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Weekly Paclitaxel in the Adjuvant Treatment of Breast Cancer

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ABSTRACT

BACKGROUND

We compared the efficacy of two different taxanes, docetaxel and paclitaxel, given either weekly or every 3 weeks, in the adjuvant treatment of breast cancer.

METHODS

We enrolled 4950 women with axillary lymph node–positive or high-risk, lymph node–negative breast cancer. After randomization, all patients first received 4 cycles of intravenous doxorubicin and cyclophosphamide at 3-week intervals and were then assigned to intravenous paclitaxel or docetaxel given at 3-week intervals for 4 cycles or at 1-week intervals for 12 cycles. The primary end point was disease-free survival.

RESULTS

As compared with patients receiving standard therapy (paclitaxel every 3 weeks), the hazard ratio for disease-free survival was 1.27 among those receiving weekly paclitaxel ($P=0.006$), 1.23 among those receiving docetaxel every 3 weeks ($P=0.02$), and 1.09 among those receiving weekly docetaxel ($P=0.29$) (with a hazard ratio >1 favoring the groups receiving experimental therapy). As compared with standard therapy, weekly paclitaxel was also associated with improved survival (hazard ratio, 1.32; $P=0.01$). An exploratory analysis of a subgroup of patients whose tumors expressed no human epidermal growth factor receptor type 2 protein found similar improvements in disease-free and overall survival with weekly paclitaxel treatment, regardless of hormone-receptor expression. Grade 2, 3, or 4 neuropathy was more frequent with weekly paclitaxel than with paclitaxel every 3 weeks (27% vs. 20%).

CONCLUSIONS

Weekly paclitaxel after standard adjuvant chemotherapy with doxorubicin and cyclophosphamide improves disease-free and overall survival in women with breast cancer. (ClinicalTrials.gov number, NCT00004125.)

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ADJUVANT CHEMOTHERAPY SUBSTANTIALLY reduces the risk of recurrence and death among women with operable breast cancer.¹ The addition of a taxane to an anthracycline-containing regimen, whether after or concurrently with anthracycline treatment, further reduces the risk of relapse. Two studies in which patients received four cycles of paclitaxel every 3 weeks after receiving four cycles of doxorubicin and cyclophosphamide every 3 weeks^{2,3} established a new standard of care for operable breast cancer and led to regulatory approval of paclitaxel for axillary lymph node–positive breast cancer. Another study demonstrating that concurrent administration of docetaxel with doxorubicin and cyclophosphamide was more effective than fluorouracil, doxorubicin, and cyclophosphamide led to regulatory approval of docetaxel for node-positive breast cancer.⁴

Questions remain, however, about the optimally effective taxane and the optimal schedule of administration of a taxane. Preclinical and indirect clinical evidence suggested that docetaxel was a more effective taxane than paclitaxel and that weekly paclitaxel was more effective than a conventional schedule of paclitaxel every 3 weeks.⁵ Moreover, phase 3 trials of patients with metastatic breast cancer demonstrated that docetaxel every 3 weeks⁶ or paclitaxel every week⁷ was superior to paclitaxel every 3 weeks.

We conducted a study to compare the efficacies of two aspects of current adjuvant chemotherapy in patients with axillary lymph node-positive or high-risk, lymph node–negative breast cancer: paclitaxel versus docetaxel and a schedule of every 3 weeks versus a weekly schedule. The factorial design of the trial allowed comparison of paclitaxel every 3 weeks for 4 cycles with three experimental regimens — paclitaxel every week for 12 cycles, docetaxel every 3 weeks for 4 cycles, or docetaxel every week for 12 cycles — with each regimen given after a standard doxorubicin–cyclophosphamide regimen.

METHODS

STUDY PATIENTS

We included in the study women who had operable, histologically confirmed adenocarcinoma of the breast with histologically involved lymph nodes (tumor stage T1, T2, or T3 and nodal stage N1 or N2) or high-risk, axillary node-negative

disease (T2 or T3, N0) without distant metastases. Other details regarding eligibility are listed in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

CHEMOTHERAPY

All women received doxorubicin (60 mg per square meter of body-surface area, given by slow intravenous push during a period of 5 to 15 minutes) and cyclophosphamide (600 mg per square meter by intravenous infusion for 30 to 60 minutes) every 3 weeks for four cycles. This therapy was followed by taxane therapy. The women were randomly assigned to 175 mg of paclitaxel per square meter by intravenous infusion for 3 hours every 3 weeks for 4 doses, 80 mg of paclitaxel per square meter by intravenous infusion for 1 hour weekly for 12 doses, 100 mg of docetaxel per square meter by intravenous infusion for 1 hour every 3 weeks for 4 doses, or 35 mg of docetaxel per square meter by intravenous infusion for 1 hour weekly for 12 doses. Guidelines for dose modification, premedication, and supportive care are given in the Supplementary Appendix.

HORMONAL THERAPY AND IRRADIATION

Patients who had breast-sparing surgery received radiotherapy according to accepted standards of care after completion of all chemotherapy. Women who had a modified radical mastectomy also were permitted to receive radiotherapy after completion of all chemotherapy, at the discretion of the treating physician. Patients with hormone receptor–positive disease (defined as disease positive for estrogen receptors, progesterone receptors, or both) were required to take 20 mg of tamoxifen daily for 5 years. In June 2005, the protocol was modified to permit postmenopausal women who were taking tamoxifen to change to an aromatase inhibitor before completing 5 years of tamoxifen or to begin taking an aromatase inhibitor after completing a 5-year course of tamoxifen.

END POINTS

The primary end point was disease-free survival, defined as the time from randomization to disease recurrence (including death from recurrence if it was the first manifestation of recurrence), death without recurrence, or contralateral breast cancer. This end point differs from the end point of disease-free survival that was used in other

trials of paclitaxel sponsored by the National Cancer Institute, which did not include contralateral breast cancer in the definition^{3,8} or which included contralateral breast cancer and second primary cancers.²

STUDY PROTOCOL

The protocol was coordinated by the Eastern Cooperative Oncology Group (ECOG) (ClinicalTrials.gov number, NCT00004125); other participating groups included the Southwest Oncology Group (SWOG), the Cancer and Leukemia Group B (CALGB), and the North Central Cancer Treatment Group (NCCTG). The protocol was reviewed and approved by the institutional review board at each participating institution, and all patients provided written informed consent. All the authors vouch for the accuracy and completeness of the data.

STATISTICAL ANALYSIS

The primary comparisons were paclitaxel with docetaxel, regardless of the dosing schedule, and weekly dosing with dosing every 3 weeks, regardless of the taxane administered. The study design required enrollment of 4762 eligible patients with total information (the number of events required for a primary analysis) after 1042 observed failures (recurrences or deaths). This design had an 86% power to detect a 17.5% reduction in the hazard rate for failure among the docetaxel groups, or with weekly dosing instead of dosing every 3 weeks, at an overall two-sided significance level of 0.05.

Annual interim analyses were planned to begin about 2 years after initiation of the study and to continue until full information was obtained, with critical values determined from the O'Brien-Fleming boundary. All eligible patients undergoing randomization were included in the efficacy analysis. All treated patients were included in the adverse-events analyses, regardless of eligibility.

The primary prespecified analysis of disease-free survival and overall survival was performed with the use of the log-rank test. Also prespecified was that the test for paclitaxel versus docetaxel was stratified according to dosing schedule, number of positive nodes (none vs. one or more), and estrogen-receptor status (positive, negative, or unknown) and that the test for the weekly schedule as compared with the schedule of every 3 weeks was stratified according to the taxane

administered, the number of positive nodes, and estrogen-receptor status. The tests for the comparisons between the groups receiving experimental treatment and the group receiving standard treatment (paclitaxel every 3 weeks) were stratified according to the number of positive nodes and estrogen-receptor status. Distributions of events with respect to time were estimated with the use of Kaplan–Meier analysis. Cox proportional-hazards models stratified according to the taxane administered, number of positive nodes, estrogen-receptor status, and dosing schedule were used to estimate hazard ratios and to test for significant differences in the times to events. All reported P values are two-sided. The significance level used in the pairwise comparisons between the groups receiving experimental treatment and the group receiving standard treatment was 0.017 on the basis of the Bonferroni correction for multiple comparisons, corresponding to an overall type I error rate of 0.05.

Because recent data suggest that patients with disease positive for hormone receptors and negative for human epidermal growth factor receptor type 2 (HER2) protein may not benefit from adjuvant paclitaxel therapy,⁹ we performed a post hoc analysis of outcomes according to hormone-receptor status and HER2 expression. Details of this analysis are in the Supplementary Appendix.

RESULTS

PATIENTS

Between October 1999 and January 2002, we enrolled 5052 patients, of whom 4950 (98%) were eligible for the study. Of the ineligible patients, 55 had a tumor margin within 1 mm of the excised specimen, 10 had fewer than six nodes removed, 6 had T4 or N3 disease, 5 had distant metastases before registration, and 26 were deemed ineligible for other reasons. The treatment groups were similar with regard to prognostic characteristics (Table 1). The median age was 51 years (range, 19 to 84). Approximately 12% of the patients had no positive lymph nodes, 56% had one to three positive nodes, and 32% had four or more positive nodes. The tumor was positive for estrogen receptor, progesterone receptor, or both in 70% of patients and positive for HER2 in 19% (as determined in local institutional laboratories). Sixty percent of the patients had undergone mastectomy, and 40% had undergone breast-sparing surgery.

Table 1. Characteristics of the Patients.

Characteristic	Paclitaxel Every 3 Wk (N=1253)	Weekly Paclitaxel (N=1231)	Docetaxel Every 3 Wk (N=1236)	Weekly Docetaxel (N=1230)
Age (yr)				
Median	51	51	51	51
Range	26–79	22–84	25–79	19–81
Positive lymph nodes (%)				
0	11.7	11.6	11.6	11.6
1–3	55.0	56.2	56.0	56.0
4–9	23.2	22.6	23.2	22.5
≥10	10.1	9.6	9.2	9.9
Expression of estrogen receptors, progesterone receptors, or both (%)				
Yes	69.2	68.2	70.1	70.7
No	26.8	27.6	25.7	25.3
Unknown	4.0	4.1	4.3	4.0
Expression of HER2 protein (%)*				
Yes	20.5	18.6	18.9	18.7
No	67.8	67.4	68.6	66.5
Unknown	11.7	14.0	12.5	14.8
Premenopausal or <50 yr of age (%)	46.1	45.6	47.3	45.6
Breast-sparing surgery (%)	39.7	39.6	39.7	39.1

* HER2 denotes human epidermal growth factor receptor type 2.

TREATMENT

The patients received a mean of 4.0 and a median of 4 (range, 1 to 5) cycles of treatment with doxorubicin and cyclophosphamide; 97% of patients received all 4 cycles. The mean number of taxane cycles received was 3.9 for the group receiving paclitaxel every 3 weeks, 11.4 for the group receiving weekly paclitaxel, 3.8 for the group receiving docetaxel every 3 weeks, and 10.8 for the group receiving weekly docetaxel. The proportion of women in whom the taxane dose was modified was 22%, 29%, 28%, and 40%, respectively. The proportion who received all doses was 95%, 88%, 87%, and 75%, respectively. The proportion who received half or less than half of the planned doses was 4%, 5%, 9%, and 11%, respectively. There were no significant differences among the four groups in the percentage of patients who received hormonal therapy; the percentages ranged from 27 to 30% for tamoxifen alone, 43 to 45% for tamoxifen followed by an aromatase inhibitor, and 3 to 4% for an aromatase inhibitor alone. The median time from randomization to initiation of an aromatase inhibitor for those who crossed over was 3.7 years.

TAXANE TYPE AND SCHEDULE OF ADMINISTRATION

At the time of the analysis after a median follow-up of 63.8 months, 1048 patients had a recurrence of breast cancer or cancer in the contralateral breast, and 686 had died. There were no significant differences in disease-free survival between the paclitaxel-treated groups and the docetaxel-treated groups (hazard ratio, 1.03; 95% confidence interval (CI), 0.91 to 1.17; $P=0.61$) or between the groups receiving weekly treatment and those receiving treatment every 3 weeks (hazard ratio, 1.06; 95% CI, 0.94 to 1.20; $P=0.33$). The results were similar when the data were analyzed according to definitions of disease-free survival used in other trials of treatment with doxorubicin and cyclophosphamide followed by a taxane (data not shown). However, in a Cox proportional-hazards model that included the taxane administered (paclitaxel or docetaxel), the schedule of administration (weekly or every 3 weeks), and their interaction, the interaction of docetaxel and the weekly schedule was significant for disease-free survival ($P=0.003$) and for overall survival ($P=0.01$).

DISEASE-FREE SURVIVAL

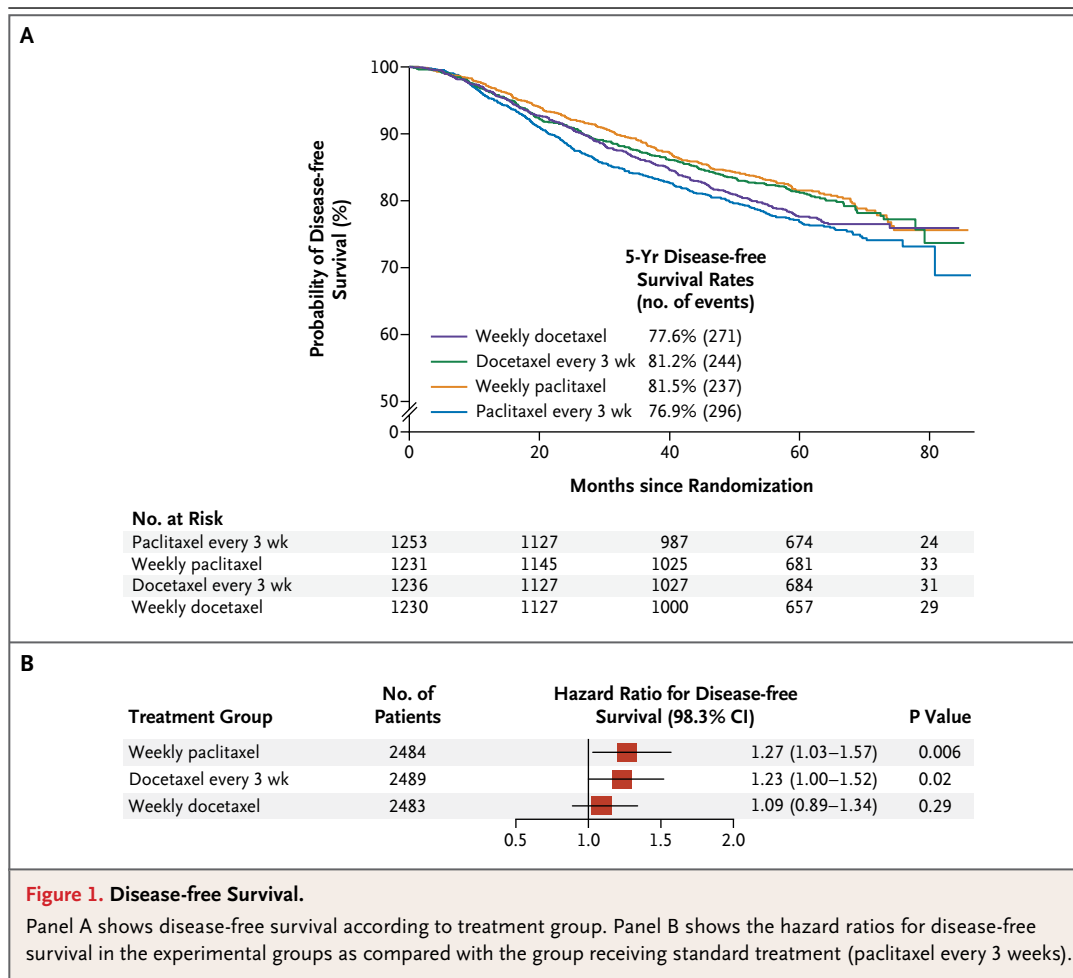
Figure 1A shows the Kaplan–Meier curves for disease-free survival in the four treatment groups. The estimated 5-year survival rates were 76.9% for the group receiving paclitaxel every 3 weeks, 81.5% for the group receiving weekly paclitaxel, 81.2% for the group receiving docetaxel every 3 weeks, and 77.6% for the group receiving weekly docetaxel. As compared with the group receiving paclitaxel every 3 weeks, there was significantly better disease-free survival in the group receiving weekly paclitaxel (hazard ratio, 1.27; $P=0.006$) and in the group receiving docetaxel every 3 weeks (hazard ratio, 1.23; $P=0.02$), but not in the group receiving weekly docetaxel (hazard ratio, 1.09; $P=0.29$) (Fig. 1B). The results were similar when the definition of end point did not include contralateral breast cancer or contralateral breast cancer and second primary nonbreast cancer (see the Supplementary Appendix for details).

OVERALL SURVIVAL

Figure 2A shows the Kaplan–Meier curves for overall survival in the four groups. The estimated 5-year overall survival rates were 86.5% for the group receiving paclitaxel every 3 weeks, 89.7% for the group receiving weekly paclitaxel, 87.3% for the group receiving docetaxel every 3 weeks, and 86.2% for the group receiving weekly docetaxel. As compared with the group receiving paclitaxel every 3 weeks, overall survival was significantly better in the group receiving weekly paclitaxel (hazard ratio, 1.32; $P=0.01$), but not in the groups receiving docetaxel every 3 weeks (hazard ratio, 1.13; $P=0.25$) or weekly docetaxel (hazard ratio, 1.02; $P=0.80$) (Fig. 2B).

EXPRESSION OF HORMONE RECEPTORS AND HER2

Because of evidence that the benefit of taxane therapy may be restricted to patients with hormone receptor–negative disease¹⁰ and HER2-positive dis-



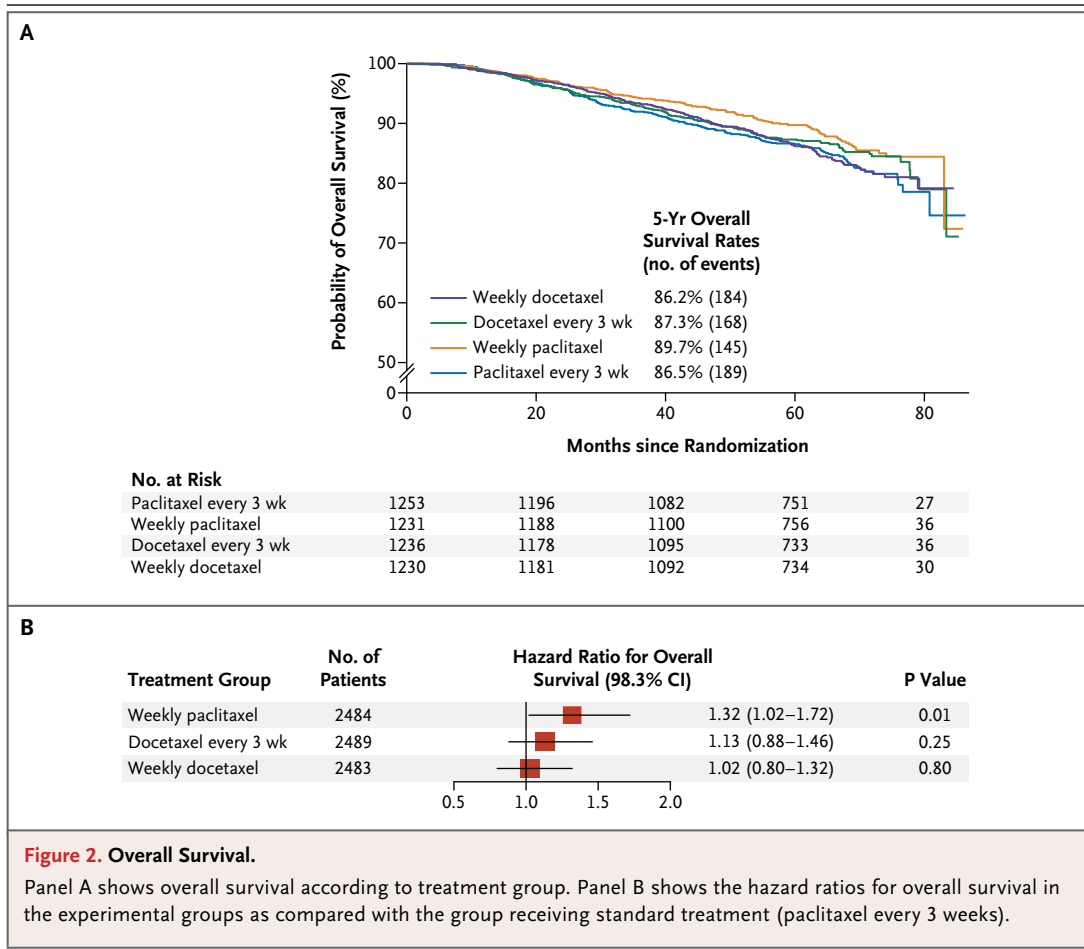


Figure 2. Overall Survival.

Panel A shows overall survival according to treatment group. Panel B shows the hazard ratios for overall survival in the experimental groups as compared with the group receiving standard treatment (paclitaxel every 3 weeks).

ease,⁹ we evaluated the influence of hormone-receptor status and HER2 expression on the effectiveness of weekly paclitaxel. This analysis should be regarded as exploratory, because it was not prespecified when the study was initiated in 1999.

Figure 3 shows that patients with HER2-negative disease who were treated with weekly paclitaxel had improved disease-free survival (Fig. 3A) and overall survival (Fig. 3B); these effects were not seen in patients with HER2-positive disease or in those treated with docetaxel. Figure 4 indicates that patients with HER2-negative disease who received weekly paclitaxel had improved disease-free survival and overall survival, irrespective of their hormone-receptor status. Similar effects were not observed in the group receiving docetaxel every 3 weeks (data not shown).

TOXIC EFFECTS

During treatment with doxorubicin and cyclophosphamide, 40% of patients had grade 2 toxic

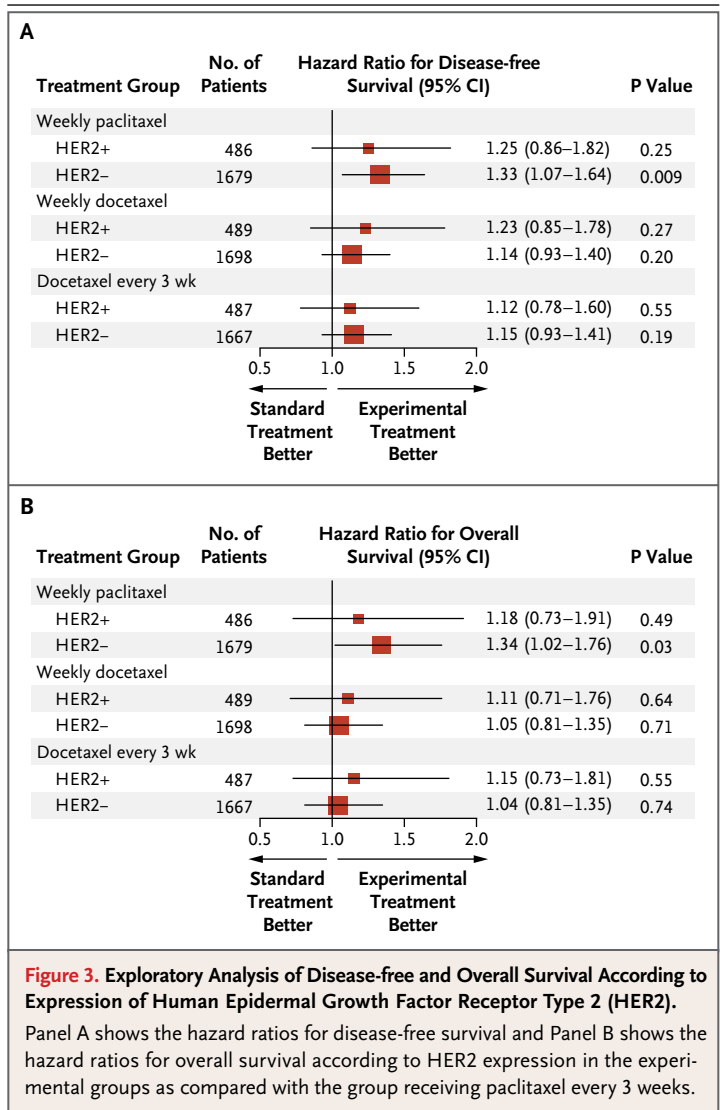
effects, 13% had grade 3 toxic effects, and 39% had grade 4 toxic effects; the percentages were similar in the four treatment groups (see Table 1 in the Supplementary Appendix). Table 2 and Table 2 in the Supplementary Appendix show the toxic-effects profile of the taxane component of therapy for each group. Twenty-eight percent of patients receiving paclitaxel weekly had grade 3 or 4 toxic effects, as compared with 30% of those receiving paclitaxel every 3 weeks (P=0.32), 71% of those receiving docetaxel every 3 weeks (P<0.001), and 45% of those receiving docetaxel weekly (P<0.001). The higher proportions of grades 3 and 4 toxic effects in the group receiving docetaxel every 3 weeks were due to a 46% incidence of neutropenia (as compared with an incidence of ≤4% for the other groups), which resulted in higher rates of febrile neutropenia (16%) and infection (13%) than in the other groups (1% and ≤4%, respectively, for all other groups). The incidence of grade 3 or 4 neuropathy in the four groups

ranged from 4 to 8%, but the group receiving weekly paclitaxel had a significantly higher incidence of grade 2, 3, or 4 neuropathy (27%) than any of the other treatment groups ($P < 0.001$ for each comparison).

DISCUSSION

This trial was designed to compare the efficacy of paclitaxel with that of docetaxel and to compare the standard taxane schedule (every 3 weeks) with a weekly schedule in nearly 5000 women with axillary lymph node–positive or high-risk, lymph node–negative breast cancer. We found no significant differences in survival between the groups treated with paclitaxel and those treated with docetaxel or between the groups treated weekly and those treated every 3 weeks. However, the interpretation of our results is complicated by an unanticipated interaction between the type of taxane administered and the treatment schedule for the group receiving weekly docetaxel. In a comparison of the three experimental groups with the group receiving standard paclitaxel treatment, the group receiving weekly paclitaxel and the group receiving docetaxel every 3 weeks had significantly improved disease-free survival, and the group receiving weekly paclitaxel had significantly improved overall survival. In comparison with the group receiving standard therapy, the group receiving weekly paclitaxel had significantly more moderate-to-severe neuropathy and the group receiving docetaxel every 3 weeks had significantly more severe neutropenia and its associated complications. The 32% reduction in the hazard ratio for death afforded by weekly paclitaxel is similar to that observed for anthracycline-containing chemotherapy as compared with no adjuvant cytotoxic therapy.¹ The results are consistent with studies of metastatic breast cancer that demonstrated a benefit of weekly paclitaxel⁷ or docetaxel every 3 weeks,⁶ as compared with paclitaxel every 3 weeks.

A similar benefit was not observed for the group receiving weekly docetaxel, a result that may be attributable in part to the less acceptable adverse-events rates and poorer adherence to treatment in this group. The findings are also consistent with the results of trials of metastatic breast and prostate cancer that indicate that docetaxel may be more effective if given every 3 weeks rather than weekly.^{11,12} The results were



not changed when the data were analyzed according to definitions of end points similar to those used in other trials evaluating paclitaxel.^{2–4} Guidelines for standardization of end-point definitions in trials of adjuvant breast-cancer treatment have recently been proposed that we think should be routinely incorporated into future trials.¹³

Other studies have suggested that the benefits of taxane-based therapy are driven largely by improved outcomes in hormone receptor–negative disease^{7,12} or HER2-positive disease and that there may be little if any benefit of taxane therapy for the 50% or more of patients with hormone receptor–positive, HER2-negative disease.⁹ In our trial, there were similar trends favoring weekly paclitaxel in patients with HER2-negative

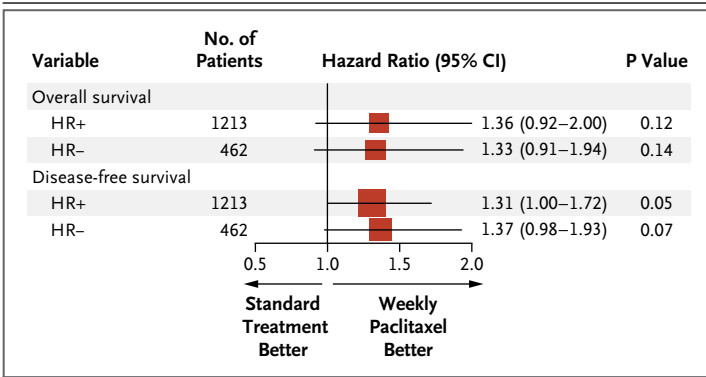


Figure 4. Exploratory Analysis of Disease-free and Overall Survival According to Expression of Hormone Receptors (HR).

The figure shows the hazard ratios for disease-free and overall survival the group receiving weekly paclitaxel in as compared with the group receiving paclitaxel every 3 weeks among patients with HER2-negative disease according to whether the disease was positive or negative for hormone receptors.

disease that was either hormone receptor-positive or hormone receptor-negative. Although hormone-receptor status was not determined centrally, analysis of an another ECOG-coordinated Intergroup trial conducted during a similar time period demonstrated 90% concordance for hormone-receptor expression between local laboratories and a central laboratory, and 95% concordance for tumors determined to be HER2-negative in local laboratories.¹⁴ Another study, which compared six cycles of fluorouracil, epirubicin, and cyclophosphamide every 3 weeks with four cycles of fluorouracil, epirubicin, and cyclophosphamide

followed by weekly paclitaxel for 8 weeks, also showed a better outcome in patients treated with weekly paclitaxel, including patients with hormone receptor-positive or hormone receptor-negative disease, as determined by testing in a central laboratory according to a prespecified analysis plan.¹⁵ Taken together, these results suggest that the benefits are similar in hormone receptor-positive and hormone receptor-negative breast cancer.

In conclusion, treatment with doxorubicin and cyclophosphamide followed by weekly paclitaxel is associated with improved disease-free survival and overall survival in comparison with treatment with doxorubicin and cyclophosphamide followed by paclitaxel given every 3 weeks. We found no evidence that women with hormone receptor-positive, HER2-negative breast cancer derived less benefit than those with breast cancer negative for hormone receptors or positive for HER2.

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No potential conflict of interest relevant to this article was reported.

Table 2. Toxic Effects of Paclitaxel and Docetaxel.*

Effect	Paclitaxel Every 3 Wk	Weekly Paclitaxel	Docetaxel Every 3 Wk	Weekly Docetaxel
	<i>percent</i>			
Neutropenia†	4	2	46	3
Febrile neutropenia†	<1	1	16	1
Infection	3	3	13	4
Stomatitis	<1	0	5	2
Fatigue	2	3	9	11
Myalgia	7	2	6	1
Arthralgia	6	2	6	1
Lacrimation	<1	0	<1	5
Grade 3 or 4 neuropathy	5	8	4	6
Grade 2, 3, or 4 neuropathy	20	27	16	16

* The table lists the most common grade 3 and 4 toxic effects and grade 2, 3, and 4 neuropathies (i.e., those that occurred in at least 5% of all treated patients) resulting from the taxane component of therapy.

† Information on only grade 4 neutropenia (<500 polymorphonuclear neutrophils per cubic millimeter) was collected.

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CORRECTION

Weekly Paclitaxel in the Adjuvant Treatment of Breast Cancer

Weekly Paclitaxel in the Adjuvant Treatment of Breast Cancer . In Figure 2B (page 1668), the label above the hazard ratio plot should read, "Hazard Ratio for Overall Survival (98.3% CI)." The figure has been corrected at NEJM.org.