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Dose Dense Cyclophosphamide, Methotrexate, Fluorouracil is Feasible at 14-Day Intervals: A Pilot Study of Every-14-Day Dosing as Adjuvant Therapy for Breast Cancer

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Abstract

Purpose—Cyclophosphamide/methotrexate/fluorouracil (CMF) is a proven adjuvant option for patients with early-stage breast cancer. Randomized trials with other regimens demonstrate that dose-dense (DD) scheduling can offer greater efficacy. We investigated the feasibility of administering CMF using a DD schedule.

Patients and Methods—Thirty-eight patients with early-stage breast cancer were accrued from March 2008 through June 2008. They were treated every 14 days with C 600, M 40, F 600 (all mg/m²) with PEG-filgrastim (Neulasta[®]) support on day 2 of each cycle. The primary endpoint was tolerability using a Simon's 2-stage optimal design. The design would effectively discriminate between true tolerability (as protocol-defined) rates of 60% and 80%.

Results—The median age was 52-years-old (range, 38–78 years of age). Twenty-nine of the 38 patients completed 8 cycles of CMF at 14-day intervals.

Conclusion—Dose-dense adjuvant CMF is tolerable and feasible at 14-day intervals with PEG-filgrastim support.

Keywords

CMF; PEG-filgrastim

Introduction

The benefit of adjuvant chemotherapy in patients with breast cancer has been demonstrated in large clinical studies, confirmed by meta-analysis, and accepted as standard of care.¹ With oral cyclophosphamide/methotrexate/fluorouracil (CMF) a 34% improvement in disease-

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free survival and overall survival (OS) was demonstrated.^{2,3} With 30 years of follow-up an OS advantage remains for those patients who received CMF.³ This version of CMF “classic” consisted of oral cyclophosphamide 100 mg/m² days 1–14, methotrexate 40 mg/m² intravenous (I.V.) days 1 and 8, and fluorouracil 600 mg/m² I.V. days 1 and 8 every 4 weeks, but concerns about compliance motivated testing of an I.V. version.^{1,4–9}

Despite the development of more effective treatment regimens including anthracyclines and taxane, CMF remains an option when adjuvant chemotherapy is indicated for patients with a low- to intermediate-risk of relapse or for those who cannot tolerate anthracycline or taxane-based therapies. In addition, a recent analysis of MA-5, which randomized premenopausal women with node-positive early-breast cancers to CMF or cyclophosphamide-epirubicin-fluorouracil (CEF) adjuvant chemotherapy, specifically suggested a possible superiority of CMF among basal type triple-negative breast cancers as compared to an anthracycline-containing regimen.¹⁰ Hence, optimizing CMF remains an important priority for some subsets of breast cancer. Therefore, we tested a dose-dense (DD) variation of the latter delivered over 8 cycles.

Patients and Methods

Eligible patients had stage I–II adenocarcinoma of the breast and had to have completed definitive breast surgery (mastectomy or breast conserving surgery) within 3 months of enrollment and were over 18 years of age. Patients with HER2/*neu* over-expressing tumors either by immunohistochemistry or fluorescence in situ hybridization were not eligible. Brachytherapy was permitted prior to the initiation of therapy. The following laboratory parameters were required: absolute neutrophil count (ANC) $\geq 1500/\mu\text{L}$ and platelet count $\geq 100,000/\mu\text{L}$, total bilirubin ≤ 1.1 mg/dL, transaminases (serum glutamic-oxaloacetic transaminase/aspartate aminotransferase and/or serum glutamic-pyruvic transaminase/alanine aminotransferase [ALT]) up to 92.5 U/L or $2.5 \times$ institutional upper limit of normal (ULN) if alkaline phosphatase $\leq$ ULN, or alkaline phosphatase $4 \times$ ULN if transaminases are $\leq$ ULN, serum creatinine within 0.6–1.3 mg/dL. Patients with a known history of unstable angina, myocardial infarction, congestive heart failure, serious medical illness, or inability to provide informed consent were excluded. Informed consent was provided by each patient. This study was reviewed and approved by the Institutional Review Board at Memorial Sloan-Kettering Cancer Center.

Treatment Plan

Eight cycles of CMF (C 600 mg/m², M 40 mg/m², and F 600 mg/m²) I.V. were administered at 14-day intervals supported by PEG-filgrastim 6 mg (Figure 1). PEG-filgrastim (Neulasta®, Amgen, Thousand Oaks, CA) 6 mg was administered subcutaneously on day 2 approximately 24 hours after chemotherapy. After cycle 8, PEG-filgrastim was omitted at the discretion of the treating physician. A complete blood count (CBC) with leukocyte differential was performed before each chemotherapy treatment. Patients were seen every 2 weeks and a history, physical examination, and assessment of performance status and toxicity were performed.

After chemotherapy was completed, radiation was provided as deemed appropriate by the treating physician for patients having had mastectomy or after breast conservation using standard dosing guidelines and techniques. Patients whose tumors were estrogen or progesterone receptor positive were offered tamoxifen or an aromatase inhibitor at the discretion of the treating physician. Follow-up history, physical exam, and laboratory tests were performed at per institutional standard of care.

Dose Modifications

There were no dose modifications or reductions during the study. If on the day that chemotherapy was due (cycle 2 and above) the platelet count was $< 100,000/\mu\text{L}$ and/or ANC $< 1000/\mu\text{L}$ and/or non-hematologic toxicities (excluding alopecia) had not recovered to grade 2, treatment was held and the patient was removed from the protocol (patients were treated if the ANC was $> 1000/\mu\text{L}$). The patient was then delayed up to 1 week and a CBC and toxicity grading were repeated weekly. If platelets, ANC or nonhematologic toxicity had not recovered, a further delay of 1 week was required. Patients were then followed for 3 weeks for toxicity only, and treated at the discretion of the treating physician. For grade 3 and 4 toxicities, treatment was withheld until the toxicity resolved to grade 1, then, re-instituted (if medically appropriate) at the discretion of the treating physician off-protocol.

Statistical Analysis

The primary endpoint was feasibility in terms of safety and toxicity for this DD regimen. The study regimen was to be deemed feasible and tolerable for patients if they demonstrated an ANC ≥ 1.5 on day 1 of treatment for all 8 cycles and did not have grade 3 or higher non-hematologic toxicity, excluding alopecia, nausea/vomiting, and bone pain on that day.

Simon's 2-stage optimal design was used to evaluate dose-dense CMF. We elected a tolerability rate below 60% as unacceptable and a tolerability rate of 80% or higher as promising. This allowed us to set the probabilities of a type I and type II error at 0.10. In the first stage, if 6 or fewer patients out of the 11 did not tolerate the 14-day regimen then the entire trial would have been terminated. Therefore, if 7 or more patients could tolerate the 14-day chemotherapy schedule in the initial stage, enrollment was extended to 38 patients. After the second stage was completed, if ≥ 27 patients had tolerated the 14-day regimen, the study was considered to have a positive result. If ≥ 26 patients were able to tolerate the regimen, the study would have been considered negative. The probability of early termination under the null hypothesis was 47%. This design would effectively discriminate between true tolerability rates of 60% and 80%.

The minimum and maximum sample sizes for this trial were 7 and 38. Selected nonhematologic and hematologic toxicities, as measured by National Cancer Institute Common Terminology Criteria for Adverse Events version 3, were described by frequency and grade over all cycles, with the maximum grade over all cycles using the summary grade per patient.

Results

Between June 2008 and October 2008, 38 patients were enrolled with a median age of 52 years (range, 38 to 78 years; Table 1). Twenty-nine of the 38 patients completed 8 cycles of CMF on schedule, rendering the regimen feasible (Figure 2). Three patients completed 7 cycles only and were withdrawn as follows: 1 patient for grade 4 depression, 1 patient for grade 2 ALT elevation (not protocol-stipulated), and 1 patient for grade 1 rash. The 6 remaining patients completed between 1 and 6 cycles of CMF and were withdrawn for the following reasons: 2 for "personal reasons," 1 for bone pain, 1 for rash, 1 for retinal bleeding, and 1 for seizure (Figure 2). Overall, grade 2 or greater toxicity was limited (Table 2).

Discussion

The emergence of DD regimens in oncology is based on mathematical modeling and pre-clinical models of breast cancer cell growth rate and their response to cytotoxic chemotherapy.^{11–14} An early interpretation of some models was that linear dose-escalation

would lead to increased cytotoxicity and tumor cures. However, dose escalation beyond standard dose-ranges has not been particularly effective in the adjuvant setting. An alternative view of this data suggested that maintenance of optimal (standard) dose sizes delivered at shortened inter-treatment intervals (DD) would be superior to conventional regimens. This has now been validated for breast cancer as well as other solid tumors and lymphomas.^{2,3,15–21}

In some analyses, summation dose intensity appears to be important in outcomes for CMF. Tannock et al compared standard 3-weekly CMF (CMF 21) with the same regimen given at half the dose every 3 weeks in metastatic breast cancer.^{7–8} The half-dose regimen was associated with better tolerance, but a lower response rate, poorer palliation of symptoms, and reduced OS. Bonadonna reported the effects of dose reduction in patients receiving 12 months of adjuvant classical CMF.⁸ He found that those patients receiving 85% or more of the planned treatment had a 5-year disease-free survival (DFS) of 77%, compared with 48% for those receiving < 65% of planned treatment, and 45% for those receiving no adjuvant chemotherapy whatsoever. The International Breast Cancer Study Group (IBCSG) reviewed the relationship of disease-free survival with dose delivery retrospectively in 1350 women with node-positive early breast cancer treated on 4 different trials with oral classical CMF.⁹ Groups of patients were stratified according to the percentage of planned dose administered: level I, > 85%, level II 65%–84%, and level III < 65%. The 10-year OS rates were 56%, 60%, and 51%, respectively. The worse outcome for patients treated at the lowest dose level (group III) compared with those treated at the intermediate dose level was attributed to not achieving the threshold for significant activity. Both studies demonstrate that treating below 65% of the intended dose resulted in an inferior outcome. The challenge of these analyses is that the dose-response relationship may not be linear for many of the included agents and their relative efficacy may vary in complex fashions across the dose-ranges tested. Therefore, the relatively simple calculation of “dose-intensity” may obscure important variables such as the time between administrations of cytotoxic drugs.²²

Although the efficacy of adjuvant chemotherapy in breast cancer is now well established, the optimum regimens and ways of administering these regimens continue to improve. With the advent of growth factors, DD regimens have been studied in an effort to increase the effectiveness of multiple regimens. Cyclophosphamide/methotrexate/fluorouracil has been utilized in early breast cancer for 30 years now, but has yet to be utilized in a DD fashion that has been shown to be superior in multiple trials with other regimens and in several diseases. For example, DD therapy involving adriamycin (A), cyclophosphamide (C), and paclitaxel (T) given in a DD fashion has now become a standard option in stage II breast cancer. This was demonstrated in a large phase III trial, CALGB 97-41.¹⁵ This trial compared the sequential approach versus the concurrent adriamycin/cyclophosphamide, followed by paclitaxel. A separate randomization in this trial compared every-2-week to every-3-week dosing to assess the relative efficacy and toxicity of more or less DD therapy. The every 2-weeks schedule utilized filgrastim (G-CSF) support. In this study, the incidence of grade 4 neutropenia and treatment delays because of hematologic toxicity was significantly reduced, while the efficacy was increased with the DD regimen over the traditional every 3-weeks regimen. The DD arm was statistically superior in terms of disease-free and OS. The 3-year DFS was 85% versus 81% ($P = .007$) and the 3-year OS was 92% versus 90% ($P = .014$).¹⁵ Building on the results of our pilot studies and then CALGB 97-41, we hypothesized that a further increase in DD of adjuvant CMF would be feasible and could provide additional benefit.^{15, 23–25}

In the present study, we demonstrate the feasibility of adjuvant CMF every 14 days with little toxicity which is consistent with the toxicity observations in the larger randomized trials. There were no treatment related non-hematologic grade 3 or 4 toxicities and most

patients were able to receive all 8 planned doses of chemotherapy (29 out of 38 patients [76%]). Out of those unable to complete all 8 cycles, 3 withdrew after 7 of the 8 planned cycles for recurrence of pre-existing depression (1), rash unrelated to treatment (1), and 1 for grade 2 ALT elevation (1) who was withdrawn by her physician although it was not stipulated by the protocol. Three patients withdrew even earlier because they decided they did not want to participate in this study. One of these had a retinal bleed that was felt to be unrelated to therapy, another patient experienced grade 3 bone pain, an expected side effect of PEG-filgrastim. One patient had a seizure after the second cycle of unclear etiology. Seizures have been reported with high-dose I.V. methotrexate, but not at the 40 mg/m² dose used in CMF. Another patient experienced a rash which was felt to be unlikely related to therapy. Leukocytosis, of > 40,000/ μ L was only seen in 1 patient. This has previously been demonstrated not to have an affect on prediction of subsequent neutropenia.²⁶

Our pilot study demonstrates that DD adjuvant CMF is feasible at 14-day intervals with PEG-filgrastim support. If, as was seen in CALGB 97-41, this results in an even lower rate of first-cycle treatment neutropenia and/or improved efficacy, then this could represent an important enhancement of a broadly available and widely used adjuvant chemotherapy regimen for specific subsets of patients with early-stage breast cancer. To demonstrate this advantage would, of course, require a randomized phase III adjuvant trial or conceivably a pre-operative trial relying on in-breast response as a surrogate for disease-free and OS.^{27,28} Alternatively, we may be able to further enhance the effectiveness of CMF through even shorter inter-treatment intervals. Previously, our group demonstrated the feasibility of DD epirubicin and cyclophosphamide followed by paclitaxel using 10- to 11-day inter-treatment intervals supported by short-acting filgrastim (Neupogen®).²⁹ The feasibility we demonstrated is the first necessary step towards a potential randomized trial to confirm this benefit of optimized scheduling for CMF.

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Figure 1.

Treatment Schema

Abbreviations: CMF = cyclophosphamide/methotrexate/5-fluorouracil; IVP = intravenous push; IVPB = intravenous piggy back; SC = subcutaneously

Figure 2.
Consort Diagram
Abbreviations: ALT = alanine aminotransferase

Table 1

Patient Characteristics (N = 38)

Characteristic	Number of Patients (%)
Median Age	52 years
< 40 years	1 (2)
40–49 years	16 (42)
50–59 years	9 (24)
60–69 years	8 (21)
70+ years	4 (11)
Stage	
I	35 (92)
IIA	3 (8)
Receptors	
ER ⁺	33 (87)
ER [−] /PgR [−]	5 (13)
HER2/ <i>neu</i> [−]	38 (100)

Abbreviations: ER = estrogen receptor; HER2 = human epidermal factor receptor 2; PgR = progesterone receptor

Table 2

Toxicity CMF Every 14 Days With PEG-Filgrastim (N = 38)

Adverse Effect	Grade 2	Grade 3	Grade 4	No Grade/ Comment
Neutropenia	0	0	0	(On treatment day)
AST	0	0	0	–
ALT	1	0	0	After 7 cycles
Alkaline Phosphatase	0	0	0	–
Pain, Bone	1	1	0	Related to PEG-Filgrastim
Depression	0	0	1	Unrelated
Neutropenia	0	0	0	–
Anemia	0	0	0	–
Thrombocytopenia	0	0	0	–

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CMF = cyclophosphamide/methotrexate/fluorouracil