Dose and Dose Intensity as Determinants of Outcome in the Adjuvant Treatment of Breast Cancer

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For The Cancer and Leukemia Group B

Background: **Both total dose and dose intensity of adjuvant chemotherapy are postulated to be important variables in the outcome for patients with operable breast cancer. The Cancer and Leukemia Group B study 8541 examined the effects of adjuvant treatment using conventional-range dose and dose intensity in female patients with stage II (axillary lymph node-positive) breast cancer.** ***Methods:*** **Within 6 weeks of surgery (radical mastectomy, modified radical mastectomy, or lumpectomy), 1550 patients with unilateral breast cancer were randomly assigned to one of three treatment arms: high-, moderate-, or low-dose intensity. The patients received cyclophosphamide, doxorubicin, and 5-fluorouracil on day 1 of each chemotherapy cycle, with 5-fluorouracil administration repeated on day 8. The high-dose arm had twice the dose intensity and twice the drug dose as the low-dose arm. The moderate-dose arm had two thirds the dose intensity as the high-dose arm but the same total drug dose. Disease-free survival and overall survival were primary end points of the study.** ***Results:*** **At a median follow-up of 9 years, disease-free survival and overall survival for patients on the moderate- and high-dose arms are superior to the corresponding survival measures for patients on the low-dose arm (two-sided *P*<.0001 and two-sided *P* = .004, respectively), with no difference in disease-free or overall survival between the moderate- and the high-dose arms. At 5 years, overall survival (average ± standard error) is 79% ± 2% for patients on the high-dose arm, 77% ± 2% for the patients on the moderate-dose arm, and 72% ± 2% for patients on the low-dose arm; disease-free survival is 66% ± 2%, 61% ± 2%, and 56% ± 2%, respectively.** ***Conclusion:*** **Within the conventional dose range for this chemotherapy regimen, a higher dose is associated with better disease-free survival and overall survival. [J Natl Cancer Inst 1998;90: 1205–11]**

The treatment of operable breast cancer has evolved during the past several decades with the demonstration that the addition of medical treatment in the form of adjuvant chemotherapy,

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See ''Notes'' following ''References.''

hormonal manipulation, or both will lead to a significant improvement in disease-free survival (DFS) and overall survival (OS) *(1).* At the present time, most patients with operable breast cancer are subjected to postoperative medical treatment *(2).* However, the absolute benefits of such treatment remain modest, thus leading to the investigation of permutations of this therapy by either combinations of agents, sequencing of drug delivery, dose escalation, or the development of putative non-cross-resistant combinations of cytotoxic agents *(3)* in an effort to improve outcome.

A major area of intense evaluation in oncologic medicine is the concept of dose intensity (dose per unit time), with retrospective analyses suggesting that increased dose intensity within the conventional range of cytotoxic drug dosage could have a marked effect on outcome *(4,5).* This hypothesis of increasing DFS and OS with an increase in dose per unit time is based on experimental data demonstrating a logarithmic increase in cytotoxicity with a linear increase in dose *(6).* In addition, the use of high-dose levels of chemotherapy may reduce the chance of the emergence of resistant tumors *(7).* The Cancer and Leukemia Group B (CALGB) developed a program in the early 1980s to evaluate whether or not dose intensity or total dose of chemotherapy administered was a critical determinant of outcome in patients with operable breast cancer *(8).* Initial findings of this research have been reported previously *(9),* but the median duration of follow-up at the time of the initial report was only 3.4 years, which has been criticized as less than an optimal observation follow-up time to determine outcome *(10).* We now report our findings with a median follow-up of 9 years (range, 3.5–12.8 years).

Patients and Methods

The patient population has been described in detail previously *(9).* CALGB 8541 enrolled women with histologically confirmed stage II adenocarcinoma of the breast (T1N1M0 or T2N1M0) *(11)* with a CALGB performance score of 0–1 (nil or minimal symptoms) who underwent a radical mastectomy, a modified radical mastectomy (sparing of the pectoralis major muscle), or a lumpectomy with an axillary dissection of lymph nodes of at least level 1 (low-axillary lymph nodes, i.e., lateral to the lateral border of pectoralis minor muscle) and level 2 (mid-axillary lymph nodes, i.e., between the medial and lateral borders of the pectoralis minor muscle and interpectoral lymph nodes) within 6 weeks of study entry. Margins of resection had to be free of tumor. Patients who had a lumpectomy completed chemotherapy before irradiation of the entire breast. Mastectomy patients did not receive radiation. In 1988, the protocol was amended to recommend tamoxifen (20 mg/day) for 5 years after termination of cytotoxic treatment for postmenopausal patients with estrogen receptor-positive tumors. All patients gave written informed consent in accordance with institutional and Federal guidelines. Patients were stratified by the type of primary surgery (mastectomy or lumpectomy), number of involved axillary lymph nodes (one to three, four to nine, or $\geqslant$10), menopausal status (premenopausal or perimenopausal/postmenopausal), and estrogen receptor status (negative or positive).

Patients were randomly assigned to receive one of three dose levels of adjuvant chemotherapy as follows: high-dose arm (cyclophosphamide at 600 mg/m^2, doxorubicin at 60 mg/m^2, and 5-fluorouracil at 600 mg/m^2); moderate-dose arm (cyclophosphamide at 400 mg/m^2, doxorubicin at 40 mg/m^2, and 5-fluorouracil at 400 mg/m^2); or low-dose arm (cyclophosphamide at 300 mg/m^2, doxorubicin at 30 mg/m^2, and 5-fluorouracil at 300 mg/m^2). All drugs were administered intravenously on day 1 of a 28-day cycle. Administration of 5-fluorouracil was repeated on day 8 independent of the hematologic values. Chemotherapy was repeated for 4 monthly cycles in the high-dose arm, for 6 monthly cycles in the moderate-dose arm, and for 4 monthly cycles in the low-dose arm. Hematologic values were obtained weekly. Patients received the drug dosages based on actual body weight, except for morbidly obese patients. The effect of obesity on treatment outcome has been reported previously *(12).* No dose reductions were allowed for hematologic toxic effects. The high- and moderate-dose arms delivered the same total dosage of cytotoxic agents, while the low-dose arm delivered one half of the dose and dose intensity (mg/m^2 per week) of the high-dose arm. The moderate-dose arm delivered two thirds of the dose intensity of the high-dose arm by administering the same total dose over 50% longer duration. After completing chemotherapy, most postmenopausal patients with estrogen receptor-positive tumors received tamoxifen at a dose of 20 mg/day for 5 years.

DFS was defined as the time from study entry to a documented relapse from the original breast cancer or death without relapse. Surviving disease-free patients were censored at the time that they were last known to be disease free during the period from study entry to death from any cause. OS was defined as the time from study entry to death from any cause. Surviving patients were censored at the date of last contact. Pretreatment information and demographics data included the following variables: *(a)* those analyzed on a continuous scale, i.e., patient age, weight, and body surface area at time of entry, performance status, number of positive axillary lymph nodes, and tumor size; and *(b)* those analyzed as dichotomous variables, i.e., race (Caucasian versus other), menopausal status (premenopausal versus postmenopausal), tumor estrogen/progesterone receptor status (positive or negative; if either one or both receptors are present, the status is considered positive), type of primary surgery (lumpectomy versus mastectomy), and treatment with tamoxifen (no versus yes). Transformations were applied to continuous data to improve predictive ability. Thus, we used the square root of the number of positive lymph nodes and the square root of tumor size in all analyses unless otherwise stated.

The statistical methodology was described previously *(9).* Cox proportional hazards models were used to relate several predictor variables individually (univariate analysis) and simultaneously (multivariate analysis) with OS and DFS *(13).* The *P* values presented in Table 1, which summarizes proportional hazards models, are derived from Wald's chi-squared statistics. Survival distributions were compared with the logrank test *(14).* The Mantel–Haenszel chi-squared test was used to evaluate linearity between chemotherapy dose and other categorical variables. Differences among treatment arms in patient characteristics were evaluated with the chi-squared test for categorical variables and Wilcoxon's rank sum test for continuous variables *(15).* All *P* values are two-sided and unadjusted for multiple comparisons.

A study may have inadequate sample size to show differences even though hundreds of patients are involved. To assess whether a study larger than the present study would be likely to show a significant difference between the moderate- and high-dose arms, we performed a Bayesian predictive analysis based on noninformative prior distributions. We used the DFS data from patients in the trial and simulated DFS data on a hypothetical set of patients from the same population as the patients in this trial. This procedure has the effect of doubling the trial sample size. We assumed exponential DFS distributions. Given the available DFS data, we calculated the posterior distribution of hazard rates for each arm *(16,17).* We then generated hazard rates from this distribution repeatedly; at each iteration, we generated DFS times for an additional 500 patients for each arm. We then censored these times to have the same follow-up distribution as the actual data.

We give some results within various subgroups of patients. These results are meant to be descriptive and hypothesis generating rather than definitive. For example, we give results by treatment arm for patients having three or fewer positive lymph nodes as compared with patients having four or more positive lymph nodes. The trial was not powered for making dose comparisons within these subgroups. Similarly, we use multivariate models that incorporate patient characteristics (number of positive lymph nodes, tumor size, tumor estrogen/progesterone receptor status, and menopausal status) as well as chemotherapy dose. The main purpose of these models is to adjust for possible differences in these variables to allow for a more appropriate comparison of the different treatment groups.

All data for analysis were extracted from the official CALGB database in December 1997. The median follow-up was 9 years. Thus, all Kaplan–Meier survival curves and Cox proportional hazards models are based on data with a median follow-up of 9 years. Members of the CALGB Data Audit Committee performed on-site verification of 26% (403 of 1550 patients) of randomly selected patients treated in this study.

Table 1. Multivariate analysis for disease-free survival and overall survival of patients with stage II breast cancer treated with variable dose and dose intensity CAF regimens*

Variable	Comparison†	Risk ratio	95% confidence interval	Two-sided *P*‡
	Disease-free survival			
Drug (CAF) dose	Low versus moderate	1.27	1.06–1.51	.0001
	Moderate versus high	1.15	0.96–1.39	
No. of positive lymph nodes§	10 versus 1	2.44	2.17–2.82	.0001
Tumor size§	5 cm versus 1 cm	1.76	1.42–2.18	.0001
Menopausal status	Premenopausal versus postmenopausal	1.23	0.99–1.53	.061
Receptor status	Negative versus positive	1.26	1.08–1.49	.0043
Age at entry§	45 y versus 55 y	1.11	1.00–1.22	.051
Body surface area§	1.8 m^2 versus 1.7 m^2	1.05	1.01–1.10	.016
	Overall survival			
Drug (CAF) dose	Low versus moderate	1.27	1.04–1.56	.0095
	Moderate versus high	1.05	0.85–1.30	
No. of positive lymph nodes§	10 versus 1	2.38	2.04–2.79	.0001
Tumor size§	5 cm versus 1 cm	1.82	1.43–2.32	.0001
Menopausal status	Premenopausal versus postmenopausal	1.06	0.83–1.36	.63
Receptor status	Negative versus positive	1.38	1.15–1.64	.0004
Age at entry§	45 y versus 55 y	1.06	0.94–1.19	.34
Body surface area§	1.8 m^2 versus 1.7 m^2	1.05	1.00–1.10	.041

*n = 1515 patients with complete data. CAF = cyclophosphamide, doxorubicin (Adriamycin) and 5-fluorouracil. *See* ''Patients and Methods'' section for details on chemotherapy regimens—low, moderate, and high doses. Comparison for risk ratio names first category as having the worse prognosis.

†Favorable characteristics were higher dose, fewer positive lymph nodes, smaller tumor size, positive estrogen/progesterone receptors.

‡Derived from Wald's chi-squared statistics.

§These variables were analyzed on a continuous scale. Specific values of each variable were selected to illustrate the risk ratio interpretation.

Results

The trial accrued 1572 patients. The arms were balanced on pretreatment variables. Twenty-two patients never received treatment because they refused randomization selection (four patients on the low-dose arm, nine patients on the moderate-dose arm, and nine patients on the high-dose arm) and were not followed. This allowed treatment of 1550 patients from 26 main member institutions and their affiliated hospitals. Sixty-nine patients (4% of the total sample size) did not meet entry criteria but were analyzed according to intended treatment *(17)*. Deleting these patients did not materially affect conclusions. Twenty-seven patients (three on the low-dose arm, seven on the moderate-dose arm, and 17 on the high-dose arm) discontinued protocol therapy prematurely because of toxic effects. The demographics of the study populations have been presented previously *(9)*. At the time of this analysis, the median follow-up time is 9 years. Complete data for all analyses are available for 1515 patients, with 1% of these study patients lost to long-term follow-up.

Toxic effects seen in patients in different treatment arms paralleled the intensity of the drug dosages in those arms. Hematologic toxic effects were measured weekly. These effects paralleled the treatment intensity ($P<.01$, Mantel–Haenszel chi-squared test) with the incidence of leukopenia of grade 3 or 4 (<1900 cells/μL) seen in 4% of patients on the low-dose arm, 17% of patients on the moderate-dose arm, and 66% of patients on the high-dose arm. There was no evidence of a cumulative effect of repetitive dosing on the grade of leukopenia. A cumulative effect was evident in platelet counts of patients on the high-dose arm, with lower platelet count nadirs seen following repetitive treatment. Two deaths attributable to the chemotherapy occurred: One patient experienced septic shock after receiving three cycles on the low-dose arm, and the other patient developed a cardiomyopathy and congestive heart failure after three cycles on the high-dose arm. Nine patients in this trial developed evidence of severe cardiac toxicity of CALGB grades 3–5 (five of 508 patients on the moderate-dose arm and four of 515 patients on the high-dose arm). There were 33 second cancers in 18 patients reported: acute leukemia (one); basal cell carcinoma of skin (one); cancers of bladder (one), breast (eight), cervix (one), colon (two), endometrium (six), ovary (two), lung (two), and kidney (two); leiomyosarcoma (one); lymphoma (two); melanoma (one); myelodysplasia (two); and an unknown primary tumor (one).

Dose of chemotherapy administered remains a significant factor in OS and DFS of these patients and thus confirms our initial findings *(9)*. At a median follow-up of 9 years, both OS and DFS of patients in the moderate- and high-dose arms continue to be superior to those of the patients in the low-dose arm (two-sided $P = .004$, and two-sided $P<.0001$; Fig. 1, A and B, respectively). The additional follow-up time in this study after our initial report shows little separation of the moderate- and high-dose arms for OS (Fig. 1, A) and DFS (Fig. 1, B); the OS (average ± standard error) at 5 years was 72% ± 2% for patients on the low-dose arm, 77% ± 2% for patients on the moderate-dose arm, and 78% ± 2% for patients on the high-dose arm (pairwise logrank comparison of moderate versus high: $P = .85$), and the DFS at 5 years was 56% ± 2% for patients on the low-dose arm, 61% ± 2% for patients on the moderate-dose arm, and 66% ± 2% for patients on the high-dose arm (pairwise logrank comparison of moderate versus high: $P = .11$). After relapse, the median time to death was 22 months regardless of initial treatment. There was no difference in local (chest wall) relapse rates at 5 years in the three arms among lumpectomy patients receiving radiation therapy after chemotherapy.

Fig. 2 shows the hazard rate of relapse depending on time since treatment for patients with one to three positive lymph

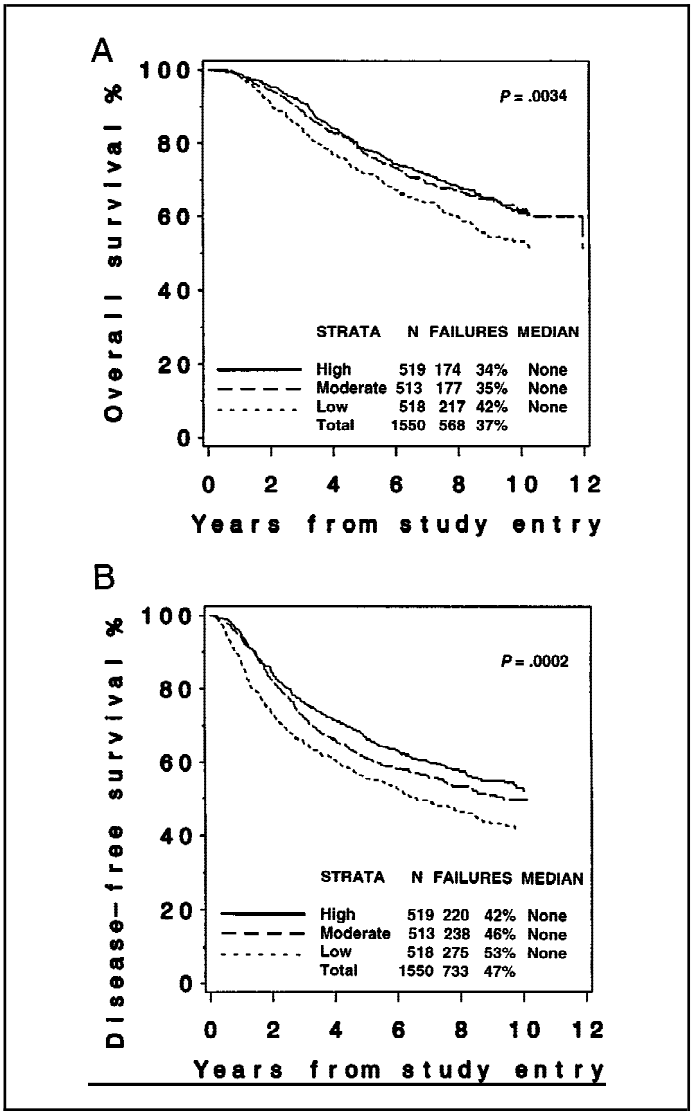

Fig. 1. A) Overall survival by treatment arm. There is no statistical difference between the outcome of patients on the high-dose-intense arm and that of patients on the moderate-dose-intense arm ($P = .11$). The cumulative dose of chemotherapy in the high-dose and moderate-dose arms is identical. Both of these strata are statistically superior to the low-dose arm. Chi-squared = 11.38; degrees of freedom = 2; two-sided $P = .0034$. The 5-year survival was 72% (95% confidence interval [CI] = 68%–75%) for patients on the low-dose arm, 77% (95% CI = 74%–81%) for patients on the moderate-dose arm, and 78% (95% CI = 75%–82%) for patients on the high-dose arm. **B)** Disease-free survival by treatment arm. The outcomes for patients on the high-dose arm and patients on the moderate-dose arm are statistically different from those for patients on the low-dose-intense arm but not from each other. Chi-squared = 17.16; degrees of freedom = 2; two-sided $P = .0002$. The 5-year disease-free survival was 56% (95% CI = 51%–60%) for patients on the low-dose arm, 61% (95% CI = 57%–65%) for patients on the moderate-dose arm, and 66% (95% CI = 62%–70%) for patients on the high-dose arm.

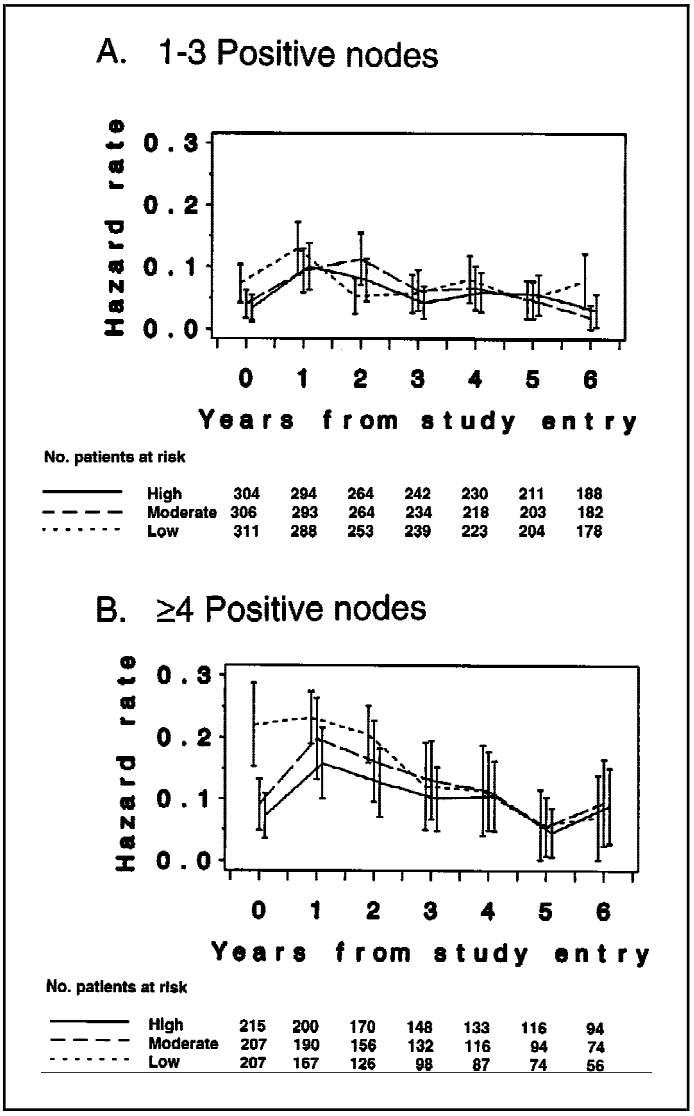

Fig. 2. A) Change in the hazard ratio of the chance of relapsing with recurrent carcinoma over time for patients with one to three positive axillary lymph nodes treated with the high-, medium-, or low-dose arm. Bars indicate the 95% confidence intervals. Note the absence of difference in the hazard ratios of the three treatment arms despite median follow-up of 9 years. **B)** Change in the hazard ratio of the chance of relapsing with recurrent carcinoma over time for patients with four or more positive axillary lymph nodes treated with the high-, medium-, or low-dose arm. Bars indicate the 95% confidence intervals. The major benefit of dose-intense therapy is seen within the first 3 years.

nodes (panel A) and four or more positive lymph nodes (panel B). Approximately 59% (921 of 1550) of the patients are in the first category. Because this finding is from a subset analysis and is not the primary end point of the study, the comparisons within and across these figures are meant to be descriptive and not definitive. The analysis of the hazard for relapse or death, which depends on time since treatment, appears to give results that are consistent with the overview published in 1992 *(1)*. That overview reported that lymph node-positive patients had a higher hazard of tumor recurrence within the first 5 years of follow-up after definitive treatment than in the later years. Fig. 2 suggests that the observations still hold within the two subsets of patients, with the effect being much more striking in patients with four or more positive lymph nodes. Comparisons of hazards of dying demonstrate similar results.

Findings from a comparison of OS of patients in the high-dose arm with that of patients in the moderate-dose arm were not statistically significant ($P = .11$). To address whether a larger trial could demonstrate a difference, we used Bayesian predictive analysis (described in the ''Patients and Methods'' section) to repeatedly simulate an additional 500 patients per arm. The probability of achieving a statistically significant difference between the moderate- and high-dose arms with approximately double trial size was only 60%.

In a univariate analysis, the following variables showed statistically significant association with OS: chemotherapy dose ($P = .002$), (square root of) the number of positive axillary lymph nodes ($P = .0001$), (square root of) tumor size ($P = .0001$), receptor status ($P = .0006$), and pretreatment weight ($P = .045$). The following factors showed statistically significant association with DFS: chemotherapy dose ($P = .0001$), patient age ($P = .0013$), menopausal status ($P = .0003$), (square root of) the number of positive axillary lymph nodes ($P = .0001$), (square root of) tumor size ($P = .0001$), receptor status ($P = .041$), pretreatment weight ($P = .023$), and body surface area ($P = .036$). Race and type of surgery were not associated with either OS or DFS. Use of tamoxifen was strongly associated with OS and DFS, but its use suffers from an important bias; patients still in remission were more likely to have received tamoxifen.

In a multivariate analysis, chemotherapy dose, (square root of) the number of positive axillary lymph nodes, (square root of) tumor size, menopausal status (postmenopausal better than premenopausal), and receptor status were significant predictors of DFS. Table 1 shows the multivariate analysis in which Cox models were used for DFS and OS. The illustrated model included drug dose, number of positive lymph nodes (square root transformation), tumor size (square root transformation), menopausal status, and receptor status. Additional models included log transformation of leukocyte count nadir, log transformation of platelet count nadir, and the combination. While we controlled for dose, nadir of either leukocyte counts or platelet counts did not add to outcome prediction. Menopausal status was also examined. However, significance (or not) of this covariant cannot be assessed separately from use of tamoxifen. Therefore, the relationship between menopausal status (or age) and survival should not be inferred from this latter model.

Of the 671 enrolled premenopausal patients, 509 (76%) reported toxic effects data regarding menstrual function. Two hundred fifty-eight (51%) of these 509 patients experienced amenorrhea within 1 year of the treatment. Forty-five percent of estrogen receptor-negative patients (77 premenopausal patients) became postmenopausal, while 54% of estrogen receptor-positive patients (175 premenopausal patients) did so. However, as shown in Fig. 3, there appears to be no advantage in OS or DFS for patients experiencing a chemical castration. Development of castration is not strongly associated with intensity of chemotherapy treatment ($P = .65$): 43% of patients (95% confidence interval [CI] = 35%–51%) in the low-dose arm, 55% (95% CI = 47%–62%) in the moderate-dose arm, and 54% (95% CI = 47%–62%) in the high-dose arm became castrate. These comparisons were not planned and are considered of exploratory nature.

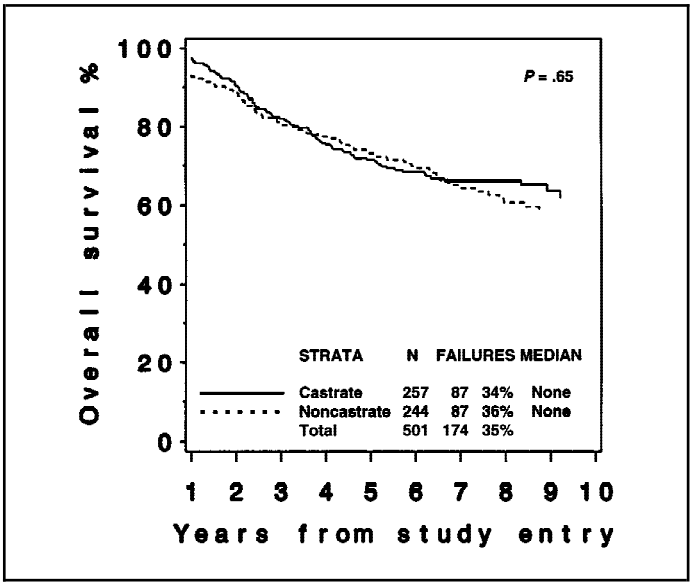

Fig. 3. Absence of a beneficial effect in premenopausal patients who become castrate within 1 year of chemotherapy. A total of 258 patients became castrate; 251 did not. Data were available on 257 and 244 patients, respectively. Two-sided P value is .65. Logrank test; chi-square = 0.21; degrees of freedom = 1. The 5-year overall survival was 71% (95% confidence interval = 65%–77%) for the castrate patients and 73% (95% confidence interval = 67%–79%) for the noncastrate patients.

Discussion

Dose and dose intensity of administered chemotherapy are clinically important variables that can be manipulated in an attempt to improve DFS and OS in patients with operable breast cancer. This trial examined these parameters within a conventional dosage range. With additional follow-up since our previous report *(9)*, we are able to confirm that total dose remains a critical determinant of outcome for this group of patients. Both the moderate-dose and high-dose arms delivered the same cumulative dose of chemotherapy with no significant difference in outcome (DFS or OS) between these arms for the study as a whole, but significantly better survival than for patients treated with a low-dose-intense arm. The data therefore suggest that dose reduction, perhaps below a threshold, leads to a relatively worse outcome with the currently available drugs for adjuvant treatment of patients with stage II breast cancer.

An exploratory subset analysis revealed that the beneficial effect of the higher dose adjuvant chemotherapy was limited to patients with four or more involved lymph nodes. This finding may reflect the worse prognosis of this cohort of patients *(18,19)*. An analysis of the hazard rates of relapse over time indicates that the major benefit of the adjuvant chemotherapy in reducing risk occurs during the first several years of follow-up. Even for patients with four or more lymph nodes involved, there is an eventual reduction in hazard rate to the same relapse rate as is seen for patients with one to three lymph nodes involved and is similar to the yearly hazard rate seen in the previous analysis for patients with negative lymph nodes *(1)*. This finding suggests that, independent of treatment intensity, a high-risk patient who is able to survive disease free for 5 years after diagnosis may have as good an outcome thereafter as a low-risk patient. The Eastern Cooperative Oncology Group *(20)* has also reported a retrospective overview analysis of seven adjuvant trials with varying treatments demonstrating that the peak hazard of recurrence in their trials of breast cancer patients occurred within the first 5 years of treatment.

The results of this trial indicate that dose of cytotoxic treatment is important. Moreover, they suggest that certain subgroups may benefit most from the dose-intense therapy of cy-

clophosphamide, doxorubicin, and 5-fluorouracil. However, any subgroup analysis should be interpreted cautiously. In contrast, the International Breast Cancer Study Group Trial I *(21)* could not demonstrate a difference in DFS and OS at 13 years despite a higher dose intensity in a CMFP arm (i.e., cyclophosphamide, methotrexate, 5-fluorouracil, and prednisone) compared with a CMF arm (i.e., cyclosphosphamide, methotrexate, and 5-fluorouracil). These differences may be due to differences in patient selection, the difference in magnitude of delivered chemotherapy between studies, or the lack of anthracycline treatment because lymph node-positive, erbB-2-positive patients with stage II disease may have a worse prognosis than lymph node-positive, erbB-2-negative patients with stage II disease when treated with CMF *(22)* and may have a better outcome when treated with anthracyclines *(23)*. A report of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-22 trial *(24)*, demonstrating no improvement of early benefit for the adjuvant treatment of breast cancer when cyclophosphamide is escalated to higher than standard levels in the presence of doxorubicin, is consistent with the hypothesis that there may be an optimal dosage range for the presently available agents. Tumors display heterogeneous characteristics *(25)*. We have confirmed our earlier findings *(9)* that lymph node status allows for identification of certain high-risk patients who may benefit from more dose-intense therapy.

A possible surrogate marker of drug dose effect is toxic effects seen in the host. The nadirs of the white blood cell count and the platelet count have been used clinically to guide chemotherapy dosing. A small trial in the adjuvant treatment of operable breast cancer indicated the feasibility of this approach without the use of growth factors *(26)*. This earlier trial did not demonstrate a superior outcome for patients when their chemotherapy dose was adjusted to a predefined leukocyte count nadir. In our multivariate analysis of prognostic factors for DFS and OS, white blood cell count nadir or platelet count nadir was determined not to predict survival for the study group as a whole after correction for administered chemotherapy dose. A weekly timed white blood cell count is an imperfect marker of biologic effect, and the current data do not allow us to determine whether the duration of count nadir or maximum count nadir value is a better predictor. Also, a biologic effect on the host is no guarantee of an antitumor effect.

The presence or absence of chemotherapy-induced castration in this study did not demonstrate an effect on the survival of premenopausal women and thus mirrored previous reports from the NSABP *(27)* and the National Cancer Institute–Milan *(28)* studies but stands in contrast to other retrospective analysis of adjuvant trials *(29)*. Our study had menstrual data on 509 premenopausal patients with 51% becoming castrate within a year of treatment and, thus, constitutes one of the larger sample sizes reviewed retrospectively. The Early Breast Trialists' Collaborative Group *(30)* has completed an overview of ovarian ablation in premenopausal women with breast cancer but noted only minor benefit in patients receiving chemotherapy and did not address whether the chemotherapeutic agents were more beneficial in the presence of drug-induced menopause. The ongoing prospective studies are therefore needed to clarify this finding.

In summary, the dose is a critical determinant of both DFS and OS outcomes in breast cancer patients receiving adjuvant chemotherapy with the currently available drugs. Reduction of dose below the currently accepted optimal conventional range leads to an inferior outcome and, thus, should be avoided.

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