Increased Dose Density Is Feasible: A Pilot Study of Adjuvant Epirubicin and Cyclophosphamide followed by Paclitaxel, at 10- or 11-Day Intervals with Filgrastim Support in Women with Breast Cancer

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Abstract

Purpose: Because Cancer and Leukemia Group B 9741 trial showed a benefit for every 14-day administration of chemotherapy compared with every 21-day treatment, we hypothesized that even greater dose density would be more effective. We conducted a pilot trial to assess the feasibility of dose-dense chemotherapy consisting of a standard regimen at 10- to 11-day intervals in the adjuvant/neoadjuvant setting. A 2-day window was allowed for scheduling logistics.

Experimental Design: Thirty-nine women with early-stage breast carcinoma were accrued from April 2004 to October 2004. Median age was 47 years (range, 26-67 years). Patients received therapy with 100 mg/m² epirubicin and 600 mg/m² cyclophosphamide (EC) q 10 to 11 days for four cycles followed by 175 mg/m² paclitaxel q 10 to 11 days for four cycles, all with filgrastim support (300 μg s.c. daily) from day 2 to 24 h before the next treatment.

Results: Thirty-five (90%) patients completed all planned therapy. The median intertreatment interval was 10 days (range, 8-28 days). Cycles (80.7%) were delivered at no more than 10- to 11-day intervals. There were five dose reductions of 25% for grade 3 nonhematologic toxicity in five patients. Six (16%) patients developed febrile neutropenia defined as temperature >38 °C with absolute neutrophil count <1,000/μL. All febrile neutropenia was during therapy with EC. Other grade 3 toxicities included bone pain, hand and foot syndrome, neuropathy, mucositis, nausea, and vomiting.

Conclusions: Therapy with EC for four cycles followed by paclitaxel for four cycles at 10- to 11-day intervals is feasible. The ~30% reduction in intertreatment interval compared with every 14-day treatment could increase the efficacy of adjuvant chemotherapy.

Breast cancer is the most commonly diagnosed malignancy and the second most common cause of cancer-related death in women in both Europe and the United States (1). Although increased patient awareness and improving screening techniques now allow the early detection of localized and resectable tumors, many women still die of recurrent breast carcinoma. Adjuvant chemotherapy significantly reduces the risks of relapse and death in women with operable breast cancer, but the prognosis for patients in high-risk subsets remains suboptimal (2).

To increase the efficacy of adjuvant chemotherapy for breast cancer by increasing drug exposure, dosing and dose scheduling modifications have been evaluated extensively over the past several decades. The most widely used method of increasing tumor drug exposure has been dose escalation, but randomized trials testing this approach using higher than standard dose levels have failed to show improved outcomes compared with the administration of standard polychemotherapy programs (3–5).

The Norton-Simon model predicts that the most efficient way to treat a heterogeneous mix of cancer cells is to eradicate the numerically dominant, faster-growing cells first followed by the eradication of the more slow-growing, resistant cells (6). This is termed as “sequential therapy” and it has been proven to be clinically superior to alternating therapy (7). The total effect of therapy could relate to the cell kill for each dose, the length of time drugs are administered, and the rate of tumor growth between each treatment. If so, then, a fixed cell kill achieved at shorter time intervals should improve the overall effect of therapy. This concept is termed dose density and the advantage of sequential therapy can be attributable to the resulting increase in density of dosing (8).

The theoretical reason for the advantage afforded by dose-dense treatment is that regrowth of resistant cells between
cycling of chemotherapy is reduced by shortening the available time between doses. This approach was tested in a large phase III adjuvant trial in node-negative breast cancer. The Cancer and Leukemia Group B (CALGB) study 9741 compared sequential doxorubicin, paclitaxel, and cyclophosphamide at standard dose levels against concurrent doxorubicin and cyclophosphamide followed by paclitaxel and also randomized patients dosing every 2 weeks or every 3rd week (9). Although all four treatment schedules were proven to be feasible and safe, disease-free survival (DFS) and overall survival (OS) were both statistically superior for the every 2-week (dose dense) regimens compared with the every 3rd-week treatments.

Motivated by these considerations, we hypothesized that even greater dose density (treatment every 10-11 days) could be even more effective and we therefore conducted this pilot trial to assess the feasibility of neoadjuvant/adjuvant dose-dense chemotherapy consisting of epirubicin and cyclophosphamide (EC) for four cycles followed by paclitaxel for four cycles at this shortened intertreatment interval.

Materials and Methods

Eligibility. Nonpregnant females >18 years of age with a diagnosis of early-stage invasive carcinoma of the breast (T1-4, N0-3, and M0), Eastern Cooperative Oncology Group performance status of 0 or 1, an absolute neutrophil count (ANC) of at least 1,500/μL, a platelet count of at least 100,000/μL, and normal liver, renal, and cardiac function were eligible. Adequate cardiac function, measured as a left ventricular ejection fraction on radionuclide scan or echocardiogram, was also required. Patients with known metastatic breast carcinoma were not eligible. Definitive breast surgery was not a requirement for study entry, as patients could receive protocol therapy either in the adjuvant or neoadjuvant setting. Patients could have received prior chemotherapy or immunotherapy for prior breast cancer >12 months before study entry, except prior anthracycline (i.e., doxorubicin and epirubicin) and taxane. Prior radiation was not allowed. The protocol was approved by the Institutional Review Board of Memorial Sloan-Kettering Cancer Center (New York, NY), and all patients provided written informed consent.

Treatment plan. Patients were treated with EC (100 mg/m² epirubicin and 600 mg/m² cyclophosphamide) delivered i.v. q 10 to 11 days for four cycles followed by 175 mg/m² paclitaxel over a 3-hour infusion, q 10 to 11 days for four cycles. The treatment plan is shown in Fig. 1. A flexible 2-day window was allowed to account for scheduling logistics, such as avoidance of weekend treatment. All cycles were supported by filgrastim (Neupogen, Amgen, Thousand Oaks, CA), which was administered s.c. at 5 μg/kg daily from day 2 to 24 h before the next cycle. A complete blood count with leucocyte differential was done before each cycle of chemotherapy; the next cycle was administered if the ANC was >1,000/μL and the platelet count was 100,000/μL or greater.

Darbepoetin alfa (Aranesp, Amgen) was administered on an “as needed” basis, at the discretion of the treating physician.

Actual body weight was used for body surface area (m²) calculations, but patients who were >40% above their ideal weight were dosed using the corrected weight (actual weight plus ideal weight divided by 2).

Statistical design. This trial was designed to assess feasibility of the proposed regimen with regard to toxicity and deliverability. Tolerability was defined as absence of any grade 3 or higher nonhematologic toxicity, excluding alopecia, nausea/vomits, and bone pain, which might be a consequence of the administration of filgrastim. A Simon two-stage design was used with a 60% tolerability rate considered not promising and an 80% tolerability rate as promising, and probability of a type I/II errors was set to be 0.10.

In the first stage, 11 patients were planned, with an additional 27 patients to the second stage if at least 7 patients tolerated the regimen. The regimen would be considered tolerable and worthy of further study if at the end of the trial 27 out 38 patients tolerated the regimen.

Dose delays/modifications. All toxicities were graded by the National Cancer Institute’s common toxicity criteria, Common Terminology Criteria for Adverse Events version 3.0.3

If on the scheduled day of administration the ANC was <1,000/μL and/or the platelet count was <100,000/μL and/or nonhematologic toxicities (excluding alopecia) had not recovered to ≤ grade 1, treatment was delayed in 1-day increments up to day 14. If by day 14, platelet counts were <100,000/μL and/or ANC was <1,000/μL and/or nonhematologic toxicities (excluding alopecia) had not recovered to ≤ grade 1, treatment was delayed up to 1 week, and complete blood count and toxicity grading were repeated weekly. If platelet and ANC and nonhematologic toxicity had not recovered, a further delay of 1 week was required. If a treatment delay of >3 consecutive weeks was required, a patient was to be removed from the study.

At the discretion of the treating physician, patients experiencing neutropenic fever (ANC, <1,000/μL; body temperature, ≥38.5°C) and/or grade 3 or 4 nonhematologic toxicity during therapy were managed with either of the following: (a) 25% dose reduction of the day 1 doses in the subsequent cycles of either EC or paclitaxel with maintenance of the 10- to 11-day intertreatment interval or (b) increase in the intertreatment interval up to 14 days with maintenance of the dose at 100%.

Hormonal therapy. All patients whose tumor expressed either (or both) the estrogen or progesterone receptor were placed on a 5-year course of either tamoxifen, or an aromatase inhibitor, depending on the menopausal status, starting approximately 4 to 6 weeks after the end of chemotherapy.

Follow-up. Posttreatment patients underwent a history and physical examinations every 4 to 6 months, along with complete blood count, renal and hepatic function tests, and carcinoembryonic antigen and cancer antigen 15.3 tests. Where applicable, patients received yearly mammograms.

Results

Patients’ characteristics. Thirty-nine women with early-stage breast carcinoma were accrued from April 2004 to October 2004. The patients’ characteristics are summarized in Table 1. The median age was 47 years (range, 26-67 years). The majority (36 patients) of patients received therapy in the adjuvant setting, but 3 (8%) patients were treated in the neoadjuvant setting and underwent definitive breast surgery at the completion of all chemotherapy.

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Fig. 1. Treatment plan: EC 4 (100 mg/m² epirubicin and 600 mg/m² cyclophosphamide) every 10 to 11 d for four cycles followed by 175 mg/m² paclitaxel (7) every 10 to 11 d for four cycles; filgrastim from day 2 up to 24 h before the next cycle.

**Toxicity.** Thirty-five women (90%) completed all planned cycles; four patients did not complete the planned treatment. One patient withdrew consent after EC cycle 1 for nonmedical reasons and she was therefore not fully evaluable for toxicity. Thirty-eight patients are considered evaluable for toxicity. Two patients developed allergic reactions/rashes after paclitaxel cycle 3 and completed therapy with a final dose of docetaxel. One patient withdrew after paclitaxel cycle 3 because of grade 3 neuropathy.

**Hematologic toxicities.** Hematologic toxicities are summarized in Table 2. The cumulative incidence of grade 2 and 3 anemia was 72% and 10% of patients, respectively. These patients all received support therapy with darbepoetin alfa, at the discretion of the treating physician. Two patients with grade 3 anemia underwent transfusions of packed RBC.

**Nonhematologic toxicity.** The incidence of nonhematologic toxicity is summarized in Table 3. There were no grade 4 nonhematologic toxicities. Grade 3 toxicities included the following: febrile neutropenia (16%), defined as temperature >38°C with ANC <1,000/μL; bone pain following the administration of paclitaxel and filgrastim (8%); peripheral neuropathy (5%); hand and foot syndrome (5%); and nausea and vomiting (3%). All episodes of febrile neutropenia occurred during the EC part of the treatment plan; there were a total of six patients and seven episodes because one patient developed febrile neutropenia twice, once after EC cycle 2, and a second time after EC cycle 3.

Grade 2 toxicities included the following: fatigue (36%), nausea (28%), mucositis (18%), constipation (15%), bone pain (13%), myalgias (8%), neuropathy (8%), rash after the administration of paclitaxel (5%), and hypersensitivity reaction (3%). Two patients completed the therapy with one final cycle of docetaxel due to a hypersensitivity-like reaction and rash after paclitaxel cycle 3.

**Hospitalization.** There were nine hospitalizations: seven were due to febrile neutropenia (as noted above, one patient had two episodes of febrile neutropenia), defined as temperature >38°C with ANC <1,000/μL; one was due to pharyngitis and afebrile grade 4 neutropenia; and one was due to a breast reconstructive tissue expander infection (without neutropenia).

**Dose reductions.** Five (13%) patients had dose reductions of 25% during therapy due to grade 3 nonhematologic toxicities: four during the EC part of therapy and one during the paclitaxel part Table 4.

The other patients who developed a grade 3 nonhematologic toxicity but did not have a dose reduction of the subsequent cycles of therapy underwent treatment at 14-day intervals, as per study guidelines. Hence, a total of six patients had protocol-stipulated dose reductions or delays.

**Interruption intervals.** The median interruption interval was 10 days (range, 8-28 days). Eighty-one percent of cycles were delivered at 10- to 11-day intervals or less, and 96% of cycles were delivered at 14 days or less. Two patients had one 8-day interval for paclitaxel cycle 2 and paclitaxel cycle 4, respectively, to accommodate their scheduling needs. One

### Table 1. Patients’ characteristics (n = 39)

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Median</th>
<th>Range</th>
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<tbody>
<tr>
<td>47</td>
<td>26-67</td>
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</tr>
<tr>
<td>Type of surgery</td>
<td>Mastectomy</td>
<td>Lumpectomy</td>
</tr>
<tr>
<td>19 (49)</td>
<td>20 (51)</td>
<td></td>
</tr>
<tr>
<td>Therapy</td>
<td>Adjuvant</td>
<td>Neoadjuvant</td>
</tr>
<tr>
<td>36 (92)</td>
<td>3 (8)</td>
<td></td>
</tr>
<tr>
<td>Nodes</td>
<td>Positive</td>
<td>Median number</td>
</tr>
<tr>
<td>30 (77)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1-23</td>
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</tr>
<tr>
<td>ER/PR</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>28 (72)</td>
<td>11 (28)</td>
<td></td>
</tr>
<tr>
<td>HER2</td>
<td>Overexpressed/amplified</td>
<td>Nonoverexpressed/amplified</td>
</tr>
<tr>
<td>4 (10)</td>
<td>35 (90)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Hematologic toxicities (n = 38)**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
<th>No. patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>4</td>
<td>7 (18)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1 (3)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Anemia</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>4 (10)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>28 (72)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

**Table 3. Nonhematologic toxicities (n = 38)**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
<th>No. patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile neutropenia</td>
<td>3</td>
<td>6 (16)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Vomit</td>
<td>2</td>
<td>11 (28)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>2</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Bone Pain</td>
<td>3</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Hand and foot syndrome</td>
<td>3</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>3</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Hypersensitivity reaction</td>
<td>2</td>
<td>14 (36)</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Constipation</td>
<td>3</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Infection (without neutropenia)</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>
patient had one 28-day interval for EC cycle 4 because of logistical delays associated with placement of a venous access device.

EC cycles: dose reductions and dose delays. Seventy-nine percent of EC cycles were delivered at full dose at 10- to 11-day intervals; 15% of cycles were dose delayed; 3.5% of cycles were dose delayed and dose reduced by 25% of the planned dose; and 2.5% of cycles were dose reduced by 25% of the planned dose Figure 2.

Paclitaxel cycles: dose reductions and dose delays. Eighty-one percent of paclitaxel cycles were delivered at full dose at 10- to 11-day intervals; 17% of cycles were dose delayed, and 2% of cycles were dose reduced by 25% of planned dose Figure 3.

Pathologic complete remission. As stated above, three patients underwent chemotherapy in the neoadjuvant setting and proceeded to surgery at the completion of treatment. Of those three, one had a clinical partial remission and two were found to have a pathologic complete remission at the time of surgery, including one patient who had bilateral breast carcinomas, one of which was inflammatory.

Trastuzumab. Four patients had disease with HER2 overexpression and/or gene amplification. Following presentation of the trastuzumab adjuvant clinical trial data at the American Society of Clinical Oncology meeting in May of 2005, three of those four patients received adjuvant trastuzumab for a total of 1 year of therapy (10).

Survival analysis. All 39 patients are assessable for survival analysis. As of July 11, 2006, the median duration of follow-up among the patients from the start of therapy is 21.3 months (range, 10.9-25.3 months). No patients have developed either local or distant recurrences, and there has been no contralateral breast cancer event. There has been no treatment-related mortality and no long-term treatment-related toxicity. No cardiac toxicity was observed. No cases of acute myelogenous leukemia or myelodysplastic syndrome have been observed. At 21.3 months, DFS and OS of the entire population are 100% and 100%, respectively.

Discussion

With the availability of hematopoietic growth factors, “dose-dense” adjuvant chemotherapy has been studied for feasibility in a series of trials at Memorial Sloan-Kettering Cancer Center since 1990 (11–14). These trials have provided support for several large prospective randomized studies, including CALGB 9741. This study compared sequential doxorubicin, paclitaxel, and cyclophosphamide at standard dose levels of 60, 175, and 600, respectively, against concurrent doxorubicin and cyclophosphamide followed by paclitaxel, at the same dose levels (9). A factorial design also allowed for a randomized comparison of treatment timing in this trial compared every 2-week to every 3-week dosing intervals to assess the relative efficacy and toxicity of more or less dose-dense therapy. The q 2-week schedule was delivered with filgrastim support. This trial was particularly informative because it was a pure test of the dose density concept, as all patients received the same drugs, the same number of drug cycles, at the same cumulative dose, and the same size individual doses, on all four arms of the trial. A total of 2,005 patients were randomized, all with node-positive resected breast carcinoma. Although all four treatment schedules were proven to be feasible and safe, at a median follow-up of 36 months, DFS and OS were superior for the q 2-week, dose-dense arm (3-year DFS, 85% versus 81%; P = 0.01; 3-year OS, 92% versus 90%; P = 0.13, respectively), thus translating increased dose density into increased clinical benefit. There was no difference in DFS or OS between the sequential and the concurrent arms. The DFS and OS advantages of dose density were not accompanied by an increase in measured toxicity, except for anemia. Indeed, the use of filgrastim in the q 2-week dose-dense regimens resulted in a statistically significant decrease in granulocyte toxicity. A recent report with 6.5 years median follow-up substantiates

### Table 4. Dose reductions (n = 5)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Grade 3 nonhematologic toxicity</th>
<th>Cycles dose reduced by 25%</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Febrile neutropenia</td>
<td>EC 3 and 4</td>
</tr>
<tr>
<td>B</td>
<td>Febrile neutropenia</td>
<td>EC 3 and 4</td>
</tr>
<tr>
<td>C</td>
<td>Hand and foot syndrome</td>
<td>EC 3 and 4</td>
</tr>
<tr>
<td>D</td>
<td>Febrile neutropenia</td>
<td>EC 3 and 4</td>
</tr>
<tr>
<td>E</td>
<td>Neuropathy</td>
<td>T 2, 3, and 4</td>
</tr>
</tbody>
</table>

Abbreviation: T, paclitaxel.

Fig. 2. Percentage of EC cycles that were delivered full dose at 10 to 11 d ( ), dose delayed ( ), dose delayed and dose reduced ( ), and dose reduced ( ).

Fig. 3. Percentage of paclitaxel cycles that were delivered full dose at 10 to 11 d ( ), dose delayed ( ), and dose reduced ( ).
the earlier findings and provides no evidence of increased long-
term toxicities (15).

Building on these results and mathematical models of tumor
growth and response to chemotherapy, we hypothesized that
even greater dose density (q 10-11 days) could be more
effective. We therefore conducted this pilot trial to first assess
the feasibility of neoadjuvant/adjuvant dose-dense chemother-
apy consisting of EC for 4 cycles followed by paclitaxel for
4 cycles at 10- to 11-day intervals.

As predefined by our statistical design, this regimen is
feasible. Thirty-five (90%) patients completed all planned
therapy and the median intertreatment interval was 10 days
(range, 8-28 days). Eighty-one percent of cycles were delivered
at up to 10- to 11-day intervals, and 96% of cycles were
delivered at 14 days or less. Nine (24%) patients experienced
a grade 3 nonhematologic toxicity, excluding alopecia, nausea/
vomit, and bone pain. The incidence of febrile neutropenia
was significant at 16% of all patients despite the use of filgrastim
and compares unfavorably, albeit indirectly, with the 2% inci-
dence reported in CALGB 9741 (9). However, there has been
no treatment-related mortality and no long-term treatment-
related toxicity. This was a pilot feasibility study, with the
limitations of a small sample size. Additionally, there was a
high incidence of febrile neutropenia and hospitalization rate,
which might affect on the practical application of this regimen.

The ~30% reduction in the intertreatment intervals com-
pared with 14-day therapy could potentially further increase the
efficacy of adjuvant chemotherapy, minimize the effect on
patients’ lives (by shortening the treatment time), and could be
justified on this basis. DFS in this cohort of patients is 100%
with a median follow-up of 21.3 months (range, 10.9-25.3
months). Although this was a phase II feasibility study and DFS
was not an end point, this result compares favorably to other
reported phase II experiences (13); 77% of patients in this study
had node-positive disease, with a median number of two
positive lymph nodes (range, 1-23). The hospitalization rate
and incidence of febrile neutropenia are such that this regimen
would be justified in practice only if proven to be superior in
efficacy when compared with an every 2-week regimen in a
properly designed phase III trial. In the design of such a trial,
the investigators might want to restrict eligibility to women
with high-risk disease, by virtue of positive nodal status and
molecular phenotype, including negative hormone-receptor
status.

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