A dose escalation trial of adjuvant cyclophosphamide and epirubicin in combination with 5-fluorouracil using G-CSF support for premenopausal women with breast cancer involving four or more positive nodes


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Background: Dose-dense and dose-intensive regimens have improved the outcome of breast cancer in high-risk women with operable disease.

Patients and methods: Sixty-three premenopausal women with Stage 2, 3 breast cancer and 4 positive axillary nodes were treated in three successive cohorts with 70 mg/m2 of epirubicin, 500 mg/m2 of 5-fluorouracil and G-CSF every 14 days for 12 cycles. Cyclophosphamide (C) was given at 700 mg/m2, 900 mg/m2, and 1100 mg/m2 doses. Patients were evaluated for dose-limiting toxicities (DLTs) in the first four cycles, the primary endpoint of the trial.

Results: No DLTs were seen at C 700 mg/m2; at C 900 mg/m2 two of 16 patients experienced febrile neutropenia and poor performance status; at C 1100 mg/m2, 1 of 31 patients experienced poor performance status. Over 6 months, febrile neutropenia, grade 4 thrombocytopenia, grade 3 anemia and severe fatigue were observed. Clinical congestive heart failure occurred in three patients over 4 years.

Conclusion: A dose-intense and dose-dense regimen of cyclophosphamide, epirubicin and 5-fluorouracil was delivered with G-CSF without apparent increase in acute toxicity. Cyclophosphamide could be increased to more than twice the standard dose at the cost of more anemia and fatigue.

Key words: breast cancer, adjuvant chemotherapy, premenopausal

Original article

introduction

Adjuvant chemotherapy for women with node-positive operable breast cancer has reduced the risk of recurrence and improved the odds of survival [1–7]. Despite the very promising results of trials in this patient population, many women still relapse and die of their disease.

The cyclophosphamide, epirubicin and 5-fluorouracil (CEF) regimen is an anthracycline-intensive regimen (cyclophosphamide 75 mg/m2 days 1–14, epirubicin 60 mg/m2 and 5-fluorouracil 500 mg/m2 days 1 and 8, given every 28 days for six cycles) [8]. In a Phase III trial conducted by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) (MA.5), 710 premenopausal node-positive patients were randomized to CEF or classical CMF [9]. The 5-year relapse-free survival (63% vs 53%, P = 0.03) and 5-year actuarial survival (77% vs 70%, P = 0.03) were both in favour of CEF. At a median follow-up of 10 years these findings were confirmed [10]. As a result, CEF has become a standard of care in Canada for this patient population, in whom more dose-intensive adjuvant therapy seems appropriate.

In 1993 the NCIC CTG undertook a Phase I study (MA.11) to develop a regimen in which escalated doses of epirubicin and cyclophosphamide were given with the support of G-CSF such that toxicity would be both acceptable and comparable to standard CEF. Epirubicin would be given at a dose of 70 mg/m2 for an acceptable total cumulative dose of 840 mg/m2. Cyclophosphamide would be escalated to a maximum dose of 1100 mg/m2 and given intravenously every 14 days. Both dose intensity and cumulative dose would be increased with an overall goal of developing a regimen which could subsequently be compared to standard CEF in a randomized trial.
patients and methods

patient population

Premenopausal women with potentially curable breast cancer treated with surgery plus axillary node dissection were enrolled. Menopausal status was defined using the International Breast Cancer Study criteria [11]. Eligible women had four or more positive axillary nodes and no evidence of metastatic disease.

Screening tests for metastases included a chest X-ray and bone scan. Liver function tests were $<1.5 \times$ the institutional upper limit of normal, unless an abdominal ultrasound, liver scan or CT scan was done to rule out metastases. A radionuclide cardiac scan with a left ventricular ejection fraction (LVEF) of $>45\%$ was required.

Exclusion criteria included prior or concurrent neoplasm, history of cardiac disease and/or antihypertensive medication, granulocytes (neutrophils and bands) $<1.5 \times 10^9$/L, platelets $<100 \times 10^9$/L, serum creatinine $>1.5 \times$ the upper limit of normal, total bilirubin $>30 \mu$mol/L, any evidence of metastatic disease and hormonal therapy planned during the period of chemotherapy.

Participating centers obtained approval by the appropriate research ethics board. All patients gave written informed consent. Registrations were done centrally, and data were received and analysed by the NCIC CTG.

Although this was not a randomized study, data on time to relapse, overall survival and quality of life, using the Breast Cancer Chemotherapy Questionnaire (BCQ) [12], were collected for descriptive purposes.

study design

This Phase I study was designed to determine a maximum tolerated dose (MTD) of CEF given intravenously every 14 days for 12 cycles. All women were treated with epirubicin 70 mg/m$^2$ and 5-fluorouracil 500 mg/m$^2$. Cyclophosphamide was escalated through three planned dose levels (Table 1).

A cohort of 15 patients would be entered at the initial dose level and followed for four cycles. If fewer than two dose-limiting toxicities (DLT) were observed, the next level was opened. If two or three DLTs were observed, 15 additional patients would be entered at this level. If fewer than six DLTs were observed in the expanded cohort, the next dose level would open. If six or more DLTs were observed in 30 patients the study would be stopped. The maximum tolerated dose was defined as one dose level below that level where the trial was stopped.

Dose-limiting toxicities were defined as follows: febrile neutropenia, platelet count $<20 \times 10^9$/L or bleeding due to thrombocytopenia requiring platelet transfusion, grade 4 stomatitis (mucosal necrosis or requiring parental support), grade 3 weight loss (20% or more of initial body weight) or performance status of ECOG 3 or 4 lasting 7 days or more and attributed to treatment. Toxicity was assessed by the NCIC CTG Expanded Common Toxicity Criteria.

statistical considerations

The sample size was larger than a typical Phase I study. The NCIC CTG had considerable experience with CEF and the regimen was known to be efficacious. The objective in this trial was to establish a dose that had a similar toxicity profile to the standard CEF regimen given without G-CSF support. Dose-limiting toxicities defined for this study were known to occur with standard CEF at rates between 5% and 11%.

A two-stage design of Fleming’s [13] was used within each level to decide whether the dose would be escalated. Cohorts of 15 patients were accrued at each dose level with a possible total accrual of 90 eligible patients. Doses would be escalated if the true toxicity rate within each cohort was less than 8%. The regimen would not be accepted if the true toxicity rate exceeded 30%. The cohort sizes and the cut-off numbers for stopping or continuing the trial were determined by considering 90% confidence intervals for given outcomes.

treatment regimen

Chemotherapy was started within 12 weeks of first histological confirmation of breast cancer. Patients were treated with epirubicin at 70 mg/m$^2$ every 14 days for a total dose of 840 mg/m$^2$, a dose selected to provide an acceptable risk of cardiotoxicity [14]. Cyclophosphamide was given at 700 mg/m$^2$ every 14 days and escalated to 900 mg/m$^2$ and 1100 mg/m$^2$ in successive cohorts. The dose of 5-fluorouracil remained unchanged from the original CEF regimen at 500 mg/m$^2$. G-CSF given at 300 µg per day subcutaneously on days 3–12 of each cycle was added to prevent febrile neutropenia.

Radiation to the breast, chest wall and regional nodes and tamoxifen were given at investigators’ discretion following the completion of chemotherapy.

dose modifications

Blood counts were monitored twice weekly including on the treatment day. Doses were not escalated above the starting dose in individual patients but were reduced for hematological and other toxicities. The first dose reduction was a 50% decrease in cyclophosphamide and 5-fluorouracil with no change in epirubicin. Subsequent dose reductions involved a 25% decrease in the dose of all three drugs.

Treatment was given at full dose if on the treatment day granulocytes were $1.5 \times 10^9$/L or more and platelets were $100 \times 10^9$/L or more. Treatment was delayed one week if on the treatment day granulocytes were $1.5 \times 10^9$/L or less and/or platelets were less than $75 \times 10^9$/L; G-CSF was increased to 600 µg/day if granulocytes were less than $1.0 \times 10^9$/L. Doses were reduced by one level if on the treatment day granulocytes were $>1.5 \times 10^9$/L or more and platelets were at least $75 \times 10^9$/L but not more than $100 \times 10^9$/L; doses were reduced by one level and G-CSF increased to 600 µg/day if on the treatment day granulocytes were at least $1.0 \times 10^9$/L but not more than $1.5 \times 10^9$/L and platelets were $75 \times 10^9$/L or more.

At any time that platelets were less than $20 \times 10^9$/L or platelet transfusion was required, subsequent doses were reduced one level. If granulocytes were less than $0.2 \times 10^9$/L on two consecutive blood counts or febrile neutropenia occurred, prophylactic ciprofloxacin 500 mg twice daily by mouth was given from days 5 to 14 or until the granulocyte count was more than $1.0 \times 10^9$/L (at investigator’s preference) and G-CSF was increased to 600 µg/day for all subsequent treatments, without any chemotherapy dose reduction. Any further occurrences led to a one-level dose reduction for the next and all subsequent treatments.

If grade 3 mucositis occurred, treatment was delayed until recovery and fluorouracil was omitted for subsequent cycles; if grade 3 mucositis occurred again, epirubicin was reduced 25% of the previous cycle and maintained at this level.

follow-up evaluation

Patients were seen on day 1 of every cycle during treatment, at 3 and 6 months after completion of treatment and then every 6 months for 5 years. History, physical exam and toxicity were recorded at each visit.
Radionuclide cardiac scan was done at completion of treatment, at 6 months and at 5 years. All patients were followed for toxicity, recurrence of disease and survival on an annual basis until 10 years after registration.

The study was centrally activated in July 1993 and closed in August 1995.

results

patient characteristics

Ten centers recruited 63 patients. The median age was 43.2 years. Thirty-eight women (60.3%) were ECOG performance status 0, while 25 women (39.7%) were ECOG 1. Thirty-six women (57.1%) had a total mastectomy. The majority (79.4%) had 4 to 10 positive nodes. The remainder had >10 positive nodes (20.6%). Thirty women (47.6%) were ER-positive and PR-positive, 10 (15.9%) were ER-negative and PR-positive, 5 (7.9%) were ER-positive and PR-negative, and 13 (20.6%) were ER-negative and PR-negative. Receptor status was unknown for the remaining five women. Forty-three women received radiotherapy (68.3%). Thirty women were treated with tamoxifen (47.6%) following completion of treatment.

dose-limiting toxicity

Sixteen patients were entered at Level 1 with no DLTs in the first four cycles. Sixteen patients were then entered at Level 2 with 1 DLT (febrile neutropenia) in the first four cycles in the first 15 patients. Patients were then recruited to Level 3. The sixteenth patient’s data in Level 2 were subsequently received after Level 3 had been opened. A second DLT of poor performance status (ECOG performance status 3, lasting 7 days) was noted. The trial committee made a decision to proceed at Level 3 with careful monitoring for toxicity.

Eighteen patients were initially entered at Level 3 with no DLTs in the first four cycles in 16 patients. The study chair and principal investigators at participating centers discussed the reported toxicity of fatigue and diminished performance status. Although DLT as defined in the protocol was not met, a decision was made to expand the Level 3 cohort so that data on at least 30 patients would be available to document toxicity. Thirteen more patients were recruited. One DLT (ECOG performance status 3, lasting for 8 days) was observed in this final cohort of 31 patients.

toxicity

Toxicity was monitored throughout treatment. One patient refused further chemotherapy after 10 cycles in Level 1 because of fatigue, nausea and food aversion. During accrual to Level 2 the consent form was amended because of new information on the risk of acute leukemia with CEF chemotherapy [15] and two patients refused to renew consent after five and six cycles. Eight patients in Level 3 stopped treatment after cycle 6 and prior to cycle 12 because of toxicity (6), patient refusal (1) or lack of venous access (1).

Hematological toxicities are described in Table 2. There were no treatment-related fatalities. Febrile neutropenia increased with increasing dose but remained at an acceptable level. Thrombocytopenia was most frequently noted at the midweek blood count and was of short duration. Anemia was very common and severe. Erythropoietin was not used and several patients refused to have blood transfusions. To date there have been no cases of acute leukemia.

Nausea and vomiting were manageable. Diarrhea and stomatitis were infrequent. The major toxicity was fatigue and deteriorating performance status. Although severe fatigue and anemia both increased with increasing dose, they did not correlate well with each other [16]. Amenorrhea, defined as loss of menses for 3 months or longer, was observed in 14 (88%), 14 (88%), and 19 (61%) women in Levels 1, 2 and 3 respectively.

Cardiac toxicity was monitored closely in this trial. Asymptomatic falls in LVEF of >20% of the baseline value occurred in 2/16, 3/16 and 6/31 patients in Levels 1, 2 and 3 respectively. Two patients in Level 1 developed symptomatic congestive heart failure (CHF) requiring therapy, with ejection fractions of 12% and 21% occurring almost 4 years and 3 years after chemotherapy. A third patient in Level 3 had a >20% fall in LVEF at 18 months with symptomatic CHF. At 5 years her LVEF has improved and she is asymptomatic with treatment. One additional patient in Level 3 developed symptoms of CHF associated with an LVEF of 31%. This occurred at the same time as a lung recurrence was suspected and it was unclear whether the symptoms were related to heart failure or lymphangitic spread. Three of these four patients had left-sided lesions and all four received radiotherapy. In three women who had breast-conserving surgery, this included total breast and regional nodal radiation. The overall incidence of grade 2 or greater cardiac toxicity was 21% and of clinical CHF 6%. Grade 3 or 4 non-hematological toxicities are described in Table 3.

Delivery of planned doses of chemotherapy was excellent in those women who completed 12 cycles of therapy. The mean total dose received is outlined in Table 4. Apart from one

Table 2. Hematologic toxicitya (worst ever) over 12 cycles

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Level 1 (n = 16)</th>
<th>Level 2 (n = 16)</th>
<th>Level 3 (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile neutropenia</td>
<td>1 (6%)</td>
<td>2 (12%)</td>
<td>5 (16%)</td>
</tr>
<tr>
<td>Platelets &lt;20 × 10⁹/l</td>
<td>1 (6%)</td>
<td>2 (12%)</td>
<td>6 (19%)</td>
</tr>
<tr>
<td>Hb &lt; 80 g/L</td>
<td>6 (38%)</td>
<td>8 (50%)</td>
<td>25 (81%)</td>
</tr>
<tr>
<td>Red cell transfusions</td>
<td>6 (38%)</td>
<td>8 (50%)</td>
<td>18 (58%)</td>
</tr>
</tbody>
</table>

*aAssessed by the NCIC CTG Expanded Common Toxicity Criteria

Table 3. Grade 3 or 4 non-hematologic toxicitya (worst ever) over 12 cycles

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Level 1 (n = 16)</th>
<th>Level 2 (n = 16)</th>
<th>Level 3 (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance status 3–4</td>
<td>0</td>
<td>3 (19%)</td>
<td>6 (19%)</td>
</tr>
<tr>
<td>Fatigue (grade 3)</td>
<td>0</td>
<td>5 (31%)</td>
<td>15 (48%)</td>
</tr>
<tr>
<td>Diarrhea (grade 3)</td>
<td>1 (6%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis (grade 3)</td>
<td>0</td>
<td>1 (6%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Nausea (grade 3, 4)</td>
<td>4 (25%)</td>
<td>3 (19%)</td>
<td>8 (26%)</td>
</tr>
<tr>
<td>Vomiting (grade 3, 4)</td>
<td>4 (25%)</td>
<td>4 (25%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>LVEF (grade 2)</td>
<td>2 (12%)</td>
<td>6 (38%)</td>
<td>4 (13%)</td>
</tr>
</tbody>
</table>

*aAssessed by the NCIC CTG Expanded Common Toxicity Criteria
Table 4. Mean total dose (mg/m^2) planned and received for patients completing 12 cycles of chemotherapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Level 1 (n = 15)</th>
<th>Level 2 (n = 14)</th>
<th>Level 3 (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Planned/ received</td>
<td>Planned/ received</td>
<td>Planned/ received</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>8400/8236 98%</td>
<td>10800/9303 86%</td>
<td>13200/12290 93%</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>840/833 99%</td>
<td>840/820 98%</td>
<td>840/836 99%</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>6000/6168 103%</td>
<td>6000/5153 86%</td>
<td>6000/5562 93%</td>
</tr>
</tbody>
</table>

Although this was primarily a Phase I toxicity and dose-finding study, recurrence and survival data were collected. At the time of this analysis, the median follow-up for all patients was 84 months (Level 1, 96 months; Level 2, 85 months; Level 3, 75 months). The 5-year disease-free survival for all eligible patients was 63% (95% CI, 52%–75%; see Figure 1). The 5-year overall survival was 81% (95% CI, 71%–91%; see Figure 2). There were no significant differences between the three cohorts in either recurrence or survival when looked at individually. In contrast with a median follow-up of 106 months, the 5-year disease-free survival for a subgroup of patients from MA.5 with four or more positive nodes who received CEF was 51% (95% CI, 43%–60%) and the 5-year overall survival was 71% (95% CI, 63%–79%; see Figures 3 and 4) [10].

Discussion

The CEF days 1 and 8 regimen is a dose-intensive regimen compared to most standard adjuvant chemotherapy regimens. It has been shown to be superior to classical CMF chemotherapy with acceptable toxicity [9, 10]. The present study was undertaken to test whether escalation of the cyclophosphamide doses within a modified CEF regimen with a higher dose-intensity of epirubicin could be given without a substantial increase in toxicity. Since febrile neutropenia was the dose-limiting toxicity in CEF, G-CSF was added to the regimen. With standard CEF in the MA.5 study, the mean total dose of epirubicin received in women who completed 6 months of chemotherapy was 608 mg/m^2. This is in contrast with 831 mg/m^2 achieved in this study, an increase of 37%. Since cyclophosphamide was given orally in CEF and intravenously in this study due to the 2-week dosing intervals, the comparison of doses between the two regimens is somewhat difficult because of variable oral absorption and unknown effects of schedule. However, the mean total dose of cyclophosphamide received in patients completing 6 months of chemotherapy was increased by 56%, 76% and 152% compared with standard CEF given in MA.5, in Levels 1, 2 and 3 respectively.

In Table 5, the toxicities in MA.11 are compared with standard CEF as described in MA.5 [9]. Despite the increased chemotherapy doses delivered, neutropenia is not worse with the use of G-CSF. The apparent increase in thrombocytopenia may reflect the increased frequency of monitoring blood counts. Cardiotoxicity as measured by LVEF did appear to be higher, with more subclinical impairment of LVEF on MA.11,
but only three cases of clinical CHF have been documented. The major difference in toxicity was the degree of anemia, lethargy and decrease in performance status. These all clearly worsened with increasing doses of cyclophosphamide.

Several studies reported in recent years have looked at intensifying the dose of both anthracyclines and cyclophosphamide. The NSABP B-22 trial compared three regimens in node-positive patients in which doxorubicin was used at a standard dose of 60 mg/m² for four cycles. The cyclophosphamide was given at conventional and escalated doses. After 3 years of follow-up there was no difference in disease-free or actuarial overall survival [17]. None of the regimens used however approached the dose intensity or dose density of MA.11.

The CALGB 8541 trial evaluated low-, intermediate- and high-dose cyclophosphamide, doxorubicin and 5-fluorouracil (CAF) in node-positive breast cancer. After a median follow-up of 3.4 years, a significant disease-free survival and overall actuarial survival advantage was seen for the high-intensity arm. Although the high-intensity arm was superior in this study, the dose intensity relative to MA.11 was very low [18].

Finally the NSABP B-25 protocol looked specifically at the role of doxorubicin with increasing doses of cyclophosphamide with three regimens supported by the use of G-CSF. In spite of a significantly higher dose of cyclophosphamide in the third arm, there was no statistically significant difference in disease-free survival or overall survival in any of the three arms. Increasing the dose of cyclophosphamide was associated, however, in the high-dose arm with a cumulative incidence of leukemia risk of approximately 2% [19].

The Phase I study reported here is not randomized and includes only 63 patients. It is interesting, however, to compare the outcomes of these patients with a similar patient population in MA.5 with four or more positive nodes who were randomized to CEF, a regimen that includes 5-fluorouracil. Although a direct comparison of outcomes cannot be made, both disease-free survival and overall survival at 5 years is higher in MA.11 than in the CEF arm of MA.5. A study looking just at increasing the dose intensity of epirubicin (FEC 50 versus FEC 100) in a similar population of high-risk women conducted by the French Adjuvant Study Group demonstrated 5-year disease-free survival and overall survival results similar to MA.11 in the FEC 100 arm, 63.3% and 77.4% respectively

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Standard CEF MA.5 (n = 351)</th>
<th>Level 1 MA.11 (n = 16)</th>
<th>Level 2 MA.11 (n = 16)</th>
<th>Level 3 MA.11 (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile neutropenia</td>
<td>31 (9%, 6–12%)</td>
<td>1 (6%, 2–27%)</td>
<td>2 (12%, 5–34%)</td>
<td>5 (16%, 9–31%)</td>
</tr>
<tr>
<td>Platelets $&lt;20 \times 10^9$/L</td>
<td>2 (1%, 0–2%)</td>
<td>1 (6%, 2–27%)</td>
<td>2 (12%, 5–34%)</td>
<td>5 (16%, 9–31%)</td>
</tr>
<tr>
<td>Hb $&lt;80$ g/L</td>
<td>26 (7%, 0–10%)</td>
<td>6 (38%, 23–61%)</td>
<td>8 (50%, 33–72%)</td>
<td>25 (80%, 69–91%)</td>
</tr>
<tr>
<td>Red cell transfusions</td>
<td>not documented</td>
<td>6 (38%, 23–61%)</td>
<td>8 (50%, 33–72%)</td>
<td>18 (58%, 45–73%)</td>
</tr>
<tr>
<td>Performance status</td>
<td>0 (0%, 0–1%)</td>
<td>0 (0%, 1–17%)</td>
<td>3 (19%, 9–42%)</td>
<td>3 (10%, 4–23%)</td>
</tr>
<tr>
<td>Fatigue/lethargy</td>
<td>8 (2%, 1–4%)</td>
<td>0 (0–17%)</td>
<td>5 (31%, 17–55%)</td>
<td>15 (48%, 36–64%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (1%, 0–1%)</td>
<td>1 (6%, 2–27%)</td>
<td>0 (0%, 0–17%)</td>
<td>0 (0%, 0–9%)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>43 (12%, 10–16%)</td>
<td>0 (0%, 0–17%)</td>
<td>1 (6%, 2–27%)</td>
<td>2 (6%, 3–19%)</td>
</tr>
<tr>
<td>LVEF (grade 2)</td>
<td>18 (5%, 4–8%)</td>
<td>2 (12%, 6–34%)</td>
<td>6 (38%, 23–61%)</td>
<td>4 (13%, 7–26%)</td>
</tr>
</tbody>
</table>

Figure 3. MA.5 Progression Free Survival CEF Patients with 4 or More Positive Nodes (Based on the Database Updated in April, 2002).

Figure 4. MA.5 Overall Survival CEF Patients with 4 or More Positive Nodes (Based on the Database Updated in April, 2002).

Table 5. Comparison of grade 3/4 toxicity in MA.11 with the CEF arm of MA.5
[20]. This observation does raise the question as to the roles respectively of epirubicin and cyclophosphamide in the MA.11 regimen and suggests that dose intensity and/or total dose in this regimen may be contributing to an apparently improved outcome. It is also interesting that both CEF and escalated CEF with G-CSF support have included 5-fluorouracil, an agent that has largely been abandoned in newer regimens. The role of taxanes and the sequencing of chemotherapy agents have become a more recent focus of clinical studies [21] but the observations from MA.11 and apparent tolerability of a dose-dense and dose-intense regimen may suggest a continued role for this approach.

Dose-escalated cyclophosphamide, epirubicin and 5-fluorouracil were associated with considerable anemia and fatigue. Treatment with erythropoietin, which was not widely available at the time of this study, would probably ameliorate some of these complications. We believe that the encouraging results seen in this study in a population of women with high risk of node-positive breast cancer, known to have a poor prognosis on standard therapy, merits further exploration.

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