (2), and adjuvant endocrine therapy has also been shown to reduce the risk of relapse (3).

Breast cancer is a partially chemotherapy-sensitive neoplasm (4), and contemporary chemotherapy regimens frequently produce tumor regression in patients with overt metastases. Tumor regression, which is usually partial and almost always temporary, translates into improvements in quality of life and provide a degree of prolonged survival. Although cure is rare, survival is increased by more than 1 or 2 years (5). The impact of these same treatments is considerably greater when they are used as postoperative adjuvant therapy in patients with early-stage disease (6), a phenome-

Affiliations of authors: South West Wales Cancer Institute and University of Wales, Swansea (RCFL); Academic Department of Oncology, University of Hull, Hull, England (ML); Cancer Research UK Cancer Research Unit, University of Bradford, Bradford, England (CT); Weston Park Hospital and University of Sheffield, Sheffield, England (RC); University Hospital of Ghent, Ghent, Belgium (SVB); Addenbrookes Hospital, Cambridge, England (CW); University College, London, England (JL); Waikato Hospital, Waikato, New Zealand (IK); Velindre NHS Trust and Welsh School of Pharmacy, Cardiff, Wales (PBL); St. James's University Hospital, Leeds, England (TP); Northern Institute for Cancer Research, Newcastle upon Tyne, England (MV); Western General Hospital and Edinburgh University, Edinburgh, Scotland (DC); Scottish Cancer Therapy Network, Edinburgh (LF); Quantics Consulting Limited, Edinburgh (AY); St. Vincent's University Hospital, Dublin, Ireland (JC).

Correspondence to: R. C. F. Leonard, MD, South West Wales Cancer Institute, Singleton Hospital, Swansea, Wales, U.K. SA2 8QA (e-mail: r.c.f.leonard@swan.ac.uk).

See "Notes" following "References."

DOI: 10.1093/jnci/djh188

Journal of the National Cancer Institute, Vol. 96, No. 14, © Oxford University Press 2004, all rights reserved.

non that is consistent with the preclinical results of Skipper and Schabel (7), who reported that all cancer cells grow and regress according to exponential kinetics and that there was invariably an inverse relationship between a tumor's size and its response to chemotherapy.

Adjuvant chemotherapy is now a widely accepted component of standard treatment for patients with lymph node-positive breast cancer or for patients with higher-risk, lymph node-negative breast cancer. There is general agreement that the anthracycline-containing combination chemotherapies are superior to older regimens that included only alkylating agents and antimetabolites, such as CMF (cyclophosphamide, methotrexate, and 5-fluorouracil). One such adjuvant therapy regimen, A-CMF (doxorubicin followed by CMF), has produced particularly promising results in breast cancer patients with multiple positive lymph nodes (8). However, the benefit of adjuvant chemotherapy, although of societal importance in reducing the death rates from this common cancer (9), has not met the expected benefit calculated by the exponential model (10). The absolute annualized survival benefits amount to a reduction in mortality of about 10% for lymph node-positive breast cancer (11).

There are several possible explanations for this modest effect on absolute annualized survival. Drug-resistant cancer cells may lead to treatment failure. Such cells may be present before drug treatment or may develop by mutation in response to the evolutionary pressure of chemotherapy (10). In addition, resistance might be relative rather than absolute. Dose-response relationships are fundamental to human pharmacology; in laboratory systems, cells can be killed by higher doses of chemotherapy drugs but can be resistant to lower doses of the same drug (12). Logarithmic degrees of dose escalation were usually required to effect cure in these models, and regimens that deliver modestly increased doses produce only inconsistent results (13,14).

Bone marrow autografting allows patients to receive much higher doses of chemotherapy agents (especially the alkylating agents) whose doses are otherwise limited by myelosuppression (15). In early studies (16,18,19), high-dose chemotherapy with autologous bone marrow cell support produced high rates of temporary response in patients with metastatic breast cancer who had already received extensive prior chemotherapy. Such prior treatments would have limited the tolerance of these patients to further chemotherapy and increased the likelihood that the cancers would be relatively resistant to further chemotherapy. Prolonged myelosuppression, however, frequently caused treatment-related death (16). This problem was addressed by the introduction of hematopoietic growth factors and peripheral blood progenitor cells that dramatically reduced the toxicity of this treatment, facilitating its use in patients at an earlier stage of the disease, especially in patients receiving adjuvant therapy (17).

The strategy that evolved and has been studied in most subsequent trials was the induction intensification strategy, in which patients receive conventional chemotherapy, followed by high-dose therapy as a late-intensification regimen. Nonrandomized studies indicated that there was a substantial benefit from high-dose therapy in patients with metastatic breast cancer and early disease in patients who had multiple positive lymph nodes (18,19), so even in the absence of appropriate evidence from randomized trials, high-dose therapy was soon established as a widely used standard therapy for breast cancer (20). Because of

the urgent need for confirmation of these results in randomized trials, the Anglo-Celtic Group was founded in 1994 for the express purpose of conducting a prospective, nonblinded, randomized trial that compared a single cycle of high-dose chemotherapy with conventional chemotherapy in patients with high-risk breast cancer.

PATIENTS AND METHODS

This study was an open-label, prospective, randomized, comparative trial. Eligible patients had operable, histologically proven, high-risk stage II or IIIa breast carcinoma (pT1-3), with involvement of four or more axillary lymph nodes and no evidence of distant metastases. Clinical staging was performed according to the standard policy of the contributing center. Adequate surgery was mandatory, as defined by pathologic confirmation of disease involving a minimum of four ipsilateral axillary lymph nodes after surgical eradication with no evidence of remaining macroscopic disease locoregionally or as defined by conventional radiologic and blood screening examinations. In addition, all patients were older than 18 years (there was no upper age limit), had an Eastern Cooperative Oncology Group (ECOG) performance status at entry of 0 or 1, had confirmed normal hematologic and biochemical parameters, and had no history of malignant disease (except basal cell carcinoma or *in situ* carcinoma of the cervix). Estrogen receptor analysis was not mandated (see below). Patients were stratified into two groups, according to the number of involved lymph nodes (4-9 or 10 or more).

After providing written informed consent and before starting any chemotherapy, 605 patients were randomly assigned to one of the two treatment arms (307 to the high-dose arm and 298 to the conventional-dose arm) by the trial management office. Treatment was allocated by use of a computer-based randomization program that balanced two patient factors: 1) hospital of treatment and 2) number of positive lymph nodes (4-9 or 10 or more). Patients were randomly assigned to their treatment by telephone from the trial management office. The conventional-dose regimen consisted of four cycles of doxorubicin (75 mg/m² of body surface area [unit of measure applies to all subsequent doses]) given at 3-week intervals followed by eight cycles of intravenous CMF given at 3-week intervals (in doses of 600, 50, and 600 mg/m², respectively). The high-dose regimen also consisted of four cycles of doxorubicin (75 mg/m²) at 3-week intervals, followed by a stem-cell mobilization cycle of cyclophosphamide (4000 mg/m²) and filgrastim (300 µg/day) until adequate CD34 cell counts were obtained. This treatment was followed by leukapheresis to harvest peripheral blood progenitor cells; a minimum of 1 × 10⁶ CD34-positive cells was required. If this criterion was not met, bone marrow was harvested. After a 7- to 10-day rest period, patients received high-dose therapy with cyclophosphamide (6000 mg/m²) and thiotepa (800 mg/m²). Cyclophosphamide (with mesna at 900 mg/m² in 1 L of normal saline over 24 hours) and thiotepa (in 1 L of normal saline over 24 hours) were administered concurrently over 24 hours on days 0, 1, 2, and 3, with 1 L of normal saline containing mesna (300 mg/m²) given over 12 hours on day 4. At the largest recruiting center with the most experienced nurses, nine patients in the high-dose arm were managed during the recovery phase as outpatients. No early deaths occurred in this group. All other patients in the high-dose arm were admitted to the hospital

within the next 2 or 3 days after infusion for protocol-guided management of the recovery phase for marrow function. After recovering from the toxic effects of chemotherapy, patients were given adjuvant radiotherapy according to institutional guidelines. The protocol mandated that, after the completion of chemotherapy, tamoxifen (20 mg/day taken orally for 5 years) be taken by all patients with known estrogen receptor–positive tumors and to all patients with unknown estrogen receptor status. The patients who were estrogen receptor–negative were given tamoxifen at the discretion of the treating physician. At the time of the trial, overview data were lacking on whether tamoxifen was beneficial for estrogen receptor–negative disease.

Radiation therapy to the chest wall was given to all patients after completion of all chemotherapy. Field size and dose were set out in the protocol. Variations in axillary fields were allowed according to the extent of axillary surgery and the presence of an extra-nodal extension of axillary lymph node metastases.

Of the 605 patients randomly assigned to treatment (Fig. 1), 307 were assigned to high-dose therapy, 296 of these patients received their allocated treatment, two of these patients were lost to follow up, and 15 discontinued treatment; all patients in the high-dose arm, except the two patients lost to follow-up, were included in the intent-to-treat analysis. In the conventional-dose arm, 298 patients were randomly assigned to treatment, 290 of these patients received their allocated treatment, no patient was lost to follow-up, and four of these patients discontinued treatment; all patients in the conventional-dose arm were included in the intent-to-treat analysis.

Statistical Methods

The 5-year relapse-free survival rate was expected to be about 50% in the conventional-dose arm from the results of Bonadonna et al. (8). With 300 patients assigned to each arm, their study was designed to have 80% power to detect an absolute difference (by a two-sided test) of 12% in relapse-free survival at 5 years with an alpha level of 5%.

Patient characteristics were compared between the two arms of the trial to check for balance. For continuous variables, the median, maximum, and minimum values were reported for each

arm, and the Wilcoxon test was used to compare the results among arms. For categorical variables, Fisher’s exact test was used to compare proportions, except that the chi-squared test was used when there were more than two classes.

Relapse-free survival was defined as the shorter of the time to first relapse or the time to death from breast cancer. Patients who were alive and disease-free had their relapse-free survival censored at the date they were last seen alive. Patients who died from causes other than breast cancer had their relapse-free survival censored at the date of death. Overall survival was defined as the time to death from any cause. Patients who were alive had overall survival censored at the date last seen alive. A further end point—event-free survival—was also defined as the shorter of either the time to first recurrence or the time to death from any cause. Toxicity was monitored by the Monitoring Committee. If treatment-related mortality had reached unacceptable levels (5%), the trial would have been stopped. A sequential decision rule was used. Analysis was to be performed on an intent-to-treat basis. No interim analyses were planned.

Survival curves for end points were estimated by the Kaplan–Meier method, and the curves were compared between treatment arms with the log-rank test, stratified by lymph node status. Five-year survival was estimated, and 95% confidence intervals (CIs) were calculated. The Cox proportional hazards model was also used to compare relapse-free survival between the treatment arms, adjusting for age, menopausal status, estrogen receptor status, and lymph node status. The hazards functions for the subgroups were compared graphically and were judged to have met the proportionality assumptions required for this analysis. All statistical tests were two-sided.

Study Organization and Support

The Anglo-Celtic Cooperative Oncology Group is a voluntary, investigator-led initiative, set up specifically to conduct this study (and future studies) in the United Kingdom and Ireland. The Group expanded in 1997 to include investigators from Belgium and New Zealand. Data management was provided through the Scottish Cancer Treatment Network. Amgen (U.K.) provided an unrestricted grant to facilitate the conduct of the trial and offered filgrastim to participating centers at reduced cost.

RESULTS

The study accrued 605 patients from 34 centers from February 23, 1995, through June 29, 1999. This analysis includes all follow-up information that was available through December 31, 2002; at this time, the median follow-up was 60 months (range = 42–82 months). Patient characteristics are presented in Table 1. The two groups were balanced, with no statistically significant differences observed in prognostic factors for breast cancer. A high percentage of patients were of unknown hormone receptor status, reflecting prevailing pathologic practices in the United Kingdom and Ireland at the beginning of the study. Primary breast cancer treatments that the patients received were well balanced, with 207 patients in the high-dose arm and 221 patients in the conventional-dose arm having received mastectomy and with 100 patients in the high-dose arm and 77 patients in the conventional-dose arm having received breast-conserving sur-

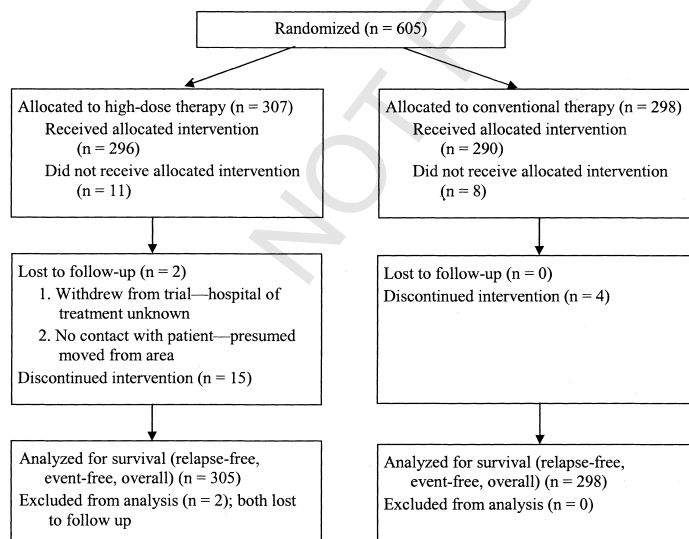


Fig. 1. Flow diagram for Anglo-Celtic Cooperative Oncology Group Trial 1 (ACCOG-1).

Table 1. Characteristics of patients by treatment allocated

Characteristic	Chemotherapy regimen		P value*
	High dose (n = 307)	Conventional dose (n = 298)	
Median age at randomization, y (range)	45 (22–63)	46 (25–64)	.09
Lymph node status, %			
4–9 positive lymph nodes	56	54	.68
≥10 positive lymph nodes	44	46	
Histologic tumor grade, %†			
1	4	5	.65
2	29	32	
3	61	56	
Unknown	6	7	
Estrogen receptor status, %			
Positive	28	35	.09
Negative	24	26	
Unknown	48	39	
Median maximum tumor diameter, cm (range)‡	3.0 (0.5–13.0)	3.0 (0.5–20.0)	.89
Vascular involvement, No. (%)	153 (53)	146 (53)	1.00
Type of surgery, No. (%)			
Mastectomy	207 (83)	221 (86)	.07
Breast-conserving	100 (17)	77 (14)	
Radiotherapy to breast and/or chest wall, No. (%)	273 (95)	274 (95)	.85
Radiotherapy to axilla, No. (%)	77 (27)	79 (27)	.93
No. given tamoxifen (%)	237 (83)	228 (79)	.24

*For continuous variables, a two-sided Wilcoxon test was used. For categorical variables, a two-sided Fisher’s exact test or chi squared test, if more than two classes, was used.

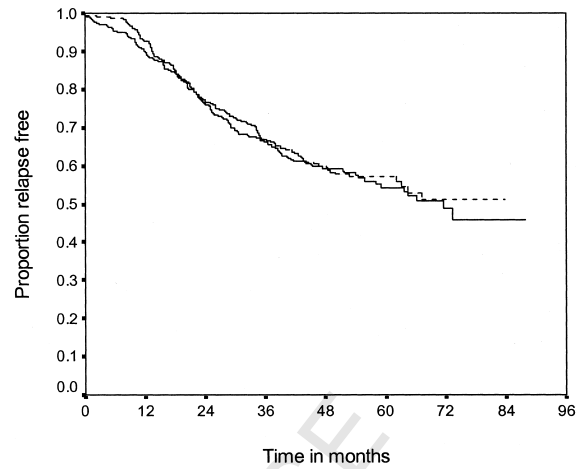
†The system described by Bloom and Richardson (40) was used.

‡Two patients on each arm had their tumor size recorded as entire breast; seven patients were missing a tumor size, all on the conventional arm.

gery. Radiotherapy was also well balanced, with 273 and 274 patients in the high-dose and conventional-dose arms, respectively, receiving radical treatment to breast and/or chest wall and with 77 and 79 patients in each arm receiving radiotherapy treatments to the axilla. At the completion of chemotherapy, 237 patients in the high-dose arm and 228 patients in the conventional-dose arm were assigned to 5 years of tamoxifen treatment. There was no statistically significant difference in the type of surgery or in the application or sites of radiation therapy. Thirty-eight patients were withdrawn from the trial, of whom 26 were in the high-dose arm. Although five of these 26 patients were found to have had metastases when screened after randomization, they were included in the analysis. Thus, all 38 of these patients were included in the survival analysis (according to intention to treat). A separate analysis in which these patients were excluded reached almost the same conclusions. Consequently, it was the view of the Data Monitoring Committee that they should be included.

Relapse-Free Survival

There was no statistically significant difference in relapse-free survival between the arms of the trial. At the time of this analysis, 253 relapses had been reported (four of which were deaths from cancer in which initial time of relapse was not reported), 124 of the 253 patients were in the high-dose arm and 129 patients were in the conventional-dose arm. Figure 2 shows the life-table estimates of the relapse-free survival probabilities for these two groups. Two patients, both on the high-dose arm of the study, were lost to follow-up immediately after random



Months	0	12	24	36	48	60	72	84	
At risk at start of interval	305	278	230	182	111	52	15	4	Conventional
								0	High dose

Fig. 2. Relapse-free survival. The 5-year relapse-free survival for the conventional-dose arm was 54% (95% confidence interval [CI] = 48% to 61%) and that for the high-dose arm was 57% (95% CI = 51% to 63%). The number of patients at risk at the start of each time interval is shown at the bottom. Solid line = conventional chemotherapy; dashed line = high-dose chemotherapy.

assignment, so the number of patients in the high-dose arm for this analysis was 305. The difference between the groups at this stage was not statistically significant ($P = .73$, log-rank test adjusted for lymph node status). The 5-year relapse-free survival rate estimated for the high-dose arm was 57% (95% CI = 51% to 63%) and that for the conventional-dose arm was 54% (95% CI = 48% to 61%). The Cox proportional hazards model was also applied to the relapse-free survival analysis to adjust for age, menopausal status, estrogen receptor status, and lymph node status. The adjusted difference between the treatment arms was not statistically significant ($P = .64$). Several subgroup analyses (which were not specified in the original protocol) were conducted. No obvious benefit for high-dose therapy over conventional-dose chemotherapy was observed in patients with four to nine involved axillary lymph nodes or 10 or more involved axillary lymph nodes in patients who were age 50 years or younger or in patients who were pre- or postmenopausal.

Overall Survival

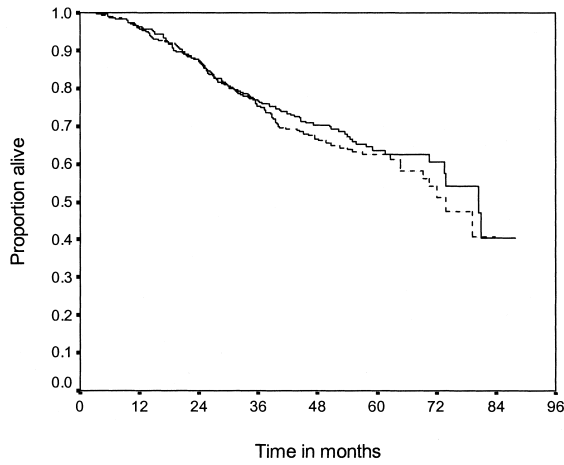
The life-table estimates of the overall survival probabilities for the two arms of the trial are shown in Fig. 3. At the time of this analysis, 211 deaths had been reported: 111 in the high-dose arm and 100 in the conventional-dose arm. The difference between the groups at this stage was not statistically significant ($P = .38$, log-rank test adjusted for lymph node status), and no statistically significant difference between the arms was observed for any subgroup. The 5-year overall survival rate estimated for the high-dose arm was 62% (95% CI = 56% to 68%) and that for the conventional-dose arm was 64% (95% CI = 57% to 70%).

Toxicity

There were five treatment-related deaths in the high-dose arm. These five patients were randomly assigned between April

F2

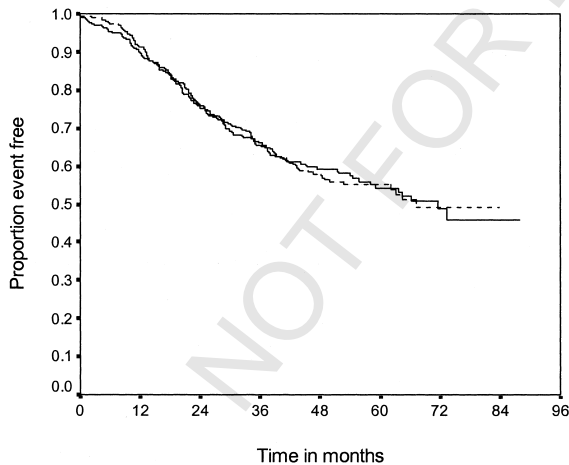
F3



Months	0	12	24	36	48	60	72	84	
At risk at start of interval	298	287	257	212	134	68	23	4	Conventional
	305	291	265	200	132	61	18	0	High dose

Fig. 3. Overall survival. The 5-year overall survival for the conventional-dose arm was 64% (95% confidence interval [CI] = 57% to 70%) and that for the high-dose arm was 62% (95% CI = 56% to 68%). The number of patients at risk at the start of each time interval is shown at the bottom. **Solid line** = conventional chemotherapy; **dashed line** = high-dose chemotherapy.

1995 and September 1998 and died between October 1996 and March 1999. The causes of death were sepsis, suspected pulmonary fibrosis, toxic shock syndrome, organ failure caused by systemic *Aspergillus* infection, and gram-negative bacterial sepsis. Because of the frequency of treatment-related deaths, it was also appropriate to examine event-free survival, where an event was defined as a relapse of cancer or a treatment-related death. These results are shown for the two treatment arms in Fig. 4. Again, the difference between the arms was not statistically significant ($P = .89$, adjusted for lymph node status). The 5-year



Months	0	12	24	36	48	60	72	84	
At risk at start of interval	298	268	224	184	111	57	19	4	Conventional
	305	278	230	182	111	52	15	0	High dose

Fig. 4. Event-free survival. The 5-year event-free survival for the conventional-dose arm was 54% (95% confidence interval [CI] = 48% to 61%) and that for the high-dose arm was 55% (95% CI = 49% to 61%). The number of patients at risk at the start of each time interval is shown at the bottom. **Solid line** = conventional chemotherapy; **dashed line** = high-dose chemotherapy.

event-free survival rate estimated for the high-dose arm was 55% (95% CI = 49% to 61%) and that for the conventional-dose arm was 54% (95% CI = 48% to 61%).

Nonlethal Toxicity

Toxicity caused by chemotherapy was largely predictable and successfully managed at all centers. A detailed analysis of toxicities from the induction phase of chemotherapy with doxorubicin found that the main hematologic toxicity was, predictably, neutropenia, which was grade 4 in 89 of the 605 patients and was associated with infection in 13 patients; none of the infections were reported as life threatening. Grade 3 nausea was reported in 51 patients, and severe vomiting was reported in 17 patients. There was no clinical cardiac toxicity, and other toxicities were minor.

Toxicities reported on the treatment summary form and on follow-up forms after completion of treatment are provided in Table 2. In addition, several cases of shingles were reported in patients in the high-dose arm, although data on this complication were not collected systematically, and all cases of shingles responded well to treatment with acyclovir. Menopausal symptoms were also a common complaint among women in both arms of the trial but, again, these data were not collected systematically.

There were, not surprisingly, marked differences in the toxicities associated with high-dose chemotherapy compared with conventional-dose chemotherapy (Table 2). Apart from the inevitable hematologic toxicities, liver function tests were transiently abnormal in approximately 6% of the patients in the high-dose group, and minor proteinuria or hematuria (presumably from chemical cystitis caused by cyclophosphamide) was

Table 2. Final chemotherapy toxicity

Toxicity	CTC* grade of at least	No. of patients	
		High-dose arm	Conventional arm
Hematologic			
Hemorrhage	2	24	3
Platelets	3	58	3
Neutrophils	4	64	67
Gastrointestinal			
Bilirubin	3	20	2
Transaminases	2	27	14
Alkaline phosphatase	2	13	1
Nausea	3	91	8
Vomiting	4	44	5
Diarrhea	3	70	3
Renal			
Blood urea nitrogen or creatinine	2	7	1
Proteinuria	2	6	0
Hematuria	2	14	1
Pulmonary			
Allergy	2	18	5
Skin			
Skin	2	23	3
Skin	3	18	6
Infection	3	86	11
Cardiac			
Rhythm	2	6	1
Function	2	3	1
Pericardial	1	3	0
Neurotoxicity			
Cortical	1	7	3
Sensory	2	1	0
Constipation	3	5	2
Local (pain)	2	19	1

*CTC = Common Toxicity Criteria (41).

also noted. Minor toxicities associated with pulmonary function, skin and allergic events, and cardiac rhythm disturbance were reported in 1%–2% of patients in the high-dose arm (Table 2). A quality-of-life assessment will be reported separately; however, the quality of life associated with high-dose therapy was only transiently lower than that associated with conventional-dose therapy.

DISCUSSION

The results of this first protocol-mandated analysis of the data from the Anglo-Celtic Cooperative Oncology Group Trial 1 (ACCOG-1) study suggest that a high-dose regimen consisting of doxorubicin followed by one cycle of intermediate-dose cyclophosphamide and finally by an autograft-supported cycle of a high-dose combination of alkylating agents is not superior to a conventional-dose adjuvant chemotherapy regimen in patients with breast cancer and multiple positive lymph nodes. Because the trial had a low incidence of treatment-related mortality, this result appears to reflect a genuine equivalence of the anticancer effect of the two treatments, a result that was not confounded by any putative impact of treatment-related mortality on overall survival.

It is important to note that the outcome of current conventional adjuvant treatment regimens may be better than that of the conventional adjuvant treatment regimens used in the uncontrolled studies of high-dose treatment of the early 1990s (19). In fact, the A-CMF regimen used in this trial appears to be an effective therapy for breast cancer patients with four or more positive lymph nodes and may not be inferior to the newer taxane-based regimens—a possibility that is currently being tested in a randomized trial in the U.K. In indirect comparisons, medium-term, disease-free survival was at least equivalent for patients treated with a block sequential A-CMF regimen and for patients treated with taxane-based regimens (21–23).

A similar argument may also explain the relative lack of benefit for patients treated with a single high-dose, late-intensification regimen, as reported in the Swedish trial by Bergh et al. (24). However, the conventional-dose arm in that trial was distinctly unconventional because of its pioneering use of a tailored, toxicity-directed, dose escalation regimen that resulted in higher total doses for several cytotoxic agents than those in the high-dose arm.

Although the results of randomized trials of high-dose chemotherapy in patients with metastatic breast cancer and in the adjuvant setting for high-risk, early-stage breast cancer have not fulfilled the expectations generated by the results of earlier nonrandomized trials, none of these randomized trials (24–33) reported improved overall survival in the high-dose arm. The accumulation of these data, coinciding with the disclosure that the results of two other allegedly positive studies were unreliable (34,35), resulted in an appropriate decline in the use of high-dose therapy as an off-study treatment for breast cancer. Regrettably, however, valid ongoing studies were also prematurely terminated. A consensus emerged that the promising results reported from single-arm studies of high-dose chemotherapy were artifacts of case selection biases (36).

Could it be that an inadequate reduction of tumor burden was achieved by the anthracycline induction phase of high-dose chemotherapy, an outcome that was ameliorated by prolonged CMF exposure in the conventional-dose arm? Three large stud-

ies of autograft-supported, high-dose, adjuvant chemotherapy given as a late-intensification regimen versus more conventional approaches have been published (24,25,30). The Bergh et al. study (24) was discussed above. The Dutch national study (25) compared FEC therapy (5-fluorouracil, epirubicin, and cyclophosphamide) followed by high-dose chemotherapy with FEC therapy alone in breast cancer patients with four or more involved lymph nodes. There was a statistically nonsignificant trend for improved relapse-free survival in the high-dose arm. For patients with 10 or more involved lymph nodes, those in the high-dose arm had statistically significantly longer relapse-free survival ($P = .05$) than those in the FEC alone arm (25). A smaller ECOG trial showed no benefit for a single high-dose intensification regimen (30). Two other small negative studies had limited power to detect differences between treatment regimens (27,28).

In a study by Peters et al. (29), a decreased rate of cancer relapse was associated with high-dose therapy compared with conventional-dose therapy, but a relatively high rate of treatment-related death in the high-dose arm undermined any survival benefit. In a French trial (PEGASE 01) (30), high-dose therapy, compared with conventional-dose control therapy (four cycles of FE₁₀₀C), was associated with superior disease-free survival but not with superior overall survival. A small Japanese (37) study was also negative. Gianni et al. (31) reported that an alternative approach to a therapeutic intensification regimen was not superior to A-CMF. In the alternative approach, higher-than-standard doses of single agents were administered in sequence, followed by a single autograft-supported cycle of high-dose sequential chemotherapy. Thus, these studies appear to indicate that high-dose chemotherapy has a weak or inconsistent impact, or perhaps no impact at all, in breast cancer. However, we urge that a meta-analysis be conducted of the currently completed trials of adjuvant high-dose chemotherapy to provide additional information.

The results of the high-dose treatment could be dependent on the specific form of high-dose chemotherapy investigated or on the order in which agents were administered. Is the dogma that high-dose chemotherapy should be given after a phase of conventional induction therapy correct? Is single-cycle, high-dose therapy ever going to be adequate to initiate cure by killing cancer cells or does it merely serve to induce chemoresistance? It has been hypothesized that multiple high-dose cycles should be administered as primary treatment in order to overcome resistance (38). It is striking that three recent studies (32,33,39), two of which showed increased disease-free survival (32,33) with the third (39) showing a compelling trend for increased disease-free survival, had at least two cycles of high-dose therapy with limited conventional induction therapy. Other explanations for the failure of high-dose chemotherapy to eradicate disease include graft contamination by tumor cells or the differential effects of high-dose therapy on distinct biologic subgroups of patients (e.g., those defined as positive or negative for HER2)—should also be considered.

In conclusion, after surgery for high-risk breast cancer, a single high-dose chemotherapeutic treatment, given after a phase of conventional-dose anthracycline chemotherapy, is not superior to conventional-dose A-CMF sequential chemotherapy. This conclusion is based on a protocol-directed analysis of the outcomes after a median follow-up of 60 months. These results both in isolation and in the context of the individual analyses of

similarly powered, single, high-dose, randomized, controlled trials, indicate that the single, high-dose, late-intensification chemotherapy strategy confers extra cost and toxicity without added anticancer benefit. The results of two similarly designed trials (24,28), however, suggest that there may be biologically discrete subgroups of patients who appear to benefit. Results of a meta-analysis of all the available data from the recent studies may allow better targeting of relevant therapy to such subgroups.

REFERENCES

- (1) Jatoi I, Hilsenbeck SG, Clark GM, Osborne CK. Significance of axillary lymph node metastasis in primary breast cancer. *J Clin Oncol* 1999;17:2334–40.
- (2) Fisher B. Laboratory and clinical research in breast cancer—a personal adventure: the David A. Karnofsky memorial lecture. *Cancer Res* 1980;40:3863–74.
- (3) Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Early Breast Cancer Trialists' Collaborative Group. *Lancet* 1992;339:1–15.
- (4) Hortobagyi GN. Treatment of breast cancer. *N Engl J Med* 1998;339:974–84.
- (5) Greenberg PA, Hortobagyi GN, Smith TL, Ziegler LD, Frye DK, Buzdar AU. Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. *J Clin Oncol* 1996;14:2197–205.
- (6) Fisher B. The evolution of paradigms for the management of breast cancer: a personal perspective. *Cancer Res* 1992;52:2371–83.
- (7) Skipper HE, Schabel FM. Quantitative and cytotoxic studies in experimental tumor systems. In: Holland J, Frei FE, editors. *Cancer medicine*. Philadelphia (PA): Lea and Febiger; 1982. p. 663–84.
- (8) Bonadonna G, Zambetti M, Valagussa P. Sequential or alternating doxorubicin and CMF regimens in breast cancer with more than three positive nodes. Ten-year results. *JAMA* 1995;273:542–7.
- (9) Peto R, Boreham J, Clarke M, Davies C, Beral V. UK and USA breast cancer deaths down 25% in year 2000 at ages 20–69 years. *Lancet* 2000;355:1822.
- (10) Goldie JH, Coldman AJ. A mathematical model for relating the drug sensitivity of tumors to their spontaneous mutation rate. *Cancer Treat Rep* 1979;63:1727–33.
- (11) Polychemotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists Collaborative Group. *Lancet* 1998;352:930–42.
- (12) Teicher BA, Holden SA, Cucchi CA, Cathcart KN, Korbut TT, Flatlow JL, et al. Combination thiotepa and cyclophosphamide in vivo and in vitro. *Cancer Res* 1988;48:94–100.
- (13) Hryniuk W, Bush H. The importance of dose intensity in chemotherapy of metastatic breast cancer. *J Clin Oncol* 1984;2:1281–8.
- (14) Hortobagyi GN, Buzdar AU, Bodey GP, Kau S, Rodriguez V, Legha SS, et al. High-dose induction chemotherapy of metastatic breast cancer in protected environment: a prospective randomized study. *J Clin Oncol* 1987;5:178–84.
- (15) Lazarus HM, Reed MD, Spitzer TR, Rabaa MS, Blumer JL. High-dose i.v. thiotepa and cryopreserved autologous bone marrow transplantation for therapy of refractory cancer. *Cancer Treat Rep* 1987;71:689–95.
- (16) Eder JP, Antman K, Peters WP, Henner WD, Schryber S, Wilmore D, et al. High-dose combination alkylating agent chemotherapy with autologous marrow support for metastatic breast cancer. *J Clin Oncol* 1986;4:1592–7.
- (17) Peters WP, Rosner G, Ross M, Vredenburgh J, Meisenberg B, Gilbert C, et al. Comparative effects of granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) on priming peripheral blood progenitor cells for use with autologous bone marrow after high-dose chemotherapy. *Blood* 1993;81:1709–19.
- (18) Antman K, Ayash L, Elias A, Wheeler C, Hunt M, Eder JP, et al. A phase II study of high-dose cyclophosphamide, thiotepa, and carboplatin with autologous marrow support in women with measurable advanced breast cancer responding to standard-dose therapy. *J Clin Oncol* 1992;10:102–10.
- (19) Peters WP, Ross M, Vredenburgh JJ, Meisenberg B, Marks LB, Winer E, et al. High-dose chemotherapy and autologous bone marrow support as consolidation after standard-dose adjuvant therapy for high-risk primary breast cancer. *J Clin Oncol* 1993;11:1132–43.
- (20) Davidson N. Out of the courtroom and into the clinic. *J Clin Oncol* 1992;10:517–9.
- (21) Cameron DA, Anderson A, Toy E, Evans TR, Le Vay JH, Kennedy IC, et al. Block sequential adriamycin CMF—optimal non-myeloablative chemotherapy for high risk adjuvant breast cancer? *Br J Cancer* 2002;87:1365–9.
- (22) Henderson IC, Berry DA, Demetri GD, Cirincione CT, Goldstein LJ, Martino S, et al. Improved outcomes from adding sequential Paclitaxel but not from escalating Doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. *J Clin Oncol* 2003;21:976–83.
- (23) Nabholz JM, Pienkowski T, Mackey J, Pawlicki M, Guastalla JP, Vogel C, et al. Phase III trial comparing TAC with FAC in the adjuvant treatment of node-positive breast cancer patients: interim analysis of the BCIRG 001 study [abstract]. *Proc ASCO* 2002;21:36a.
- (24) Bergh J, Wiklund T, Erikstein B, Lidbrink E, Lindman H, Malmstrom P, et al. Tailored fluorouracil, epirubicin, and cyclophosphamide compared with marrow-supported high-dose chemotherapy as adjuvant treatment for high-risk breast cancer: a randomised trial. *Scandinavian Breast Group 9401 study [Erratum in: Lancet 2000;356:2196]*. *Lancet* 2000;356:1384–91.
- (25) Rodenhuis S, Bontenbal M, Beex LV, Wagstaff J, Richel DJ, Nooij MA, et al. High-dose chemotherapy and hematopoietic stem-cell rescue for high-risk breast cancer. *N Engl J Med* 2003;349:7–16.
- (26) Tallman MS, Gray R, Robert NJ, LeMaistre CF, Osbourne CK, Vaughan WP, et al. Conventional adjuvant chemotherapy with or without high-dose chemotherapy and autologous stem-cell transplantation in high-risk breast cancer. *N Engl J Med* 2003;349:17–26.
- (27) Rodenhuis S, Richel DJ, van der Wall E, Schornagel JH, Baars JW, Koning CC, et al. Randomised trial of high-dose chemotherapy and haemopoietic progenitor-cell support in operable breast cancer with extensive axillary lymph-node involvement. *Lancet* 1998;352:515–21.
- (28) Hortobagyi GN, Buzdar AU, Theriault RL, Valero V, Frye D, Booser DJ, et al. Randomized trial of high-dose chemotherapy and blood cell autografts for high-risk primary breast carcinoma. *J Natl Cancer Inst* 2000;92:225–33.
- (29) Peters W, Rosner G, Vredenburgh J, Shpall E, Crump M, Richardson P, et al. for CALGB, SWOG and NCIC. A prospective, randomized comparison of two doses of combination alkylating agents as consolidation after CAF in high-risk primary breast cancer involving ten or more axillary lymph nodes: Preliminary results of CALGB 9082/SWOG 9114/NCIC MA-13 [abstract]. *Proc ASCO* 1999;18:1a.
- (30) Roche H, Pouillart P, Meyer N, Biron P, Spielmann M, Janvier M, et al. Adjuvant high-dose chemotherapy improves early outcome for high-risk breast cancer patients: the PEGASE 01 Trial [abstract]. *Proc ASCO* 2001;20:26a.
- (31) Gianni A, Bonadonna G. Five year results of the randomized clinical trial comparing standard versus high-dose myeloablative chemotherapy in the adjuvant treatment of breast cancer with >3 positive nodes [abstract]. *Proc ASCO* 2001;20:21a.
- (32) Nitz UA, Frick M, Mohrmann S, Lindemann H, Jackisch C, Werner C, et al. Tandem high dose chemotherapy versus dose-dense conventional chemotherapy for patients with high risk breast cancer: interim results from a multi-center phase III trial. Heinrich-Heine-University, Dusseldorf, Germany; West German Study Group (WSG), Dusseldorf, Germany [abstract]. *Proc ASCO* 2003;22:3344.]
- (33) Basser R, O'Neill A, Martinelli G, Nasi ML, Peccatori F, Cinieri S, et al. Randomized trial comparing up-front multi-cycle dose-intensive chemotherapy versus standard dose chemotherapy in women with high-risk stage 2 or 3 breast cancer [abstract]. *Proc ASCO* 2003;22:6a.
- (34) Weiss RB, Gill GG, Hudis CA. An on-site audit of the South African trial of high-dose chemotherapy for metastatic breast cancer and associated publications. *J Clin Oncol* 2001;19:2771–7.
- (35) Weiss RB, Rifkin RM, Stewart FM, Theriault RL, Williams LA, Herman AA, et al. High-dose chemotherapy for high-risk primary breast cancer: an on-site review of the Bezwoda study. *Lancet* 2000;355:999–1003.

- (36) Rahman ZU, Frye DK, Buzdar AU. Impact of selection process on response rate and long-term survival of potential high-dose chemotherapy candidates treated with standard-dose doxorubicin-containing chemotherapy in patients with metastatic breast cancer. *J Clin Oncol* 1997;15:3171-7.
- (37) Tokuda Y, Tajima T, Narabayashi M, Takeyama K, Watanabe T, Fukutomi T, et al. Randomized phase III study of high-dose chemotherapy with autologous stem cell support as consolidation in high-risk post-operative breast cancer. Japanese Clinical Oncology Group (JCOG 9208) [abstract]. *Proc ASCO* 2001;20:38a.
- (38) Crown J, Norton L. Potential strategies for improving the results of high-dose chemotherapy in patients with metastatic breast cancer. *Ann Oncol* 1995;6 Suppl 4:21-6.
- (39) Crown J, Perey L, Lind M, Guillem V, Efremedis A, Garcia-Conde J, et al. Superiority of tandem high-dose chemotherapy (HDC) versus optimized conventionally-dosed chemotherapy (CDC) in patients (pts) with metastatic breast cancer (MBC): The International Randomized Breast Cancer Dose Intensity Study (IBDIS 1) [abstract]. *Proc ASCO* 2003; 22:23a.
- (40) Bloom HJ, Richardson WW. Histological grading and prognosis in breast cancer; a study of 1409 cases of which 359 have been followed for 15 years. *Br J Cancer* 1957;11:359-77.
- (41) Common Toxicity Criteria (CTC), version 2.0. National Institutes of Health, National Cancer Institute; September 1999. Available at: https://webapps.ctep.nci.nih.gov/webobj/ctc/webhelp/Common_Toxicity_Criteria_CTC_v2.htm. [Last accessed: June 15, 2004.]

NOTES

R. C. F. Leonard and J. Crown contributed equally to this research.

Dr. Cameron has received financial support to conduct research and honoraria from Amgen, Pfizer, and Roche. R. C. F. Leonard is a consultant for Amgen, U.K., and his unit received an educational grant from Amgen, U.K., in 2001.

Manuscript received December 23, 2003; revised May 4, 2004; accepted May 13, 2004.

NOT FOR PUBLIC RELEASE