original reports

Avoiding Peg-Filgrastim Prophylaxis During the Paclitaxel Portion of the Dose-Dense Doxorubicin-Cyclophosphamide and Paclitaxel Regimen: A Prospective Study

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abstract

PURPOSE The use of growth factors adds considerable expense and some toxicity to adjuvant breast cancer chemotherapy. We tested the feasibility and safety of omitting routine peg-filgrastim use during the paclitaxel portion of the dose-dense doxorubicin-cyclophosphamide–paclitaxel regimen.

PATIENTS AND METHODS This was a prospective, single-arm study in which patients 18 to 65 years of age who completed 4 cycles of dose-dense doxorubicin-cyclophosphamide for stage I-III breast cancer received paclitaxel 175 mg/m^2 every 2 weeks. Peg-filgrastim was administered after paclitaxel only if patients had had febrile neutropenia in a prior cycle or at investigator discretion if patients had infections or treatment delays of $>$ 1 week. Once a patient received peg-filgrastim, it was administered in all future cycles. The primary end point was the rate of paclitaxel completion within 7 weeks from cycle 1 day 1 to cycle 4 day 1. If $\geq$ 100 out of 125 patients completed 4 cycles of paclitaxel without dose delay, the regimen would be considered feasible.

RESULTS The enrollment goal of 125 patients was met. Median age was 46 years (range, 21-65 years), and 112 patients (90% [95% CI, 83% to 94%]) completed dose-dense paclitaxel within 7 weeks. Omission of peg-filgrastim was not causally related to noncompletion of paclitaxel in any patients. The most common reasons for dose reduction or delays were nonhematologic. One patient experienced febrile neutropenia but was able to complete paclitaxel on time. Eight patients (6.4%) received peg-filgrastim during the trial. Overall, peg-filgrastim was administered in only 4.3% of paclitaxel cycles.

CONCLUSION Omission of routine peg-filgrastim during dose-dense paclitaxel according to a prespecified algorithm seems to be safe and feasible and was associated with a 95.7% reduction in the use of peg-filgrastim relative to the current standard of care.

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INTRODUCTION

The Cancer and Leukemia Group B (CALGB) 9741 clinical trial established the superiority of a dose-dense, every-2-week schedule of 4 cycles of doxorubicin (adriamycin) and cyclophosphamide (AC), followed by 4 cycles of paclitaxel, compared with an every-3-week schedule of the same drugs, in the adjuvant treatment of patients with node-positive breast cancer.[1] A subsequent meta-analysis of 10 randomized controlled trials comparing standard and dose-dense chemotherapy regimens confirmed improved survival outcomes with dose-dense scheduling in the adjuvant breast cancer setting.[2] As a result, dose-dense AC followed by paclitaxel is firmly established as a standard-of-care option and is included in the National Comprehensive Cancer Network breast cancer treatment guidelines.[3]

Historically, neutrophil recovery was the limiting factor in the spacing of chemotherapy cycles. In the CALGB 9741 clinical trial, filgrastim support was administered routinely on days 3-10 in all cycles, to allow for every-2-week chemotherapy administration (both AC and paclitaxel).[1] In a later single-arm, prospective study of 135 women with stage I-III breast cancer receiving dose-dense AC-paclitaxel, the use of peg-filgrastim 6 mg subcutaneous on day 2 was associated with an acceptable safety profile, with 88.6% of patients who started paclitaxel completing 4 cycles, with

ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objectives

To test the feasibility and safety of omitting routine peg-filgrastim during the paclitaxel portion of the dose-dense doxorubicin-cyclophosphamide–paclitaxel regimen.

Knowledge Generated

In patients 18-65 years of age, omission of routine peg-filgrastim during dose-dense paclitaxel appears safe and feasible, and is associated with a substantial reduction in the use of growth factor relative to the current standard of care

Relevance

Implementation of the algorithm tested in this prospective study has the potential to reduce health care costs in the setting of dose-dense paclitaxel.

a mean cycle duration of 14 days, and > 85% receiving their planned chemotherapy on time.[4]

However, myeloid growth factors are associated with bone pain in at least 25% of patients.[5] In addition, other adverse events such as leukocytosis, allergic reactions, and rare cases of splenic rupture and adult respiratory distress syndrome have been reported.[6] Moreover, the use of granulocyte-colony stimulating factor (G-CSF) adds a considerable (up to 20-fold) increase in the costs of the dose-dense AC-paclitaxel regimen,[7] compared with regimens (such as once-weekly paclitaxel) that do not require routine growth factor support.

It has been questioned whether the support of G-CSF is needed in the paclitaxel portion of the dose-dense AC-paclitaxel regimen, given evidence that AC and paclitaxel have different hematologic toxicity profiles; in particular, the CALGB 40101 trial showed that the incidence of any grade 3 or higher hematologic toxicity was considerably higher in the AC arms compared with the paclitaxel arms.[8] In this setting, we previously reported our retrospective experience describing patterns of growth factor use during the paclitaxel portion of dose-dense AC-paclitaxel.[9] We observed substantial variation among and within providers in terms of growth factor use, with fewer than one half of patients administered G-CSF with all 4 cycles of paclitaxel. Among the subset of 21 patients who did not receive G-CSF during any cycle of paclitaxel, 90% completed 4 cycles of paclitaxel without treatment delays or febrile neutropenia. A similar retrospective study from State University of New York Upstate Medical University reported that 88 of 109 patients who did not receive G-CSF during dose-dense paclitaxel were able to complete all 4 planned cycles, with only 5 patients experiencing dose delays.[10]

We therefore launched a multicenter, single-arm phase II study to test prospectively the feasibility and safety of omitting routine growth factor prophylaxis during the paclitaxel portion of dose-dense AC-paclitaxel. We aimed to define whether, by using clearly defined inclusion criteria and prespecified dosing algorithms for G-CSF, we could identify patients who could be spared the expense and toxicity of growth factor support while completing paclitaxel safely and on time.

PATIENTS AND METHODS

Eligibility

Women or men with stage I-III breast cancer for whom neoadjuvant or adjuvant dose-dense AC-paclitaxel was deemed clinically indicated by the treating oncologist were eligible for inclusion. Other key eligibility criteria were 18 to 65 years of age, Eastern Cooperative Oncology Group performance status of 0-1, absolute neutrophil count (ANC) $\geq$ 1,500 μL, hemoglobin $\geq$ 9.0 g/dL, platelets $\geq$ 100,000/μL, normal liver and kidney function (total bilirubin $\leq 1.2 \times$ institutional upper limit of normal [ULN]; aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase $\leq 1.5 \times$ ULN; serum creatinine $\leq 1.5 \times$ ULN). Patients who had experienced febrile neutropenia during AC chemotherapy were excluded, as were patients who had received prior cytotoxic chemotherapy (other than the immediately preceding AC) or previous therapeutic radiation within the previous 5 years. Patients taking lithium and those with HIV, hepatitis B or C, immunodeficiency status, or hematologic disease (eg, myelodysplasia, bone marrow malignancies) were also excluded. No concurrent use of investigational agents was permitted.

The study was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board. (The full protocol is available [online only]). All participants signed informed consent before initiation of any study procedures (Appendix Fig A1, online only). Participating centers were Dana-Farber Cancer Institute (Boston, MA), Dana-Farber Cancer Institute Milford (Milford, MA), South Shore Hospital (South Weymouth, MA), New-Hampshire Oncology-Hematology (Londonderry, NH), and St. Elizabeth's Medical Center (Boston, MA).

TABLE 1. Patient and Disease Characteristics (n = 125)

Characteristic	Patients
Age at registration, years, median (range)	46 (21-65)
Age at registration, years	
< 40	37 (30)
40-49	36 (29)
50-59	40 (32)
60-65	12 (10)
BSA, median (range)	1.81 (1.41-2.39)
Race	
White	101 (81)
Black or African American	9 (7)
Asian	5 (4)
Other	10 (8)
Ethnicity	
Hispanic or Latino	7 (6)
Non-Hispanic	113 (90)
Unknown	5 (4)
ECOG PS at baseline	
0	119 (95)
1	6 (5)
Menopausal status	
Premenopausal	84 (67)
Postmenopausal	41 (33)
Stage at initial diagnosis	
I	16 (13)
II	81 (65)
III	27 (22)
Unknown	1 (1)
Histology	
Ductal carcinoma	94 (75)
Lobular carcinoma	16 (13)
Mixed ductal lobular carcinoma	13 (10)
Other	2 (2)
Hormone receptor status	
ER and/or PR positive	80 (64)
ER and PR negative	44 (35)
Unknown	1 (1)
Chemotherapy setting	
Neoadjuvant	57 (46)
Adjuvant	68 (54)

NOTE. Data are presented as No. (%) unless indicated otherwise.

Abbreviations: BSA, body surface area; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; PR, progesterone receptor.

Treatment Plan

Chemotherapy could be administered in either the neoadjuvant or the adjuvant setting. Two weeks after the completion of 4 cycles of dose-dense AC chemotherapy, paclitaxel was administered at 175 mg/m^2 intravenously once every 2 weeks for 4 cycles.

To initiate each cycle of paclitaxel, patients were required to have ANC $\geq$ 1,000 μL and platelets $\geq$ 100,000/μL. Peg-filgrastim was required only if there was febrile neutropenia in a prior cycle; it could be administered at the discretion of the treating investigator in the case of an active infection or treatment delays of $>$ 1 week. If grade 3 or 4 neutropenia without fever occurred for $\leq$ 7 days in the absence of peg-filgrastim, the paclitaxel dose was maintained for the next cycle. In this situation, the use of peg-filgrastim in future cycles was allowed but was not mandated. If grade 3 or 4 neutropenia occurred in the presence of growth factor support, a 20% dose reduction to paclitaxel was applied in future cycles. Once peg-filgrastim was administered, it was administered in all future cycles for that patient. The use of prophylactic antibiotics to prevent febrile neutropenia was not permitted. Other grade 3 or clinically significant grade 2 (with the exception of alopecia) nonhematologic toxicities were required to have resolved to grade 1 before retreatment. Paclitaxel was to be discontinued for grade $\geq$ 3 neurotoxicity. Treatment was administered until unacceptable toxicity, withdrawal of consent, or other changes to the participant's condition that would make additional treatment unacceptable to either the participant or the treating investigator.

Toxicity Assessments

Adverse events were graded using Common Terminology Criteria for Adverse Events version 4.0. Patients were assessed at each study visit, which included a physical examination and a review of systems. A poststudy safety assessment, conducted either in person or by telephone, occurred 4-8 weeks after the last dose of paclitaxel. Blood counts, including ANC, were collected centrally via a review of laboratory reports. In this pragmatic trial, a simplified assessment for nonhematologic toxicity was incorporated, including only a prospective collection of relevant toxicities, such as grade 3-4 toxicities or any toxicity that led to dose reduction/dose delay/discontinuation.

Statistical Plan

This single-arm, phase II study was designed to evaluate the completion rate of 4 cycles of paclitaxel omitting the routine use of peg-filgrastim using prespecified safety rules within an acceptable time frame of 7 weeks (total treatment delay $<$ 1 week from cycle 1 day 1 to cycle 4 day 1). Any treatment delay (hematologic or not) was considered an event. A Simon 2-stage design was used, with an overall 1-sided type I error of 10% and 90% power to detect a difference between an unacceptable (75%) and an acceptable (85%) completion rate.[4]

The target sample size was 125 evaluable patients, defined as patients who completed 4 cycles of AC and received at least 1 cycle of paclitaxel on study. In the first stage, the enrollment of 51 evaluable patients was planned. If ≥ 12 patients enrolled in the first stage did not complete 4 cycles of paclitaxel within 7 weeks, the trial would have been closed early. Otherwise, by design, an additional 74 evaluable patients would be enrolled. If at any point during the second stage, ≥ 26 patients were unable to complete treatment on time, the study would be closed early. If ≥ 100 out of 125 patients completed 4 cycles of paclitaxel without dose delay, the regimen would be considered feasible. Finally, to further ensure safety, the observation of 3 febrile neutropenia events at any time would trigger review by the Data Safety Monitoring Committee to make a recommendation as to whether the study should close permanently. With this design, if the true completion rate was 75%, the chance the regimen would be declared unfeasible was 91%, and if the true completion rate was 85%, the chance the regimen would be falsely declared unfeasible was 10%.

Secondary end points included the actual use of pegfilgrastim, the impact of the omission of routine pegfilgrastim on the paclitaxel schedule (including cycle length, rate of completion of 4 cycles of therapy, reasons for delay, dose hold/reduction, and noncompletion of therapy), and safety (including the rate of hematologic, particularly neutropenia and febrile neutropenia, and nonhematologic toxicity). In addition, a post hoc end point included the rate of any (≥ 1 day) treatment delay and associated reasons, to further characterize minor delays leading to the completion of paclitaxel at between 43 and 49 days (ie, > 6 but < 7 weeks from cycle 1 day 1).

TABLE 2. Paclitaxel Treatment Details

Detail	Patients
Duration of treatment	
Completed 4 cycles in ≤ 7 weeks,[a] No. (% [95% CI])	112 (90 [83 to 94])
Completed 4 cycles in > 7 weeks	3 (2)
Total No. of paclitaxel cycles completed	
4	115 (92)
3	122 (98)
2	124 (99)
1	125 (100)
ANC > 1,000 on planned day 1 of each cycle	
Cycle 2	119 (96)
Cycle 3	117 (96)
Cycle 4	113 (96)

NOTE. Data are presented as No. (%) unless indicated otherwise.
Abbreviation: ANC, absolute neutrophil count.
[a]Study primary end point.

Statistical Analysis

Descriptive statistics were used to describe the patient and disease characteristics, the treatment situation, and the toxicity status. The CI of rate of completion of treatment within 7 weeks was conducted following exact binomial calculations. All analyses were performed using R version 3.2.3.

RESULTS

Patient Characteristics

Between May 2016 and November 2018, 127 patients were registered, of whom 125 received at least 1 dose of paclitaxel on protocol and were included in the final analysis. Of the 2 unevaluable patients, one withdrew consent and one was found ineligible after registration but before the start of paclitaxel. Baseline characteristics are listed in Table 1. Median age was 46 years (range, 21-65 years). Most (81%) of the study population self-identified as white, and most (95%) had an Eastern Cooperative Oncology Group performance status of 0. Two thirds of the patients (67%) were premenopausal. Chemotherapy was delivered in the neoadjuvant setting in 46% of participants. Median ANC on cycle 1 day 1 of paclitaxel was 7,500/μL (range, 1,500-20,500/μL).

Paclitaxel Completion

Among the first 51 evaluable patients enrolled in the first stage, 6 patients did not complete 4 cycles of paclitaxel on time; no cases of noncompletion were caused by hematologic toxicity. The study thus proceeded to full accrual. Table 2 lists the number of paclitaxel cycles completed, as well as the proportion of patients with ANC ≥ 1,000/μL on the planned day 1 of each cycle. Only 4% of patients in each cycle experienced ANC < 1,000/μL and required a dose delay of any duration because of neutropenia; count recovery was generally rapid.

Overall, 112 of 125 patients (90%; 95% CI, 83% to 94%) completed 4 cycles of paclitaxel within 7 weeks (Table 2). Thus, the study met its primary end point. Of the remaining 13 patients, 3 patients completed 4 cycles in > 7 weeks and 10 patients did not complete 4 cycles of therapy. As listed in Table 3, the most common reasons for not meeting the primary end point were nonhematologic in nature. Of the 23 patients who completed 4 cycles of paclitaxel within 43 to 49 days (ie, > 6 but < 7 weeks), dose delays were caused by scheduling/holidays/patient preference (n = 12), neutropenia without fever (n = 9), febrile neutropenia (n = 1), and nonhematologic toxicity (n = 1). Thus, among the entire cohort of 125 patients, only 11 (8.8%) had a dose delay of any duration that was caused by neutropenia, and this delay lasted longer than 7 days in only 1 patient (0.8%). Appendix Tables A1 and A2 (online only) present selected characteristics of patients who experienced a dose delay of any duration that was caused by neutropenia.

TABLE 3. Reasons for Not Completing 4 Cycles of Paclitaxel Within 7 Weeks

Patient No.	Reason
Patients who completed 4 cycles of dose-dense paclitaxel in > 7 weeks (n = 3)	
13	Cardiotoxicity
93[a]	Active infection at cycle 2 (non-neutropenic); grade 3 neutropenia at cycle 3[b]
120	Nonhematologic
Patients who did not complete 4 cycles of dose-dense paclitaxel per protocol (n = 10)	
2	No cycle 4, significant neuropathy
4	No cycle 4, multifocal pneumonia (non-neutropenic), cardiomyopathy
5	No cycle 2-4, pneumonitis
23	No cycle 4, significant neuropathy
26	Switched to weekly paclitaxel after cycle 2, multiple grade 1-2 toxicities (non-neutropenic)
43	Switched to weekly paclitaxel after cycle 3, grade 2 bone pain (non-neutropenic)
87	No cycle 4, grade 2 neuropathy, arthralgias, myalgias
88	No cycle 4, grade 3 fatigue, neuropathy, grade 2 myalgia, weakness
90	No cycle 4, infusion reactions after cycle 2 and 3
111	No cycle 3-4, patient withdrew consent after cycle 2

[a]Adverse event likely related to omission of prophylactic peg-filgrastim.
[b]Per protocol, patient received peg-filgrastim at cycle 3.

Use of Peg-Filgrastim

Patients completed a total of 486 paclitaxel cycles on protocol. Peg-filgrastim was administered in only 21 cycles (4.3%; Table 4). Overall, only 8 patients (6.4%) received 1 or more doses of peg-filgrastim, most commonly for neutropenia without fever.

Toxicity

In this pragmatic trial, the only prospectively collected toxicities were all-grade hematologic toxicities; grade 3-4 nonhematologic toxicities; hypersensitivity reactions; and any toxicities leading to treatment delay, dose reduction, or treatment discontinuation. As shown in Appendix Tables A3 and A4 (online only), the most common grade 3-4 adverse event was neutropenia (9.6%). All other events were uncommon. Appendix Table A5 (online only) lists reasons for paclitaxel dose delay or dose reduction, which were varied but not primarily related to neutropenia. Reasons for treatment discontinuation are listed in Table 3.

DISCUSSION

We prospectively tested the feasibility and safety of omitting the routine use of prophylactic peg-filgrastim during the paclitaxel portion of the dose-dense AC-paclitaxel regimen for stage I-III breast cancer. We found that the omission of routine peg-filgrastim was feasible, with 90% (95% CI, 83% to 94%) of patients able to complete 4 cycles of paclitaxel within 7 weeks. Moreover, paclitaxel noncompletion

TABLE 4. Use of Peg-Filgrastim

Peg-Filgrastim Use	Patients
Administration during paclitaxel treatment	
Cycle 2	5 (4.0)
Cycle 3	8 (6.4)
Cycle 4	8 (6.4)
No. of patients who experienced febrile neutropenia	1 (0.8)
Total No. of paclitaxel cycles completed on protocol (500 planned)	486 (97.2)
Total No. of paclitaxel cycles in which peg-filgrastim was administered	21 (4.3)
No. of patients who received ≥ 1 dose of peg-filgrastim	8 (6.4)
Reasons for receiving peg-filgrastim on protocol	
Febrile neutropenia	1
Neutropenia	7

NOTE. Data are presented as No. (%).

was mostly caused by nonhematologic toxicities unrelated to the omission of peg-filgrastim.

At least 2 retrospective studies had been reported at the time we designed our prospective trial, and both suggested the potential feasibility and safety of omitting growth factor support during dose-dense paclitaxel.[9,10] However, selection bias could not be ruled out, because it was uncertain how patients were chosen for growth factor omission, and thus uncertain whether results could truly be generalized. To our knowledge, only 1 previous prospective trial has been conducted to test the feasibility of delivering dose-dense paclitaxel without routine growth factor support.[11] In that study, the primary end point was defined as the absence of febrile neutropenia or ANC $< 1{,}000/\mu L$ on the day of planned treatment. The study was stopped early after 54 patients were enrolled, when the sixth patient could not be treated on time because of neutropenia.

In our study, using clearly defined eligibility criteria, and prespecified rules for the use of peg-filgrastim in the case of febrile neutropenia, infection, or treatment delays, we found that the vast majority of patients were able to complete 4 cycles of paclitaxel within the protocol prespecified "on-time" period of 7 weeks. Admittedly, our criteria for declaring paclitaxel receipt "on time" differed from the study of Sugarman et al.[11] However, even applying a more stringent threshold of any ($\geq$ 1 day) delay in paclitaxel administration, only 11 of 125 patients (8.8%) experienced any paclitaxel delay caused by neutropenia.

These results show that patients receiving dose-dense paclitaxel every 2 weeks need not receive routine concomitant growth support. Assuming an average wholesale price in the United States ranging from $1,361 to $4,655 for myeloid growth factors such as filgrastim (8 days of growth factor support/cycle) and peg-filgrastim ($5,443 to $18,622 for 4 cycles on the basis of April 2019 Medicare Part B Drug Average Sales Price), and applying a 95.7% reduction in the use of peg-filgrastim during paclitaxel as observed in our study, implementing the algorithm tested in our prospective trial into clinical practice could translate into a drug cost savings of between $0.5 and $1.7 million per 100 patients treated with dose-dense paclitaxel. The use of growth factors can represent, in addition to costs to the overall medical system, important out-of-pocket costs to patients. It is estimated that 85% of prescriptions for neulasta for patients with commercial insurance will have a copay of $5 or less; however, for the remaining 15% of patients, the average out-of-pocket cost per dose is $697.[12] In addition, because the omission of routine growth factor support was feasible without undue delays in the timing of therapy receipt or unacceptable rates of febrile neutropenia (the proportion of patients experiencing hematologic or nonhematologic grade 3-4 adverse events is in line with those reported previously), additional costs from the management of infections or other complications are not expected with this approach.[1,8,13]

In many parts of the world including the United States, dose-dense paclitaxel is not an option because of cost considerations related to the use of growth factors, despite a convenient schedule, with the need for only 4 infusions (*v* 12 infusions of once-weekly paclitaxel), as well as reduced chemotherapy chair time. The dose-dense paclitaxel schedule without growth factor support overcomes these limitations.

We believe our study is potentially practice changing, and on the basis of the results of this study, our institution (Dana-Farber Cancer Institute) has implemented the algorithm tested in this trial into routine clinical practice in patients who meet the eligibility criteria of the study. Nevertheless, we acknowledge several caveats and limitations. It is important to note that all patients received peg-filgrastim with their preceding AC chemotherapy, and our study should not be construed to suggest that it is safe to omit peg-filgrastim through the entire dose-dense AC-paclitaxel regimen, particularly given the greater degree of myelosuppression with AC chemotherapy. Next, in designing our study, we selected the final eligibility criteria carefully, taking into account existing literature reporting higher rates of severe neutropenia or febrile neutropenia in several populations, including those with a history of previous chemotherapy, receiving immunosuppressive medications, with abnormal liver or renal function and individuals older than 65 years.[14-16] Our results cannot speak to the safety of growth factor omission in these populations, because they were not included in this study. In addition, we cannot rule out that physicians considered other factors beyond the stated eligibility criteria to select more medically fit patients for trial participation. We also acknowledge the underrepresentation of some subgroups in our study population: only 10% of patients were 60 to 65 years of age. In addition, only 19% of the overall study population self-identified as nonwhite (7% black, 4% Asian, 8% other). Other studies have reported lower baseline neutrophil counts in individuals of African descent.[17-19] Although we did not include a sufficient number of black or Asian participants to perform formal subset analyses, an exploratory analysis did not show any signal of a different outcome for nonwhite individuals (Appendix Table A6, online only). Finally, in the setting of this nonrandomized study, we did not prospectively collect patient-reported outcomes, nor did we collect data on patient out-of-pocket expenditures, and the study design does not allow us to quantify the impact of the omission of peg-filgrastim on bone pain, the financial toxicity of treatment, the social impact including maintaining work ability during treatment or time to return to work, and overall quality of life.

In conclusion, in properly selected patients 18 to 65 years of age, the omission of routine peg-filgrastim use during dose-dense paclitaxel according to a prespecified algorithm seems safe and feasible and was associated with a 95.7% reduction in the use of peg-filgrastim, relative to the current standard of care.

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Avoiding Peg-Filgrastim Prophylaxis During the Paclitaxel Portion of the Dose-Dense Doxorubicin-Cyclophosphamide and Paclitaxel Regimen: A Prospective Study

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APPENDIX

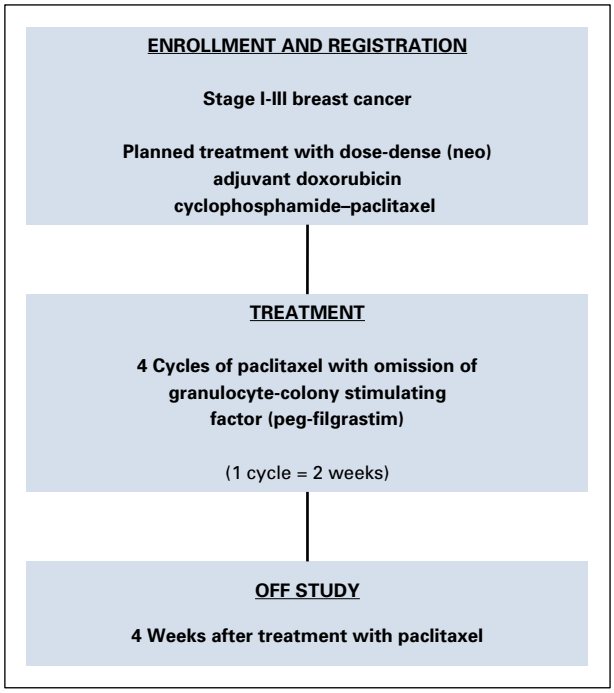

FIG A1. Study schema.

TABLE A1. Patient and Disease Characteristics of Patients Who Had Dose Delay Caused by Neutropenia

Patient No.	Race	Ethnicity	Age (years)	BSA	ECOG PS	Menopausal Status	Stage	Histology	Hormone Receptor Status	Chemotherapy Setting
3	Asian	Ethnicity not known	38	1.45	0	Premenopausal	II	Invasive ductal	ER and/or PR positive	Neoadjuvant
9	White	Non-Hispanic	31	1.57	0	Premenopausal	III	Invasive ductal	ER and/or PR positive	Adjuvant
36	Black or African American	Non-Hispanic	43	2.02	1	Premenopausal	II	Invasive ductal	ER and PR negative	Adjuvant
39	White	Hispanic or Latino	34	1.85	0	Premenopausal	II	Invasive ductal	ER and PR negative	Neoadjuvant
44	White	Non-Hispanic	39	1.9	0	Premenopausal	II	Invasive ductal	Not performed	Neoadjuvant
50	White	Non-Hispanic	54	1.63	0	Postmenopausal	II	Invasive lobular	ER and/or PR positive	Adjuvant
93	White	Non-Hispanic	33	1.68	0	Premenopausal	II	Invasive ductal	ER and PR negative	Neoadjuvant
116	White	Non-Hispanic	30	1.78	0	Premenopausal	III	Invasive ductal	ER and/or PR positive	Neoadjuvant
117	Other	Non-Hispanic	33	1.76	0	Premenopausal	III	Invasive ductal	ER and PR negative	Adjuvant
125	White	Non-Hispanic	37	1.56	0	Premenopausal	II	Mixed	ER and/or PR positive	Adjuvant
126	White	Non-Hispanic	48	2.03	0	Premenopausal	II	Invasive lobular	ER and/or PR positive	Adjuvant

Abbreviations: BSA, body surface area; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; PR, progesterone receptor.

TABLE A2. Association of Patient and Disease Characteristics With Having (1) Neutropenia and (2) Any Dose Delay Caused by Neutropenia

Characteristics	All (N = 125)	No Neutropenia (n = 101)	Neutropenia (n = 24)	*P*	No Dose Delays Caused by Neutropenia (n = 114)	Dose Delays Caused by Neutropenia (n = 11)	*P*
Age at registration, years, median (range)	46 (21-65)	46 (21-65)	43 (30-61)	.08	46 (21-65)	37 (30-54)	< .01
Age category, years							
< 40	37 (30)	27 (27)	10 (42)	.53	29 (25)	8 (73)	.02
40-49	36 (29)	30 (30)	6 (25)		34 (30)	2 (18)	
50-59	40 (32)	33 (33)	7 (29)		39 (34)	1 (9)	
60-65	12 (10)	11 (11)	1 (45)		12 (11)	0 (0)	
BSA, median (range)	1.81 (1.41-2.39)	1.81 (1.41-2.39)	1.80 (1.45-2.15)	.72	1.81 (1.41-2.39)	1.80 (1.45-2.15)	.20
Race							
White	101 (81)	82 (81)	19 (79)	.75	93 (82)	8 (73)	.41
Black or African American	9 (7)	8 (8)	1 (4)		8 (7)	1 (9)	
Asian	5 (4)	4 (4)	1 (4)		4 (4)	1 (9)	
Other	10 (8)	7 (7)	3 (12)		9 (8)	1 (9)	
Ethnicity							
Hispanic or Latino	7 (6)	6 (6)	1 (4)		6 (5)	1 (9)	.28
Non-Hispanic	113 (90)	92 (91)	21 (88)		104 (91)	9 (82)	
Unknown	5 (4)	3 (3)	2 (8)	.41	4 (4)	1 (9)	
ECOG PS at baseline							
0	119 (95)	96 (95)	23 (96)	> .99	109 (96)	10 (91)	.43
1	6 (5)	5 (5)	1 (4)		5 (4)	1 (9)	
Menopausal status							
Postmenopausal	41 (33)	35 (35)	6 (25)	.47	40 (35)	1 (9)	.10
Premenopausal	84 (68)	66 (65)	18 (75)		74 (65)	10 (91)	
Stage							
I	16 (13)	13 (13)	3 (12)	.41	16 (14)	0 (0)	.56
II	81 (65)	68 (67)	13 (54)		73 (64)	8 (73)	
III	27 (22)	19 (19)	8 (33)		24 (17)	3 (27)	
Unknown	1 (1)	1 (1)	0 (0)		1 (1)	0 (0)	
Histology							
Invasive ductal	94 (75)	77 (76)	17 (71)	.70	86 (75)	8 (73)	.88
Invasive lobular	16 (13)	13 (13)	3 (12)		14 (12)	2 (18)	
Mixed	13 (10)	9 (9)	4 (17)		12 (11)	1 (9)	
Other, specify	2 (2)	2 (2)	0 (0)		2 (2)	0 (0)	
Hormone receptor status							
ER and PR negative	44 (35)	35 (35)	9 (38)	.20	40 (35)	4 (36)	.08
ER and/or PR positive	80 (64)	66 (65)	14 (58)		74 (65)	6 (55)	
Unknown	1 (1)	0 (0)	1 (4)		0 (0)	1 (9)	
Chemotherapy setting							
Adjuvant	68 (54)	54 (53)	14 (58)	.82	62 (54)	6 (55)	> .99
Neoadjuvant	57 (46)	47 (47)	10 (42)		52 (46)	5 (45)	

NOTE. Data are presented as No. (%) unless indicated otherwise.

Abbreviations: BSA, body surface area; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; PR, progesterone receptor.

TABLE A3. Summary of All-Grades Hematologic Adverse Events

	Grade According to CTCAE v 4.0, No. (%)				
Toxicity	**1**	**2**	**3**	**4**	**Any**
Anemia	12 (9.6)	14 (11.2)	1 (0.8)	0	27 (21.6)
Neutropenia	6 (4.8)	6 (4.8)	9 (7.2)	3 (2.4)	24 (19.2)
Thrombocytopenia	3 (2.4)	0	0	0	3 (2.4)
Febrile neutropenia	—	—	1 (0.8)	0	1 (0.8)
Any grade 3-4 hematologic adverse events			14 (11.2)		

Abbreviation: CTCAE v 4.0: Common Terminology Criteria for Adverse Events version 4.0.

TABLE A4. Summary of all Grade 3-4 Nonhematologic AEs

	Grade According to CTCAE v 4.0, No. (%)	
Toxicity	**3**	**4**
Edema limbs	1 (0.8)	0 (0)
Fatigue	1 (0.8)	0 (0)
Infusion-related reaction	1 (0.8)	0 (0)
Arthralgia	1 (0.8)	0 (0)
Bone pain	1 (0.8)	0 (0)
Left ventricular systolic dysfunction	1 (0.8)	0 (0)
Peripheral motor neuropathy	2 (1.6)	0 (0)
Peripheral sensory neuropathy	3 (2.4)	0 (0)
Pneumonitis	1 (0.8)	0 (0)
Other respiratory adverse event	0 (0)	1 (0.8)
Any grade 3-4 nonhematologic adverse events	13 (10.4)	

NOTE. Per protocol, only grade 3-4 adverse events (AEs), any grade AEs leading to dose hold or modification, and all hematologic toxicities were prospectively collected. Grade 1-2 nonhematologic AEs not leading to dose hold or dose modification were not prospectively captured.

Abbreviation: CTCAE v 4.0: Common Terminology Criteria for Adverse Events version 4.0.

TABLE A5. Reasons for Paclitaxel Dose Hold or Dose Reduction

Reason	No. (%)
Dose delay	
Cardiotoxicity	1 (1)
Febrile neutropenia	1 (1)
Infection	1 (1)
Nonhematologic	3 (2)
Neurotoxicity	3 (2)
Neutropenia[a]	12 (10)
Other	3 (2)
Dose reduction	
Cardiotoxicity	1(1)
Nonhematologic	2 (2)
Neurotoxicity	6 (5)
Neutropenia	2 (2)
Other	6 (5)

[a]One additional patient experienced grade 3 neutropenia on cycle 2 but received the 4 cycles of paclitaxel within 42 days and thus was not considered dose delayed, per protocol.

TABLE A6. Completion of Therapy Within 7 Weeks, Reason for Delay by Race, Completion of 4 Cycles of Paclitaxel, and Use of Peg-Filgrastim Stratified by Race

	Race				
Treatment Details	White (n = 101)	Black or African American (n = 9)	Asian (n = 5)	More Than 1 Race (n = 7)	Other (n = 3)
Duration of treatment					
≤ 7 weeks (and completed 4 cycles of paclitaxel)	90	9	4	6	3
> 7 weeks (and completed 4 cycles of paclitaxel)	3	0	0	0	0
Did not complete 4 cycles of paclitaxel	8	0	1	1	0
Reason for delay					
Cardiotoxicity	1	0	0	0	0
Febrile neutropenia	1	0	0	0	0
Infection	1	0	0	0	0
Nonhematologic	4	0	0	0	0
Peripheral neuropathy	3	0	0	0	0
Neutropenia	10	1	1	1	0
Other	3	0	0	0	0
Completion of 4 cycles of paclitaxel					
Yes	93	9	4	6	3
No	8	0	1	1	0
No. of individuals using peg-filgrastim					
Cycle 1	0	0	0	0	0
Cycle 2	3	0	1	0	0
Cycle 3	5	0	1	0	1
Cycle 4	5	0	1	0	1