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The use of taxanes in early breast cancer

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Abstract

The evidence is now clear that taxanes added to standard adjuvant regimens have acceptable toxicity and can improve outcomes for patients with breast cancer. The North American Intergroup 0148 study (CALGB 9344) clearly showed a benefit in terms of disease-free survival and overall survival when paclitaxel 175 mg/m^2 was added to adjuvant doxorubicin (A) and cyclophosphamide (C) therapy in 3121 patients with node-positive breast cancer. Adding paclitaxel to AC therapy resulted in a hazard reduction of 17% for recurrence (adjusted Wald χ^2 $P = 0.0023$) and 18% for death (adjusted Wald χ^2 $P = 0.0064$). Results from a similar trial, NSABP B28, in which paclitaxel was also added to standard AC adjuvant therapy and compared with standard AC therapy alone in 3060 patients with node-positive breast cancer are consistent with those of the CALGB trial. This trial also demonstrated a 17% reduction in disease-free survival events ($P = 0.008$) and a non-significant trend in overall survival when paclitaxel was added. A third large trial (BCIRG 001) testing taxanes as adjuvant therapy comparing 5-fluorouracil plus AC with docetaxel (T) plus AC (TAC vs FAC) yielded a significant improvement in disease-free survival (32% reduction in risk of recurrence, $P = 0.0011$), as well as a favourable trend in overall survival with the substitution of the taxane in place of 5-fluorouracil. Additional studies in the preoperative setting demonstrate benefits in terms of local tumour response and overall outcomes when taxanes are added to standard therapy. Very recent results suggest that dose-dense administration of chemotherapy including paclitaxel is associated with better outcomes than standard regimens in adjuvant therapy. Hence, the available data are clearly consistent with the hypothesis that taxanes can add to the benefits of existing chemotherapy regimens in the adjuvant setting. Future studies will need to identify subgroups of patients with greater or lesser benefits from taxanes and focus on optimisation of this class of agents.

Keywords: Adjuvant chemotherapy; BCIRG 001; CALGB 9344; Neoadjuvant chemotherapy; Taxanes

1. Introduction

Adjuvant therapy for early stage breast cancer represents a significant public health advance and is likely to have contributed to the declining mortality seen for this disease in many Western countries over the past 10 years [1–4]. Current options in the adjuvant setting include hormonal manipulations, such as ovarian ablation, anti-oestrogens and aromatase inhibitors, and chemotherapy. Important advances are being made in all stages and therapeutic areas, but this paper focuses specifically on chemotherapy and the role of the taxanes.

2. Taxanes in adjuvant therapy

The taxanes, paclitaxel and docetaxel, are candidate agents for use in adjuvant therapy because of their significant and consistent activity in the advanced disease setting, their lack of some overlapping toxicities with other standard chemotherapy agents, and the feasibility of their use in concurrent or sequential combinations with the established effective agents [5–7]. There are now dozens of trials, including both those that use a randomised design and those that do not, that explore the optimal means of incorporating the taxanes in the adjuvant setting. To place some of these key studies in perspective, we will review the present state of the art in this area.

The earlier development of paclitaxel compared with docetaxel means that more mature data are available for

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paclitaxel at this moment. However, there are an increasing number of trials incorporating docetaxel that will be available for interpretation in the coming years. Direct comparisons between these taxanes are not yet available but are anticipated shortly in both the metastatic and adjuvant setting.

In the first pilot studies reported, paclitaxel was added as a single agent to anthracycline (doxorubicin) and cyclophosphamide (C) regimens. At Memorial Sloan-Kettering Cancer Center (MSKCC), paclitaxel (T) was administered between doxorubicin (A) and cyclophosphamide, and all were given as single agents (A–T–C). At Dana-Farber Cancer Center, paclitaxel followed the AC combination using high-dose cyclophosphamide [8,9]. These studies clearly demonstrated feasibility but could not properly address relative efficacy.

As the National Surgical Adjuvant Bowel and Breast Project (NSABP) studies B22 and B25 suggested that dose-escalation of cyclophosphamide was not useful, the Intergroup embarked on a trial coordinated by Cancer and Leukemia Group B (CALGB) utilising a factorial design to answer two presumably unrelated questions [10,11]. First, patients with positive nodes were randomly assigned to receive four courses of doxorubicin at doses of 60 mg/m^2 on day 1, 37.5 mg/m^2 on days 1 and 2 (75 mg/m^2 total), or 45 mg/m^2 on days 1 and 2 (90 mg/m^2 total), all combined with cyclophosphamide at a set dose of 600 mg/m^2. Hence, this study explored a 50% dose-escalation and increase in dose-intensity for doxorubicin. No differences in disease-free survival were seen in these three arms; at 5 years, disease-free survival was 69%, 66% and 67% for patients randomly assigned to 60, 75 and 90 mg/m^2, respectively. The second question addressed in this study (INT 0148/CALGB 9344) concerned the value of adding paclitaxel at a dose of 175 mg/m^2 as a 3-hour infusion once every 21 days after four courses of AC for four cycles. Patients in this study were treated with tamoxifen after the completion of chemotherapy if they had evidence of oestrogen or progesterone receptor expression. When reported in the *J Clin Oncol* in 2003, this study with 69 months of follow-up clearly demonstrated significant improvements in both disease-free and overall survival [12]. Disease-free survival was increased from 65% to 70% with the addition of paclitaxel therapy, with a hazard reduction for recurrence of 17% (adjusted Wald χ^2 $P = 0.0023$; unadjusted Wilcoxon $P = 0.0011$). Overall survival was increased from 77% to 80% with the addition of paclitaxel, with an 18% hazard reduction in the risk of death (adjusted Wald χ^2 $P = 0.0064$; unadjusted Wilcoxon $P = 0.0098$). Hence, this study, with more than 5 years of follow-up, is unequivocally positive for the addition of paclitaxel and negative for the escalation of doxorubicin dosing above 60 mg/m^2 (Fig. 1).

In an unplanned subset analysis, the hazard ratio for recurrence comparing AC followed by paclitaxel versus AC alone was 0.72 in patients with oestrogen-receptor negative tumours compared with 0.91 for patients with oestrogen-receptor positive tumours, almost all of whom received adjuvant tamoxifen. However, after correction for multiple comparisons this was not a statistically significant finding. Hence, this hypothesis-generating subset analysis could be important in refining and optimising our use of taxanes in the adjuvant setting if it is confirmed in additional studies, but in itself it could not be a conclusive finding of this study. It is, therefore, critical to note that this analysis, because of its exploratory nature and lack of statistical power, is inadequate for guiding treatment outside clinical trials.

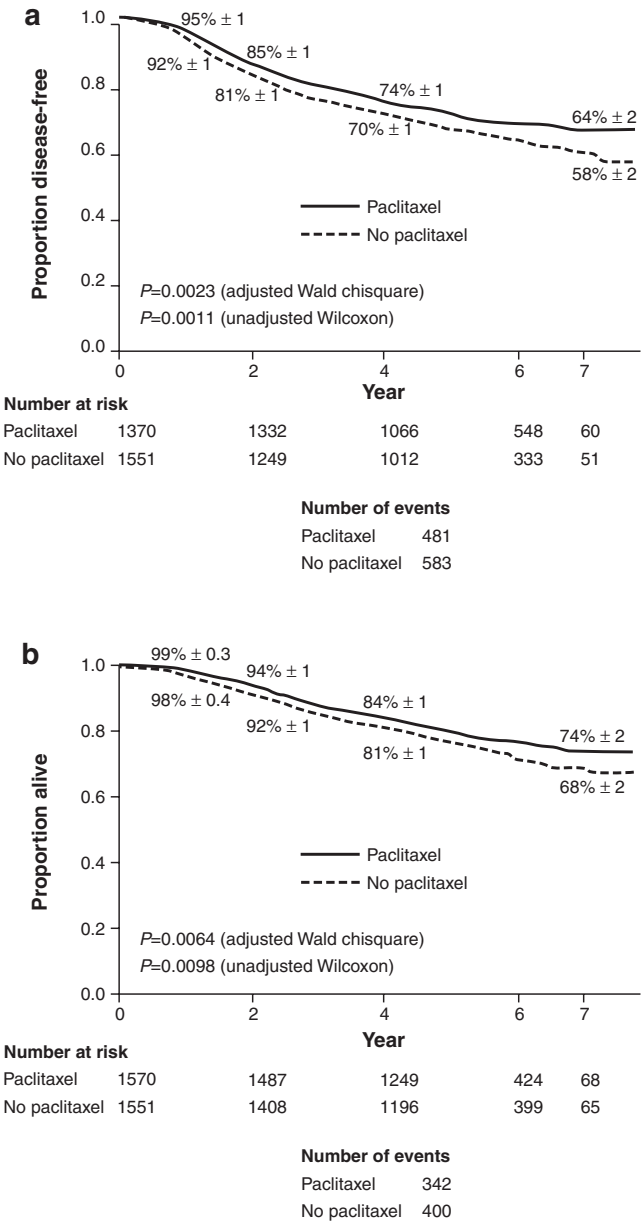


Fig. 1. Paclitaxel improves disease-free and overall survival when added to four courses of standard AC in the adjuvant setting. Reproduced with permission from the American Society of Clinical Oncology [12].

At about the same time that the CALGB trial was accruing, the NSABP conducted a similarly designed and sized trial with 3060 patients (B-28) in which patients with positive nodes were treated with AC for four cycles or the same standard regimen followed by paclitaxel at a dose of 225 mg/m^2 for four cycles. Definitive reporting for this trial was dependent on 490 deaths although the primary endpoints of this study included both overall and disease-free survival. Results presented at the 2003 annual meeting of the American Society of Clinical Oncology revealed a 17% reduction in events for patients treated with paclitaxel and a trend, without statistical significance, in favour of paclitaxel for overall survival. Of interest, there was no significant interaction between oestrogen-receptor status and benefit from tamoxifen and, depending on the specific definition of 'disease-free survival', the impact of paclitaxel might have been greater in patients with receptor expression [13]. This observation was consistent with the CALGB trial in terms of disease-free survival, and yet different in that it did not suggest any hormone-receptor and tamoxifen use interaction with paclitaxel. In addition, it differed significantly from the preliminary report of B-28 made at the 2000 NIH consensus conference, reminding us to view early analyses with caution [14].

The third large trial testing taxanes as adjuvant therapy was reported by Nabholtz *et al.* from the Breast Cancer International Research Group (BCIRG) at ASCO 2002 [15]. Here, the substitution of docetaxel (T) for 5-fluorouracil (F) as part of the FAC regimen (TAC vs FAC) yielded a significant improvement in disease-free survival, as well as a favourable trend in overall survival (Fig. 2). This study did not suggest an association between receptor status and benefit from the taxane. At a median follow-up of 33 months, a log-rank test showed that disease-free survival was significantly greater in the TAC arm than in the FAC arm (82% vs 74%; $P = 0.0011$). Overall survival was also greater in the TAC arm (92%) than in the FAC arm (87%) at this time point. Planned subset analyses demonstrated that in patients with 1–3 positive nodes, disease-free survival was 90% in the TAC arm and 79% in the FAC arm ($P = 0.0002$) and the greater effect of TAC over FAC on disease-free survival was maintained in both hormone-receptor positive ($P = 0.02$) and hormone-receptor negative patients ($P = 0.005$), but was greater in patients with HER2 positive status (TAC vs FAC RR $= 0.59$, $P = 0.02$) than in patients with HER2 negative status (RR $= 0.74$, $P = 0.06$). The results of these subset analyses are provocative, but not definitive. On the other hand, the incidence of febrile neutropenia, neutropenia and anaemia were significantly ($P \leq 0.05$) greater with TAC than with FAC. Prophylactic use of G-CSF should significantly reduce these haematological toxicities. Regarding non-haematological toxicities, nausea and vomiting were significantly greater with FAC ($P \leq 0.05$) than TAC, and diarrhoea, asthenia and amenorrhoea were significantly greater with TAC than FAC ($P \leq 0.05$).

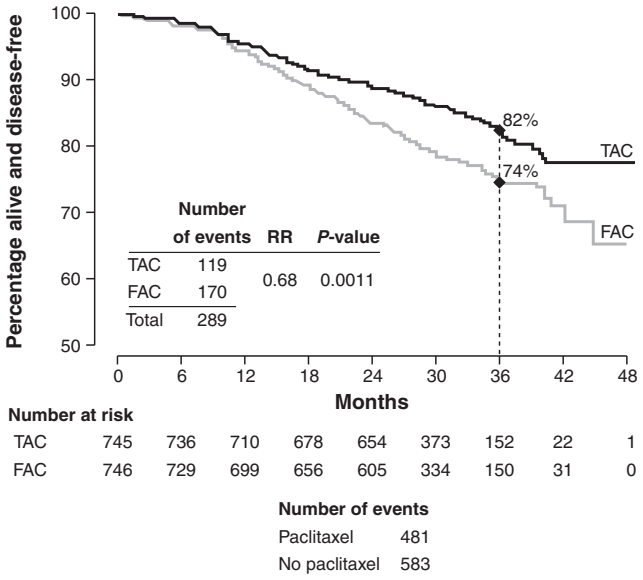
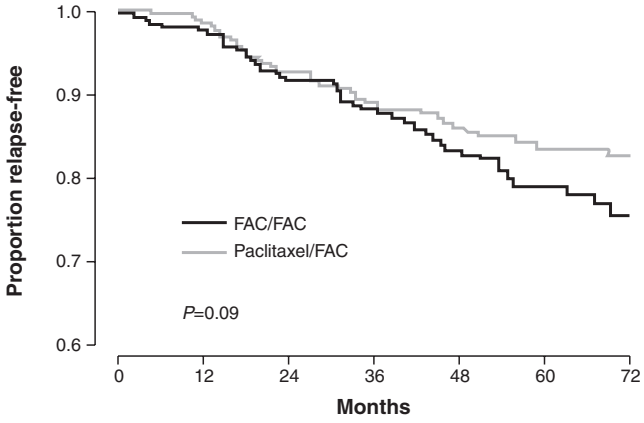


Fig. 2. Disease-free survival in the BCIRG 001 study after a median follow-up of 33 months [15]. Reproduced with permission.

Several smaller studies in the adjuvant and neoadjuvant setting have been reported and most suggest benefits when a taxane is added. At MD Anderson Cancer Center (MDACC), the 94-002 trial randomised 524 patients to receive either paclitaxel 250 mg/m^2 given over 24 hours every 3 weeks for four courses or standard FAC (fluorouracil 500 mg/m^2 on days 1 and 4, cyclophosphamide 500 mg/m^2 on day 1 only, and doxorubicin 50 mg/m^2 given as a 72-hour continuous infusion) for four courses before surgery [16]. Following surgery, all patients received a further four courses of FAC, followed by radiotherapy. All patients with oestrogen-receptor positive disease were given tamoxifen initially if they were postmenopausal, but during the course of the study it was administered regardless of age. Additional patients were similarly randomised, but treated entirely in the postoperative adjuvant setting. Pre- or postoperative treatment was dependent on whether the patients were seen pre- or postoperatively. Patient characteristics were similar in both groups and 42–44% of women received tamoxifen. In MDACC 94-002, relapse-free and overall survival was statistically similar in the two groups but there was a trend in favour of the taxane-containing arm (Fig. 3). In oestrogen-receptor positive disease, an improved outcome was suggested in the paclitaxel arm only after 4.5 years. In oestrogen-receptor negative disease, there was a trend favouring the paclitaxel arm from the beginning of the trial. However, a significant limitation of this study is its modest (for the modern era) accrual. Hence, statistical significance is unlikely in this study. In fact, this trial is no more than about 25% of the size of even the smallest current Cooperative Group studies, significantly limiting its statistical power. None-the-less, the results reported are quite consistent with those of the Intergroup/CALGB trial.



	Total	Failed	4 years
FAC/FAC	259	53	0.83
Paclitaxel/FAC	265	39	0.86

Fig. 3. Relapse-free survival in all patients in the MDACC 94-002 study. Reproduced with permission [16].

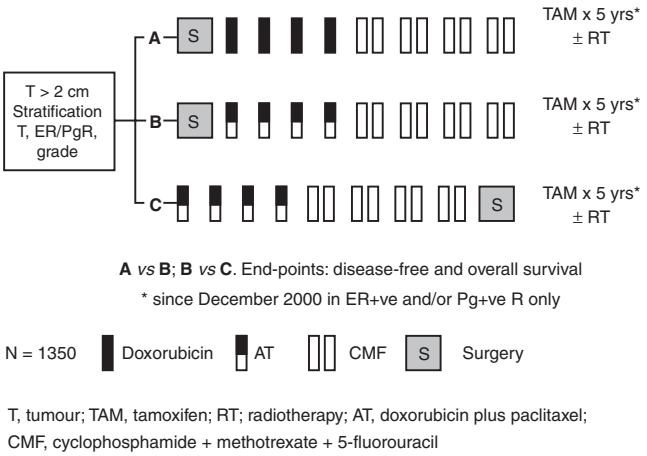


Fig. 4. ECTO study design.

3. Neoadjuvant taxanes

Further indirect support for the use of taxanes as adjuvant therapy derives from the neoadjuvant setting. The largest preoperative trial testing a taxane is NSABP B-27 study in which patients received AC alone preoperatively or AC followed by docetaxel preoperatively. Of the patients receiving only AC, one half were treated with postoperative docetaxel. Hence, this three-arm trial has the potential to demonstrate the value of the taxane in the preoperative setting and the value of the taxane on long-term outcomes. Mature data are awaited, but the preliminary report from this trial showed a significant increase in response in the unresected breast, increased breast conservation, and acceptable toxicity when four courses of docetaxel were given after AC and before surgery [17]. The disease-free and overall survival benefits that might result from docetaxel administration have not been reached for this study at the time of publication.

Preliminary results from the European Cooperative Trial in Operable Breast Cancer (ECTO) investigating the effects of primary systemic therapy versus adjuvant therapy in early breast cancer are promising [18]. Patients with tumours greater than 2 cm were randomised to one of three treatment groups (Fig. 4). Patients in group A received surgery first, then doxorubicin for four cycles followed by CMF for four cycles. Patients in group B received surgery first, then doxorubicin plus paclitaxel for four cycles. Patients in group C received preoperative doxorubicin plus paclitaxel for four cycles followed by four cycles of CMF followed by surgery. Following chemotherapy, all patients with oestrogen-receptor positive or progesterone-receptor positive disease received tamoxifen for 5 years with or without radiotherapy. The study has recruited 1350 patients. The main non-cardiac toxicities were generally similar in arm A (without paclitaxel) and in arms B plus C (including paclitaxel), although the incidence of reversible peripheral neuropathy was greater in arms B plus C. The rate of congestive heart failure was 0.3% in all these arms after a median of 17 months follow-up. The overall response rate to doxorubicin plus paclitaxel followed by CMF was 81% (52% complete response) and the rate of pathological complete response (pCR) was 22%. The rate of breast-conserving surgery was significantly greater ($P < 0.001$) in patients who received preoperative (neoadjuvant) chemotherapy (arm C) than in patients who received postoperative (adjuvant) chemotherapy (68% vs 34%). Univariate analysis showed that receptor status was a significant predictor of a pathological complete response, which was seen in 10% of oestrogen-receptor positive patients and 45% of oestrogen-receptor negative patients ($P = 0.001$), in those patients who did not receive concurrent hormonal therapy (Table 1). Similarly, significantly ($P = 0.001$) more patients with progesterone-receptor negative disease had a pathological complete response than those with progesterone-receptor positive disease (36% vs 13%). Thus, the two chemotherapy regimens appeared to be equally feasible; 90% of patients completed therapy in the arm with paclitaxel compared to 89% in the arm without paclitaxel. Furthermore, cardiac tolerability was similar with the two regimens. Although the incidence of peripheral neuropathy was greater with the inclusion of paclitaxel therapy, this was reversible and only 2% of patients had grade 3 neuropathy. Doxorubicin plus paclitaxel followed by CMF afforded a high rate of clinical response (81%) with evidence of activity for both regimens and a high rate of pathological complete response (22%). Multivariate analysis showed that oestrogen-receptor status is predictive for the eradication of loco-regional invasive breast cancer. However, in the long-term, the prognosis was the same for both groups of patients and the pathological complete response may not be a good marker on which to measure the efficacy of treatment in patients with oestrogen-receptor positive disease.

Table 1
Univariate analysis of evaluable patients at the time of presentation of the likelihood of pathological complete response plus non-invasive disease in patients receiving neoadjuvant doxorubicin plus paclitaxel followed by CMF [18]. Reproduced with permission

Variable		*N*	pCR + pnon-invasive (%)	Other (%)	*P*
Age	<50 years	139	23	77	NS
	≥50 years	176	22	78	
T size	≤4 cm	226	23	77	NS
	>4 cm	89	21	79	
Clinical	N0	179	25	75	NS
	N1–2	130	19	81	
Tumour grade	Low/intermediate	199	19	81	0.10
	High	106	27	73	
Oestrogen-receptor status	Positive	114	10	90	0.001
	Negative	197	45	55	
Progesterone-receptor status	Positive	134	13	87	0.001
	Negative	176	36	64	

pCR, pathological complete response.

A much smaller study from Aberdeen also suggests benefit in this setting [19]. In this trial, patients were treated with an anthracycline-containing combination preoperatively. Those with no response were then treated with docetaxel while those with a response were randomly assigned to additional anthracycline-based treatment or to docetaxel. The latter group had the best outcome including improved survival. This modestly sized trial is important because it demonstrates that sequential crossover (to a presumably non-cross-resistant regimen) is superior to continued treatment with one regimen even when that regimen appears to be effective. Thus, the in-breast response cannot yet be used to identify the best treatment approach. All patients benefited from the switch to a taxane. Another interpretation of the data is that the taxanes are simply superior agents regardless of the timing of administration. It remains to be proven whether or not preoperative therapy offers any advantage for patients presenting with resectable disease.

4. Dose density

An aspect of the sequential regimens of AC followed by paclitaxel is that they can be dose dense [20]. This can be an advantage because dose–response relationships of chemotherapeutic agents may not be linear and, therefore, while high doses of chemotherapeutic agents may not always produce a better outcome in terms of cell kill, more frequent treatment may increase overall cytotoxicity. This has been shown to be true with doxorubicin and with cyclophosphamide, where 50% and 400% increases in dose size, respectively, have not yielded improved outcomes in node-positive disease [10–12]. However, if a lower dose is as effective as a higher dose, then it may be possible to deliver a drug more often — because the toxicities are limited — and thereby increase dose density. Computer simulations show that clones of sensitive cells may be more completely eliminated in this fashion, even if they had survived more conventionally spaced treatments (Fig. 5). This is because, with standard treatment, cells have more time to recover and grow from each prior chemotherapy cycle than with dose-dense therapy.

Pilot trials of dose-dense therapy performed at the MSKCC showed that high-dose cyclophosphamide treatment could be accelerated with granulocyte colony-stimulating factor (G-CSF) support [21]. A subsequent study showed that doxorubicin dosing could be similarly accelerated, as could paclitaxel dosing [8]. Finally, data from a randomised controlled trial showed that paclitaxel could be more easily incorporated into a regimen with these agents given as sequential single-agent therapy than as part of a concurrent combination with paclitaxel [9].

Based on the pilot trials from MSKCC and the results of CALGB 9344 showing that the AC plus paclitaxel regimen was superior to standard AC, the Intergroup performed another CALGB-led trial designed specifically to test the value of dose-density, as well as the value of combination chemotherapy, compared to a sequence of single agents. In CALGB 9741, 2005 patients with positive nodes were randomised postoperatively between September 1997 and March 1999 [22]. Again using a factorial design, two issues were addressed in this study. First, concurrent treatment with standard doses of AC (60/600 mg/m^2 respectively) was compared to sequential application of the same agents. Hence, patients received either AC followed by paclitaxel, as in the earlier CALGB trial (9344), or

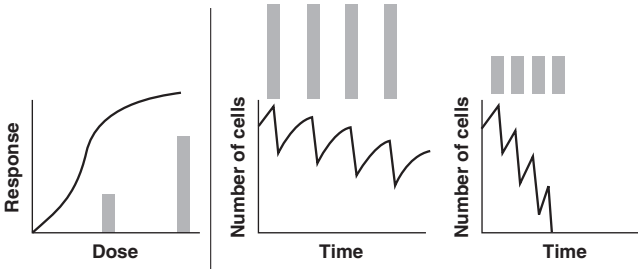


Fig. 5. Dose density to overcome drug resistance.

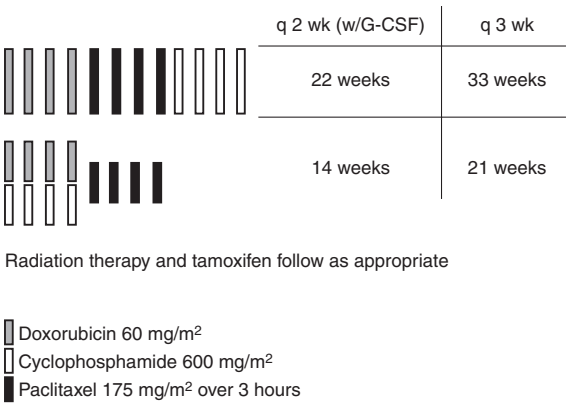


Fig. 6. The 2×2 factorial design of CALGB 9741.

they received four doses of doxorubicin alone followed by four doses of paclitaxel and then four doses of cyclophosphamide (Fig. 6). A strength of this study was that every patient received four equally sized doses of the same three drugs. Hence, total drug exposure for all patients was the same. When reported by Citron *et al.* in December 2002 there was no difference in disease-free survival or overall survival between sequential or concurrent AC [23].

The second question addressed in this study was dose-density. Hence, patients were randomly assigned to receive chemotherapy (either sequential or concurrent) using either the standard 3-week interval or, with G-CSF support, a more dose-dense 2-week interval. Dose-dense therapy was associated with a 26% reduction in the risk of relapse (82% vs 75% disease-free survival) and a 31% reduction in the risk of death (92% vs 90% survival) at the first protocol-specified report, generated 36 months after the last patient completed therapy. This trial stands in contrast to many other trials testing dose-dense regimens because the doses of all drugs were the same in all arms, so that dose-density was truly isolated as an unconfounded variable. Aside from an earlier trial of alternating or sequential doxorubicin and CMF conducted in Milan [24], there are very few other studies that are pure tests of dose-density.

Side-effects were mostly no more severe among patients on dose-dense regimens than among those receiving conventionally spaced treatments. Patients on dose-dense regimens suffered less severe neutropenia and fewer hospital admissions for neutropenic fever. Patients on the dose-dense arm utilising concurrent AC followed by paclitaxel had a greater likelihood of packed red blood cell transfusion. The reason for this is uncertain as there was not a significant difference in the incidence of severe anaemia among the four regimens tested. This will be further studied.

4.1. Other ongoing studies of dose-dense taxanes

A number of trials are testing variations of dose and schedule for the taxanes in the adjuvant setting. Again, while many of these regimens use more frequent (hence 'dose-dense') treatment plans, it is critically important to note that these trials are not specifically able to address dose-density because they are confounded by variations in number of cycles and dose size. For example, a recently completed ECOG-led Intergroup trial directly compared the two taxanes and also compared low-dose weekly administration with conventional dose levels every 3 weeks. In all four arms, different dose sizes and cycle numbers are used for each of the taxanes.

A German group has compared sequential dose-dense epirubicin–paclitaxel against standard epirubicin–paclitaxel as preoperative treatment of breast cancer [25]. The clinical rationale for preoperative chemotherapy is that it has been shown to produce equivalent survival to postoperative chemotherapy in the NSABP B-18 trial. It also increased the rates of breast conserving surgery and pathological complete response, which is a predictor of outcome. In this trial, patients with a primary breast cancer diameter greater than 3 cm or with inflammatory disease were randomised to receive epirubicin plus paclitaxel as either dose-dense or standard therapy preoperatively for 12 weeks. In the dose-dense arm, patients received alternately epirubicin 150 mg/m^2 followed 2 weeks later by paclitaxel 250 mg/m^2 for three cycles plus G-CSF on days 3–10 of each cycle. In the standard dosing arm, patients received epirubicin 90 mg/m^2 plus paclitaxel 175 mg/m^2 every 3 weeks. As discussed above, the differences in dose size and number will confound the interpretation of this study's results. Following surgery, all patients received CMF (cyclophosphamide 500 mg/m^2, methotrexate 40 mg/m^2, 5-fluorouracil 600 mg/m^2) on days 1 and 8 every 4 weeks for three cycles, followed by radiotherapy. Patient characteristics were similar in the two groups; 14–15% of patients had inflammatory cancer, and mastectomy as initial treatment was proposed in 74–75% of patients. Response after 12 weeks was measured by ultrasound, mammography and, in some cases, by magnetic resonance imaging (MRI). Significantly more patients in the dose-dense arm responded to treatment than in the standard therapy arm (68% vs 59%, $P = 0.03$). Pathological complete response in the breast was also greater in the dose-dense arm compared with the standard therapy arm (19% vs 10%, $P = 0.006$). In the lymph nodes, a complete pathological response was seen in 50% of patients in the dose-dense arm compared with 41% in the standard therapy arm ($P = 0.039$). In addition, significantly more patients in the dose-dense arm were able to have breast-conserving therapy than in the standard therapy arm (61% vs 50%). Toxicities were comparable between the two arms with no significant increase in grade 3 and 4 toxicities in the dose-dense arms.

Another ongoing trial (Prepare), conducted in Germany in patients with HER2/neu negative disease, is testing dose-dense epirubicin and paclitaxel for 12 weeks, as in the first study, followed by CMF (days 1 and 8) for three cycles before surgery and comparing this to epiru-

bicin 90 mg/m^2 plus cyclophosphamide 600 mg/m^2 every 3 weeks for four cycles followed by paclitaxel 175 mg/m^2 every 3 weeks for four cycles followed by surgery. All patients receive G-CSF with or without darbepoetin. Again, this is an important trial with a real possibility of informing practitioners making difficult treatment decisions, but because of the numerous variables in design, it cannot be a test of dose-density *per se*.

5. Selected other ongoing studies of taxanes as adjuvant therapy

There is a remarkably large number of ongoing and unreported trials testing taxanes as adjuvant therapy. A limited selection of these is reviewed here.

GEICAM 9906 is a Spanish randomised phase III clinical trial of adjuvant chemotherapy in patients with node-positive breast cancer comparing six courses of 5-fluorouracil 600 mg/m^2, epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2 (FEC_{90}) every 3 weeks, with four courses of 3-weekly FEC_{90} followed by eight courses of weekly paclitaxel 100 mg/m^2. Postsurgical patients with stage II–IIIA disease (T1–T3, N1, M0) aged 18–70 years were recruited and stratified by centre, menopausal status and number of positive nodes (1–3 or 4+). Based on the estimate that 1250 patients would be needed to show an 8% increase in the primary endpoint of 5-year disease-free survival, recruitment was completed in May 2002. Patient and tumour characteristics were similar in the two treatment groups. The percentage of patients completing treatment and the median relative dose intensities received by each group were also similar, as were toxicities. Efficacy results are awaited.

A new UK multicentre adjuvant breast trial compares paclitaxel, an anthracycline (epirubicin), gemcitabine, and cyclophosphamide (tAnGo) against a similar treatment without gemcitabine. The two arms are: epirubicin 90 mg/m^2 plus cyclophosphamide 600 mg/m^2 (given on day 1) for four cycles then paclitaxel 175 mg/m^2 over 3 hours also given on day 1 every 3 weeks for four cycles, or the same regimen with gemcitabine 1250 mg/m^2 over 30 minutes given on days 1 and 8 concurrent with the taxane. Both regimens are eight cycles (24 weeks) in duration. The primary endpoint is 5-year disease-free survival.

In a preliminary report of a study comparing docetaxel combined with cyclophosphamide against a standard AC regimen, acceptable comparative toxicity and a trend (without statistical significance) in favour of the taxane-containing regimen was found [26]. It will be interesting to see whether, in this study, from US Oncology, a significant advantage emerges with adequate follow-up.

6. Weekly paclitaxel

Weekly paclitaxel has an established role in the routine treatment of patients with metastatic disease and is now being actively studied as adjuvant therapy. As described above, ECOG 1199 tests this approach in comparison to standard paclitaxel given every third week after conventional AC in the adjuvant setting. Prior studies in the metastatic setting confirmed its safety and efficacy. In an early study with weekly dosing, paclitaxel was given over 1 hour at a dose of 100 mg/m^2/week to 30 patients with metastatic breast cancer [27]. A standard premedication regimen of two doses of oral dexamethasone 20 mg plus intravenous diphenhydramine 50 mg plus intravenous cimetidine 300 mg was given. Each patient received a median of 14 infusions (range 1–44), with a total number of 469. The median dose of paclitaxel delivered was 91 mg/m^2/week with a dose intensity of 80–108 mg/m^2. Grade 3–4 neutropenia occurred in 13% of patients with no incidences of febrile neutropenia. Grade 3 neurotoxicity occurred in 5 of 9 patients who received dose escalations to 110–120 mg/m^2/week and grade 2 neurotoxicity occurred in 21% of patients. The incidence of neutropenia was lower in this study (13%) than in the CALGB 9342 study (grade 4 neutropenia 33%) [28], despite a higher weekly dose intensity (90 mg/m^2 vs 60 mg/m^2). The overall response rate was 53% with a median response duration of 7.5 months. Thus, this was a well-tolerated and active regimen. An ongoing CALGB study, 9840, randomly assigns patients with measurable metastatic breast cancer to compare weekly dose-dense (80 mg/m^2/week) with standard paclitaxel therapy (175 mg/m^2 every 3 weeks) in patients with inoperable, recurrent or metastatic breast cancer. The study design was subsequently modified to include trastuzumab for patients with overexpression of HER2 while those with normal levels of HER2 are randomly assigned to receive trastuzumab or not.

While awaiting the results of the randomised CALGB trial, there is already preliminary evidence favouring weekly taxanes in terms of efficacy. The MDACC 98-240 trial randomised 560 patients with operable breast cancer to receive either weekly or 3-weekly paclitaxel. In the weekly paclitaxel therapy group, patients with node-positive disease received weekly paclitaxel 150 mg/m^2 over 3 hours for 3 weeks followed by a 1-week break and patients with node-negative disease received weekly paclitaxel 80 mg/m^2 over 1 hour for 12 weeks [29]. In the 3-weekly paclitaxel group, patients received paclitaxel 225 mg/m^2 over 24 hours every 3 weeks for four courses. All patients then received FAC every 3 weeks for four courses, followed by local therapy. Following this, patients with hormone-receptor positive disease also received tamoxifen for 5 years. Although overall response rates were the same in the two groups (86%), the complete response rate was higher with the weekly regimen (54% vs 43%). In

Table 2
Pathological complete response rates in patients with node-positive and node-negative operable breast cancer with weekly and 3-weekly paclitaxel followed by FAC every 3 weeks for four courses in both groups [29]

	Node positive		Node negative	
	3-Weekly $n = 54$	Weekly $n = 56$	3-Weekly $n = 73$	Weekly $n = 75$
pCR	15%	29%	15%	28%

pCR, pathological complete response.

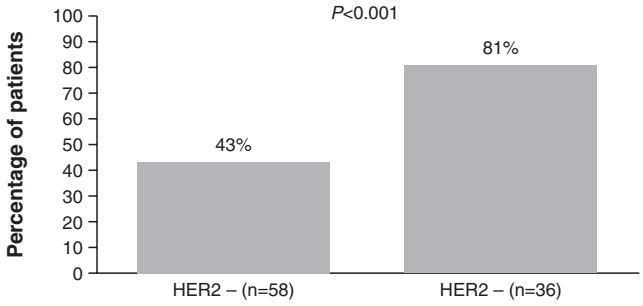


Fig. 7. Weekly paclitaxel plus trastuzumab in metastatic breast cancer. HER2 assay was performed with TAB250 [30].

both node-positive and node-negative patients, the pathological response rate was higher with the weekly than with the 3-weekly paclitaxel treatment (Table 2, $P = 0.01$). Transcriptional profile unsupervised clustering has identified a group of about 150 genes that predicts with about 80% certainty the pathological complete remission group. To confirm these results, the test is being performed in a prospective sample of patients who received the same treatment. They will then use the profiling in a clinical trial to select patients who should perform better with this therapy.

One aspect of weekly therapy that may be important is the role and toxicities associated with weekly steroid administration. Steroids may contribute an anti-tumour effect, but can complicate the care of some patients, including those with diabetes. Controlled studies to define the minimal safe doses of steroids with weekly taxanes may be justified.

6.1. A next step: weekly paclitaxel plus trastuzumab

In another study, paclitaxel 90 mg/m^2/week over 1 hour was given together with trastuzumab 2 mg/kg after a 4 mg/kg loading dose [30]. The premedication regimen consisted of dexamethasone 10 mg, diphenhydramine 50 mg and cimetidine 300 mg, all given intravenously. If no hypersensitivity reactions occurred, the dexamethasone dose was lowered by serial dose reduction to 4 mg. Multiple gated acquisition (MUGA) scans showed that left ventricular function was maintained at a median of about 60% over 1 year. Many of these patients had previously received anthracyclines. Treatment was generally well tolerated. Two cases of congestive heart failure occurred; one patient had previously received more than 600 mg/m^2 doxorubicin in the adjuvant and metastatic settings and the other patient had received standard doxorubicin plus cyclophosphamide adjuvant therapy. Patients with HER2 negative disease had a 43% response rate, those with HER2 positive disease had an 80.5% response rate, and the overall response rate was 56.8% (Fig. 7). The median response duration was 7 months (range 2–20 months). HER2 status was shown to be a significant predictor of response by all antibody tests (DAKO, PAb-1, TAB250 and CB11) and FISH (all $P < 0.05$). Following these results, the design of CALGB 9840 was modified to include trastuzumab treatment for all HER2 positive patients, and those who were HER2 negative were randomised to receive either trastuzumab plus paclitaxel or paclitaxel-only treatment. The CALGB Correlative Science Committee is exploring indicators of response to paclitaxel and trastuzumab in the entire cohort of patients.

Ongoing studies in the adjuvant setting are now testing the potential contribution of trastuzumab added to a taxane. The HERA (HER2 Adjuvant) Trial assesses the duration of trastuzumab therapy (0, 1 or 2 years of treatment) given in a 3-weekly schedule following surgery and adjuvant chemotherapy or local or loco-regional radiotherapy in patients with HER2 positive disease. In North America, three trials of trastuzumab are ongoing. A BCIRG trial aims to recruit 3000 patients with HER2 positive disease to one of three treatment arms: doxorubicin plus cyclophosphamide for four cycles followed by docetaxel for four cycles; the same regimen plus trastuzumab given with docetaxel and continued for 1 year; or carboplatin plus docetaxel for six cycles together with trastuzumab for 1 year. The inclusion of carboplatin in this trial reflects the translation of promising preclinical data as well as the demonstrated activity of carboplatin with paclitaxel and trastuzumab in metastatic breast cancer [31]. The NSABP B-31 trial is comparing AC for four cycles followed by either paclitaxel alone for four cycles or with trastuzumab in patients with node-positive and HER2 positive disease. In a trial by the North Central Cancer Treatment Group (NCCTG 9831), patients with node-positive and HER2-positive disease are given AC for four cycles followed by paclitaxel 80 mg/m^2/week for 12 weeks or the same regimen followed by 1 year of trastuzumab treatment, or AC then paclitaxel for 12 weeks with trastuzumab for 1 year.

7. Conclusion

The role of taxanes as adjuvant treatment is established but evolving as evidence supporting their use is increasing. As of early 2003, every mature adequately sized randomised trial testing either paclitaxel or docetaxel in the adjuvant setting is positive for disease-free survival

and at least one is positive for overall survival. In addition, trials testing taxanes as preoperative therapy have yielded improved in-breast response rates that may, given time, translate into long-term benefits. One important next step includes improved selection of patients, perhaps based on gene profiling as is being explored in many centres [32]. In addition, optimisation of the use of taxanes through improved scheduling and dosing is well underway. Weekly paclitaxel is widely utilised in metastatic disease because it is less myelosuppressive and has been demonstrated to be superior in the preoperative setting. In the adjuvant setting, a pure test of dose-density has demonstrated that a regimen including every other week full-dose paclitaxel is superior to conventional paclitaxel given every third week. The relative worth of lower dose weekly treatment and higher dose every other week administration will only be determined through prospective randomised studies. Going forward, we need the results of studies designed to optimise the use of these active agents so that the maximum number of patients can benefit. At the same time, we must note that non-taxane containing regimens have, in many studies, also been superior to "standard" treatments and, therefore, not all patients will necessarily need taxanes, even given their proven efficacy.

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