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DOSE-ESCALATION OF FILGRASTIM DOES NOT IMPROVE EFFICACY: CLINICAL TOLERABILITY AND LONG-TERM FOLLOW-UP ON CALGB STUDY 9141 ADJUVANT CHEMOTHERAPY FOR NODE-POSITIVE BREAST CANCER PATIENTS USING DOSE-INTENSIFIED DOXORUBICIN PLUS CYCLOPHOSPHAMIDE FOLLOWED BY PACLITAXEL

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for the Cancer and Leukemia Group B**Introduction**

In theory, maximizing tumor exposure to chemotherapy should more effectively eliminate clonogenic malignant cells and prolong disease control (1). Given the preclinical evidence that demonstrates that the steepest dose response curves occur during the period of logarithmic growth, increased chemotherapy exposure should be most effective in the setting of micrometastatic disease. This principle should translate into higher survival rates when patients

are treated in a minimal disease state, as in the case of adjuvant chemotherapy for early-stage breast cancer (1-3). One measure of chemotherapy exposure is *dose-intensity*, which is defined as the amount of a specific agent given over a fixed interval of time. Under this definition, dose-intensity can be increased by increasing the dose size (*escalation*), decreasing the inter-treatment interval (*density*), or both. Dose-escalation is supported by both retrospective analyses and prospective studies that demonstrate a clinically relevant dose-response effect in treating breast cancer patients with some agents, in some dose-ranges (3).

One pivotal, prospective, randomized clinical trial (CALGB 8541) demonstrated that the dose and dose-intensity of doxorubicin (Adriamycin, A) and cyclophosphamide (Cytosan, C) administered with 5-fluorouracil (Adrucil, F) impact significantly on the clinical outcomes of women receiving adjuvant chemotherapy for resected node-positive breast cancer (4;5). However, treatment in this clinical trial was limited to conventional doses and schedules of chemotherapy because of the lack of supportive care technology during the period of patient accrual (1985-1991). It was not until the development of hematopoietic supportive care (e.g., autologous bone marrow transplantation and myeloid growth factor support) and improved antiemetics (e.g., serotonin antagonists) in the 1990's that oncologists could prescribe higher doses and/or more intensive schedules of chemotherapy with an acceptable level of patient tolerability. Such dose and schedule modifications could fall into one of several approaches: (i) the one-time administration of very high dose chemotherapy (e.g., with bone marrow or peripheral blood stem cell support); (ii) the repetitive administration of standard dose chemotherapy with shortened inter-treatment intervals (e.g., dose-dense treatment); and (iii) the repetitive administration of higher dose chemotherapy with standard inter-treatment variables, as studied in the protocol described herein.

In addition to dose escalation and dose intensification, novel therapeutics (including the taxanes paclitaxel and docetaxel) became available in the 1980's and 1990's. These chemotherapeutic agents demonstrated impressive non-cross-resistance to the other available therapies, as clinical responses were observed in metastatic breast cancer patients who had progressed on prior anthracyclines or alkylating agents (6-9). The demonstration of benefit in advanced disease generated interest in incorporating these agents into adjuvant treatment regimens, and trials evaluating the benefit of the taxanes following standard combination chemotherapy with AC were initiated.

Two promising strategies were therefore presented to breast cancer clinical researchers in the early 1990's: (i) the dose-intensification of conventional agents, and (ii) the incorporation of novel agents into the adjuvant therapy of early stage breast cancer. The Cancer and Leukemia Group B (CALGB) elected to test both strategies in adequately powered, multicenter clinical trials for patients with early stage breast cancer. Thus, CALGB 9141 was designed as a pilot study with the primary goal of assessing tolerance to paclitaxel following repetitive, nonmyeloablative cycles of maximally dose-intensified doxorubicin and cyclophosphamide (AC) with G-CSF for hematopoietic growth factor support. A secondary objective was to determine if there were additional benefits with higher than conventional doses of G-CSF (10 vs. 5 mcg/kg/day). This manuscript provides the results of this multicenter pilot study.

Patients and Study Design

The CALGB designed Protocol 9141 as a pilot trial that would accrue patients from a subset of group member institutions. The Eastern Cooperative Oncology Group (ECOG) also participated to allow one of its member institutions to enroll patients on the study. The CALGB Central Office and Statistical Center provided the infrastructure for study design and implementation, as well as data collection and analysis.

Eligible patients were defined as those women with histologically confirmed, operable carcinoma of the breast and at least one involved axillary lymph node, adequate end-organ function, and an ECOG performance status of 0-2. Patients with >10 positive axillary lymph nodes were encouraged to participate in CALGB 9082, a randomized clinical trial of high-dose chemotherapy with stem cell transplantation; if these patients were deemed ineligible for participation in CALGB 9082, or if they declined participation in CALGB 9082, they were considered for participation in this pilot clinical trial.

As part of the quality assurance program of the CALGB, members of the Data Audit Committee visit all participating institutions at least once every three years to review source documents. The auditors verify compliance with federal regulations and protocol requirements, including those pertaining to eligibility, treatment, adverse events, tumor response, and outcome in a sample of protocols at each institution. Such on-site review of medical records was performed for a subgroup of 10 patients (5.8%) of the 172 patients under this study.

The planned chemotherapy regimen involved the sequential administration of five 21-day cycles of dose-escalated AC followed by four 21-day cycles of conventional-dose paclitaxel. Doxorubicin was administered as a 37.5 mg/m² intravenous push on days 1 and 2 of each cycle to minimize the potential for treatment related cardiotoxicity. Cyclophosphamide was administered as a 2000 mg/m² intravenous bolus with aggressive hydration on day 1 of each cycle. Paclitaxel was administered as a 175 mg/m² intravenous infusion over three hours. The total duration of adjuvant chemotherapy was therefore 15 weeks of AC and 12 weeks of paclitaxel, for a total of 27 weeks overall. Patient monitoring during the course of chemotherapy administration included a complete blood cell count (including a white blood cell differential and platelet count) three times weekly, as well as a complete physical examination on day one of each treatment cycle. Dose reductions and dose delays were allowed per protocol for recovery from unacceptable toxicities. In addition, antibiotics (ciprofloxacin 750 mg orally twice daily) and G-CSF were administered as supportive care during the period of treatment with AC; patients were prospectively randomized to receive 5 vs. 10 mcg/kg/day of G-CSF subcutaneously, starting approximately 24 hours after completion of the chemotherapy infusion and continuing through at least day 12 until hematologic recovery. The administration of these prophylactic medications was not mandated for the first cycle of paclitaxel, but ciprofloxacin and/or G-CSF could be prescribed as needed at the discretion of the treating oncologist.

Postmenopausal patients were strongly encouraged to receive a five year course of adjuvant tamoxifen if they had estrogen receptor positive or unknown breast cancer; tamoxifen was administered at a dose of 10 mg orally twice a day, beginning upon hematologic recovery from the last cycle of paclitaxel. In addition, those patients who opted for breast conserving surgery received adjuvant radiotherapy upon the completion of their chemotherapy course as per the standard of care. Tamoxifen could be given concomitantly or in sequence with radiation in accordance with protocol guidelines.

Statistical Considerations

From a statistical design standpoint, there were two major considerations in this study. One was to obtain feasibility information for use in planning a larger randomized trial, with a particular focus on obtaining estimates of such important design parameters as the incidence of unacceptable toxicities (*e.g.*, fever with neutropenia and severe non-hematologic adverse effects) and the feasibility of administering paclitaxel after an aggressive AC combination chemotherapy regimen. The other consideration was a planned comparison between the two doses of G-CSF, such that the Wilcoxon test was used to compare the number of days of severe neutropenia between patients who received 5 vs. 10 mcg/kg/day of G-CSF.

The initial sample size was calculated based on plans to estimate accurately the duration of hospitalizations for toxicity. Using a conservative assumption that the standard deviation of the length of hospital stays was 4 days, to have a standard error of the sample mean of <0.4 days required a sample size of 100, which was the target size of this study. Assuming $n=100$ and a standard deviation of 4 days, a 95% confidence interval for the true mean hospital stay was the observed mean ± 0.8 days. If the observed rate of toxicity (of any type) is 2%, a 95% confidence interval for the true rate of toxicity is from 0.6% to 7.0%; for an observed rate of 8%, a 95% confidence interval is from 4.1% to 15%.

The trial sample size was increased from the original target of 100 to 170 patients for several reasons. One was to enable a more accurate assessment of toxicity rates. There was also an interest in increasing the statistical power to detect a difference between the two doses of G-CSF. Conventional statistical analyses of clinical outcomes were used. The probabilities of RFS and OS were calculated by the Kaplan-Meier method and measured from the date of study entry. Events were defined as relapses for RFS and as deaths for OS. Events were censored at the date of last follow-up if an event was not observed. Multivariate Cox proportional hazards regression analyses were performed to indicate if hormone receptor status (estrogen and/or progesterone receptors) and nodal status were significant variables in predicting RFS and OS.

Results

Patient Accrual and Demographics

172 patients from forty CALGB or ECOG institutions were accrued to this trial between February 1993 and April 1994. At study entry, 30% of patients were <40 years old, 42% were between 40-49 years old, 23% between 50-59 years old, and 5% were >60 years old. Axillary lymph node positivity was required for study entry, with a distribution of patients as follows: 46% with 1-3, 37% with 4-9, and 17% with ≥ 10 positive nodes. The details of patient demographics are presented in Table 1.

Overall Treatment Feasibility

130 of the 172 patients (76%) completed all protocol-specified therapy. Of the 42 early withdrawals (EW), 23 were due to unacceptable, acute, treatment-related toxicity. 27 of the 42 EW (64%) occurred during the course of AC, and 15 EW (36%) occurred during the course of paclitaxel. Those patients who withdrew from the study during AC were not eligible to proceed to further treatment with paclitaxel. 98 patients were hospitalized for therapy-related toxicity at least once during protocol participation.

Delivered Dose Intensity of Therapy

Approximately 35% of patients required a concurrent dose reduction of $\geq 10\%$ of doxorubicin and cyclophosphamide per protocol. Of the patients who completed all five cycles of AC, 74% were able to receive the full planned doses of therapy. Approximately 85% of patients who received all four cycles of paclitaxel were able to receive the full planned doses. There were no differences in the levels of delivered dose intensity between the two doses of G-CSF. After the third cycle of AC, however, the incidence of dose delays increased, as 34-48% of patients required a treatment delay for the fourth or fifth cycle to allow for recovery from treatment-associated toxicities.

Hematologic Tolerability of AC

Platelet and/or red blood cell transfusions were required at least once in 114 patients (67%) and 133 patients (77%), respectively.

Severe neutropenia was a universal finding despite the routine use of G-CSF during the dose-intensified AC portion of therapy. 170 patients (99%) experienced Grade 4 neutropenia during treatment on protocol. No differences were noted between the duration of neutropenia in patients who received G-CSF at 5 mcg/kg/day vs. those who received G-CSF at 10 mcg/kg/day. The median duration of severe neutropenia (ANC<500) in each cycle was two days regardless of the G-CSF dose (Figure 1). The median duration of moderately severe or severe neutropenia (ANC <1000) in each cycle was three days regardless of the G-CSF dose (Figure 2). Febrile neutropenia was not captured as a specific adverse event, but data regarding the incidence of fever with neutropenia was derived from the study case report forms. Specifically, febrile neutropenia during a given cycle was considered a toxicity if a patient was hospitalized with severe neutropenia (ANC<500) and fever (>100.4°F) and/or had received intravenous antibiotics. By these criteria, a total of 83 patients (48% of the study population) experienced febrile neutropenia at least once during protocol participation. No differences were noted in the incidence or duration of hospitalization for toxicity between the two dose levels of G-CSF.

Grade 3 or higher thrombocytopenia (platelet count <50,000/mm³) occurred at least once in 160 patients (93%). Of the patients who exhibited this degree of thrombocytopenia, the median duration was three days for patients who received 5 mcg/kg/day of G-CSF and four days for patients who received 10 mcg/kg/day. This difference was not statistically significant (Wilcoxon p-value = 0.67). Platelet transfusions were required at least once in 114 patients (67%) during the entire course of chemotherapy. There were no differences in the degree of treatment related thrombocytopenia or in the incidence of platelet transfusions between the two dose levels of G-CSF.

Anemia was a universal finding among all patients treated on this study. There were no parameters for mandatory transfusions, but 133 patients (77%) received at least one red blood cell transfusion during protocol participation. In addition, five patients (3%) received supportive therapy with erythropoietin alfa in response to a decline in hemoglobin levels.

Hematologic Tolerability of Paclitaxel

The hematologic tolerability of paclitaxel was excellent despite the preceding five cycles of dose-intensified AC chemotherapy, even without mandatory G-CSF support. 25% and 4% of patients experienced grade 4 leukopenia and thrombocytopenia, respectively. Approximately 9% of patients required G-CSF support during the first cycle of paclitaxel therapy. By the last cycle of paclitaxel, only 15% of patients had received G-CSF as supportive care.

Other Toxicities

102 patients (60%) experienced grade 3 or 4 nonhematologic toxicity at least once. 136 patients experienced stomatitis or esophagitis during the course of treatment with AC with the following levels of severity: 78 with grade 1, 33 with grade 2, 18 with grade 3, and 7 with grade 4 toxicity. There were no significant differences between the two doses of G-CSF. One death occurred during treatment but does not appear to be treatment-related as no grade 5 toxicities were reported. A summary of reported adverse events and toxicities is presented in Tables 2A-C.

Long-Term Follow-up and Clinical Outcomes

At a median follow-up of 11.8 years, the five-year rates of RFS and OS for all patients were 70% (95% confidence interval (CI), 64-77%) and 78% (95% CI, 72-85%), respectively (Figures 3 and 4). Subset analyses of patients with ≥10 positive lymph nodes revealed a RFS of 52% (95% CI, 36-75%) (Figure 5). As expected, univariate analyses showed that estrogen and progesterone receptor negativity is predictive of worse RFS and OS in comparison to estrogen and/or progesterone receptor positivity (Wilcoxon p-value = 0.001 for both RFS and OS). In addition, multivariate Cox analyses showed that patients with hormone receptor

positive disease treated with tamoxifen and/or 1-3 positive nodes had significantly improved rates of RFS and OS compared to patients with hormone receptor negative disease and/or ≥ 4 positive nodes.

A maximum of 6% of patients experienced grade 3 or 4 dysrhythmias, changes in cardiac function, ischemia, and pericardial or other cardiac toxicity during the follow-up period. In addition, few secondary primary malignancies were noted in patients during long-term follow-up with ten patients in total: three patients with hematologic malignancies (one myelodysplasia and two acute myeloid leukemias), and seven patients with solid tumors (including breast, bladder, cervix, and ovarian cancer). An increased risk of secondary hematologic malignancies was of concern given the dose intensification of doxorubicin and the higher dose of G-CSF, but a dose effect was not demonstrated. In fact, the majority of these primaries occurred on the 5 $\mu\text{g/kg/day}$ arm of G-CSF, but the limited number of events in this study does not allow for any final conclusions.

Discussion

The use of cytotoxic chemotherapy as adjuvant therapy to improve the outcomes of patients with node-positive breast cancer has been the subject of intensive investigation for more than thirty years. The optimal chemotherapy regimen remains controversial, and subsets of patients may benefit from different approaches based on their risk profiles and the biology of their tumors. With the wide usage of largely empiric combination chemotherapy regimens, advances in supportive care – including the hematopoietic cytokines (*e.g.*, G-CSF and GM-CSF) and the newer antiemetics (*e.g.*, serotonin antagonists) – were likely to facilitate improved outcomes by allowing for the administration of higher doses and/or longer regimens of chemotherapy with improved tolerability and safety. Before this was known, feasibility had to be established.

The trial presented in this manuscript was intended to serve as a feasibility study for subsequent larger, randomized trials. The clinical strategies of interest included (i) the simultaneous dose-intensification of both doxorubicin and cyclophosphamide (AC) with increased dose rate (*i.e.*, higher doses delivered per unit time) and increased total dose (*i.e.*, higher total doses delivered over the entire treatment course); (ii) the use of standard vs. higher doses of G-CSF in allowing for chemotherapy dose-intensification; and (iii) the addition of paclitaxel after the administration of dose-intensified combination chemotherapy with AC. The conduct of a multicenter adjuvant pilot study is particularly important when there is a plan to incorporate a novel treatment regimen into a large adjuvant trial. This approach allows investigators to proactively address potential challenges before beginning the randomized trial.

The data from this trial document that maximal dose-intensification of AC, delivered over five consecutive cycles with G-CSF support, was clinically feasible for the majority of patients. The tolerability of this intensive regimen with G-CSF support did not improve when the dose of G-CSF was doubled over that recommended for conventional practice. The duration of severe and moderately severe neutropenia was the same regardless of whether G-CSF was administered at 5 or 10 mcg/kg/day . As G-CSF use becomes more widespread, the observation that doubling its dose does not reduce toxicity assumes greater importance. It is also notable that the hematologic toxicities of this dose-intensified AC regimen remained significant despite the use of optimal supportive care. By current standards the regimen was unquestionably very toxic, with a high proportion of patients requiring hospitalization and transfusions. In this regard, our study demonstrates the extent to which adjuvant therapy for breast cancer has evolved over the past decade.

Long-term follow up of these patients is presented in this manuscript. The outcomes of patients treated with this intensive therapy are favorable in comparison to older historical controls (4; 5;10;11). However, we recognize that only limited conclusions can be made from single-arm, uncontrolled trials in breast cancer. Late toxicity in the form of secondary malignancies, particularly hematologic malignancies, is a major concern with dose-intensified regimens (12). A low but apparently elevated rate of AML/MDS is reported here; there was no discernible difference between patients who received G-CSF at 5 vs. 10 mcg/kg/d, but the low statistical power associated with a small number of events precludes making any definitive statements.

The CALGB began this pilot study to provide the foundation for CALGB 9344 – the larger, multicenter, prospective, statistically powered, randomized clinical trial that would ultimately determine the relative value of dose-intensification of doxorubicin and the addition of paclitaxel in the adjuvant therapy of early-stage breast cancer. The data from 9141 illustrated the impracticality of simultaneous dose-intensification of doxorubicin plus cyclophosphamide, even with maximal supportive care. Since intensive dosing of both an anthracycline and an alkylating agent led to excessive rates of myelotoxicity and mucosal injury (especially symptomatic stomatitis and esophagitis), and because two large clinical trials (NSABP B22 and B25) were already testing the impact of cyclophosphamide dose-intensification without benefit (13;14), the CALGB opted to evaluate the dose intensification of doxorubicin alone in the subsequent trial. CALGB 9344 used a 3×2 factorial design to test this hypothesis as well as the addition of paclitaxel following the administration of AC based chemotherapy. Using the Intergroup mechanism to include the participation of other national oncology cooperative groups, CALGB 9344 successfully tested these dual hypotheses and demonstrated the absence of benefit to dose-intensification with doxorubicin and the presence of benefit to the sequential administration of AC and paclitaxel in patients with node-positive breast cancer (15).

In the end, neither doxorubicin dose intensification nor cyclophosphamide dose intensification proved to be a useful strategy (13-15). The results of the adjuvant dose intensification trials provide an important reminder that preclinical modeling does not always lead to effective treatment in the clinic. With the appreciation that dose escalation would not alter the outcome of women with breast cancer, other strategies, such as novel scheduling (16) and incorporation of targeted therapy (17;18), have become the focus of large adjuvant trials.

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Figure 1.
Duration of severe neutropenia (ANC<500) in each treatment cycle.

Figure 2.
Duration of moderately severe and severe neutropenia (ANC<1000) in each treatment cycle.

-----	Low G-CSF	N= 87	Events= 36	Median= NA	Chi-square=	0.11
————	High G-CSF	N= 85	Events= 32	Median= NA	p-value=	0.74

Figure 3.
Relapse free survival based on G-CSF dose.

Figure 4.
Overall survival based on G-CSF dose.

Figure 5.
Relapse free survival based on nodal status.

TABLE 1
Patient Demographics and Entering Characteristics

Variable	Number	(Percent)
<u>Age</u>		
< 40	51	(30)
40-49	73	(42)
50-59	39	(23)
60+	9	(5)
<u>Menopausal Status</u>		
Premenopausal	108	(63)
Postmenopausal	63	(27)
<u>Positive Lymph Nodes</u>		
1-3	80	(46)
4-9	63	(37)
≥10	29	(17)
<u>ER/PR status</u>		
Either positive	116	(67)
Both negative	50	(29)
Data not available	6	(4)
<u>Performance Status</u>		
0	162	(95)
1	9	(5)
Data not available	1	(<1)
<u>Race</u>		
White	148	(86)
Hispanic	3	(2)
Black	17	(10)
Oriental	1	(<1)
Native Hawaiian	1	(<1)
Other	2	(1)
<u>Tumor Size</u>		
≤ 2 cm	47	(27)
> 2 cm	113	(66)
Data not available	12	(7)

TABLE 2

A		
Grade 3 and 4 Non-hematologic Toxicities with a Combined Incidence >5%		
Toxicity	Grade 3/4	
Nausea	22%	
Vomiting	17%	
Stomatitis	10%	
Anorexia	9%	
Dyspnea	6%	
Neuro-sensory	8%	
Neuro-headache	14%	
Pain	10%	
Myalgias/Arthralgias	7%	
Malaise/Fatigue	11%	
Hyperglycemia	7%	

B		
Toxicity during Five Cycles of Dose-Intensified AC by Study Arm		
	Study Arm	
	AC+5ug/kg G-CSF	AC+10ug/kg G-CSF
Grade ≥ 4 hematologic toxicity	87/87 (100%)	84/84 (100%)
Grade ≥ 3 nonhematologic toxicity	49/87 (56%)	52/84 (62%)

C		
Toxicity during Four cycles of T (following AC) by Study Arm		
	Study Arm	
	AC+5ug/kg G-CSF	AC+10ug/kg G-CSF
Grade ≥ 4 hematologic toxicity	56/73 (77%)	43/55 (78%)
Grade ≥ 3 nonhematologic toxicity	24/73 (33%)	18/55 (33%)