

Perspective

Evidence-Based Use of Neoadjuvant Taxane in Operable and Inoperable Breast Cancer

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Abstract

Neoadjuvant chemotherapy (NC) is standard therapy for patients with locally advanced breast cancer and is increasingly used for early-stage operable disease. The aim of NC is a pathological complete response (pCR) in the breast and axillary lymph nodes, which is the best predictor of improved outcome and prolonged survival. The taxanes docetaxel and paclitaxel are potent agents in breast cancer management, with promising single-agent activity and acceptable tolerability in the neoadjuvant setting. In this review of the taxanes as NC for operable and inoperable breast cancer, we include all fully published Phase II–III studies enrolling ≥ 30 patients. Current evidence suggests that the sequential administration of taxane- and anthracycline-based therapy may be superior to concomitant administration. Indeed, until the recent Phase III Aberdeen study ($n = 162$), it was uncertain whether NC could prolong survival. In this study, sequential docetaxel after anthracycline-based NC significantly enhanced the clinical response rate and pathological complete response, and yielded a significant 3-year survival advantage, *versus* anthracycline-based NC alone. Recently, the Phase III National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B27 trial ($n = 2411$) showed that sequential docetaxel after doxorubicin–cyclophosphamide significantly increased both clinical and pathological response rates for operable breast cancer, with the benefit evident in both estrogen receptor-positive and estrogen receptor-negative patients. This apparent superiority of a sequential anthracycline–taxane regimen is limited to docetaxel, with no similar Phase III trials of paclitaxel *versus* a non-taxane-based comparator having been conducted to date. In conclusion, current evidence supports the inclusion of a taxane in NC schedules for patients with large and locally advanced breast cancer.

Introduction

Neoadjuvant chemotherapy (NC), also known as primary or preoperative chemotherapy, consists of chemotherapy deliv-

ered before local treatment such as surgery or radiotherapy. NC was initially introduced in patients with locally advanced breast cancer (LABC), and was first reported in 1978 as part of a multidisciplinary approach proposed for stage III disease (1). At that time, LABC was conventionally treated with radiotherapy and/or surgery, and although local control was achieved in some cases, patients eventually succumbed to metastatic disease (2). Since then, NC has become the standard of care for patients with LABC and, with the advent of more effective drugs, has come to the forefront of potential treatments for early-stage operable disease.

What Are the Advantages of Neoadjuvant Chemotherapy?

The major role of NC in inoperable breast cancer is to render the disease operable. In contrast, in operable breast cancer, NC is used to downstage tumors to facilitate breast conservation in patients who would otherwise undergo mastectomy, or to enable surgical resection with the best possible cosmetic outcome (3). NC takes advantage of the less favorable growth kinetics for metastasis characteristic of early breast cancer, thus potentially eliminating micrometastases and improving survival (4). Early systemic treatment may also reduce the emergence of drug-resistant mutations, which are likely to form spontaneously early in the natural history of the disease. Finally, NC enables the rapid assessment of tumor sensitivity to chemotherapy within 3–4 months compared with a follow-up period of ≥ 5 years to evaluate the sensitivity of adjuvant chemotherapy.

A potential disadvantage of NC is the loss of prognostic information provided by tumor size and nodal status at surgery and before adjuvant chemotherapy. However, a recent retrospective study has shown pathological axillary lymph node (ALN) involvement after NC to be an early surrogate biological marker of long-term outcome (5). In this study, the 7-year disease-free survival (DFS) and overall survival (OS) were significantly improved for patients with negative *versus* positive nodal status after NC ($P < 0.0001$).

How Does Neoadjuvant Chemotherapy Compare with the Adjuvant Approach?

Several randomized trials have compared NC followed by surgery with surgical resection followed by adjuvant chemotherapy (3, 6–11). Albeit these trials used various chemotherapy regimens in heterogeneous populations, the generally consistent finding was that DFS and OS were equivalent for the neoadjuvant and adjuvant arms. For example, in the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B18, 1523 patients with stage I–III breast cancer were randomized to receive four cycles of doxorubicin and cyclophosphamide (AC) as either neoadjuvant or adjuvant chemotherapy (3). There was no difference in DFS and OS between the two groups at a median follow-up of 5 years.

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Table 1 Pathological response classification systems^a

Classification system	Key definitions
Chevallier <i>et al.</i> (13)	Classification using both microscopic and macroscopic evidence Grade 1 (pCR) = disappearance of all tumor on either macroscopic or microscopic assessment Grade 2 = presence of <i>in situ</i> carcinoma in the breast, no invasive tumor, no tumor in the ALNs Grade 3 = presence of invasive carcinoma with stromal alteration Grade 4 = no/few modifications of the tumor appearance
Fisher <i>et al.</i> (3)	Classification based on microscopic evidence pCR = no histological evidence of invasive tumor cells (specimens with only noninvasive cells included) pINV = histological evidence of invasive disease of any extent
Honkoop <i>et al.</i> (15)	Classification using both microscopic and macroscopic evidence pCR = no residual tumor in the breast or ALNs MPR = normal macroscopic examination but microscopic evidence of scattered foci of tumor Minimal residual disease = patients with pCR and MPR Gross residual disease = tumor observed macroscopically
Miller and Payne classification (16)	Classification based on microscopic evidence Grade 1 = some alteration to individual malignant cells but no reduction in overall number Grade 2 = minor loss of invasive tumor cells but overall cellularity still high Grade 3 = moderate reduction in tumor cells up to an estimated 90% loss Grade 4 = marked disappearance of invasive tumor cells such that only small clusters of widely dispersed cells detected Grade 5 (pCR of the primary tumor) = no invasive cells identifiable in sections from the site of the previous tumor ALN response classification A = true ALN negative B = ALN positive, no therapeutic response C = ALN positive, evidence of partial pathological response D = ALN previously positive but converted to node negative after NC
Sataloff <i>et al.</i> (17)	Grading of therapeutic effect related to the primary tumor site and ALNs, as defined by microscopic changes Primary site response classification T-A = total/near total therapeutic effect T-B = subjectively >50% therapeutic effect but <total/near-total therapeutic effect T-C = <50% therapeutic effect, but effect evident T-D = no therapeutic effect ALN response classification: N-A = evidence of therapeutic effect, no metastases N-B = no therapeutic effect, no nodal metastases N-C = evidence of therapeutic effect, nodal metastases present N-D = no therapeutic effect, viable metastatic disease

^a pCR, pathological complete response; ALN, axillary lymph node; pINV, pathological invasive disease; MPR, microscopic pathological response; NC, neoadjuvant chemotherapy.

pCR in the Assessment of Neoadjuvant Chemotherapy

Although clinical response is often selected as the primary end point in trials of NC, the main goal of therapy should be a pathological complete response (pCR), because pCR more accurately predicts improved patient outcome and prolonged survival. In the NSABP B18 trial, it was demonstrated that patients achieving a pCR had improved DFS and OS compared with those with residual tumor (3). However, even longer-term outcomes from robust trials are required to confirm this theory. Cholle *et al.* (12) recently conducted a retrospective analysis of patients with a pCR in both the breast and the ALNs after NC for operable breast cancer. Of 396 patients who underwent surgery, 15% had a pCR (the classification of Chevallier *et al.*; Ref. 13), and these patients had significantly higher 15-year DFS rates *versus* patients with *in situ* carcinoma or residual invasive disease ($P = 0.024$). A similar difference in favor of pCR was observed for 15-year OS rates ($P = 0.047$). Unfortunately, the low rate of pCR observed is a practical limitation when correlating pCR with outcome.

The main aim of treatment remains the complete eradication of tumor in both the breast and the ALNs, and the site of any residual tumor impact outcome. In a trial of 372 LABC patients, a pCR in both the breast and the ALNs was observed in 12% of patients, and the 5-year OS and DFS rates were significantly higher in this group (89 and 87%, respectively) than in those with an incomplete pathological response (64 and 58%, respectively; $P < 0.01$; Ref. 14).

A hindrance to the comparison of pCR in trials of NC is the use of divergent classification systems, the most common of which are summarized in Table 1 (3, 13, 15–17). Of these classifications, the Miller and Payne (16) is arguably the most complete because it grades pathological remission in both the primary tumor and the ALNs, with comparison of negative nodes with those that have already responded to chemotherapy. We recommend that the Miller and Payne classification system be used universally and consistently in the grading of pCR in clinical trials. Of the published Phase III trials of neoadjuvant taxanes in breast cancer, only that of Smith *et al.* (18) has used the Miller and Payne system.

Table 2 Factors predictive for response to neoadjuvant chemotherapy

Predictive factor	Marker for improved outcome	Correlation	Study reference
ER ^a status	ER negative	cRR,pCR	Bonadonna <i>et al.</i> (19); Chang <i>et al.</i> (20); Kuerer <i>et al.</i> (14); Mauriac <i>et al.</i> (8); Gianni <i>et al.</i> (27)
Lymph node involvement	Negative lymph node	cRR	Fisher <i>et al.</i> (3); Pierga <i>et al.</i> (24)
p53	Normal p53 levels	pCR	Kandioler-Eckersberger <i>et al.</i> (22)
Tumor size	Smaller tumors	cRR,pCR	Fisher <i>et al.</i> (3); Bonadonna <i>et al.</i> (19); Kuerer <i>et al.</i> (14)
Ki-67 labeling index	High level	cRR	Mauriac <i>et al.</i> (8); Remvikos <i>et al.</i> (25)
c- <i>erbB</i> -2 (<i>her-2/neu</i>)	c- <i>erbB</i> -2 negative	cRR	Chang <i>et al.</i> (20); Gregory <i>et al.</i> (21); Makris <i>et al.</i> (23); Willsher <i>et al.</i> (26)

^a ER, estrogen receptor; cRR, clinical response rate; pCR, pathological complete response.

Predictive Factors for Response to Neoadjuvant Chemotherapy

The role of molecular and biological determinants as potential predictive factors for response to NC is an exciting area of research. Access to the primary tumor before treatment facilitates the assessment of biological markers and their correlation with response to treatment. The results from several trials that have considered predictive factors in NC are summarized in Table 2 (3, 8, 14, 19–27). These findings are by no means conclusive and are often contradictory, which may be attributed to the trial designs: the majority of analyses are retrospective, and the patient populations are often heterogeneous; different assays are used; and the biological markers are sometimes correlated to clinical response and at other times to pCR.

Two recent studies illustrate the potential of gene expression profiling for the prediction of response to breast cancer therapy. In the first study, molecular profiles for *de novo* and acquired docetaxel resistance are identified (28), whereas a second study describes the molecular profile that predicts pCR after neoadjuvant weekly paclitaxel followed by 5-fluorouracil–doxorubicin–cyclophosphamide (FAC; Ref. 29).

Taxanes in the Management of Breast Cancer

The introduction of the taxanes docetaxel and paclitaxel has revolutionized breast cancer therapy (30). Initially, the taxanes were introduced in metastatic breast cancer (MBC), for which they are now standard second-line therapy, with an emerging first-line role. Phase III studies have confirmed that increased tumor response and increased time-to-treatment failure or progression can be achieved with taxane-based therapy (31, 32). In addition, 50% of patients with anthracycline-resistant disease have been shown to respond to taxane chemotherapy. A recent early report from a Phase III trial of 3-weekly docetaxel 100 mg/m² *versus* paclitaxel 175 mg/m² in patients with MBC has shown statistically superior OS and time to progression for docetaxel *versus* paclitaxel, but at the expense of increased toxicity (33).

The taxanes realize their cytotoxicity via tubulin stabilization and cell cycle arrest. They have been shown to promote apoptosis (34), inhibit angiogenesis (35, 36), and induce several genes that mediate diverse cellular processes (37). Notwithstanding their similar mode of action, the taxanes are not identical. For example, docetaxel has a longer plasma half-life and longer intracellular retention, in addition to greater potency as a

tubulin assembly promoter and microtubule stabilizer compared with paclitaxel (38). The major toxicities include neurotoxicity for paclitaxel, peripheral neuropathy with docetaxel, albeit to a lesser extent, and neutropenia, which appears to be more prevalent with docetaxel than with paclitaxel. Other important toxicities include hypersensitivity reactions for paclitaxel, and fluid retention and gastroenteric toxicity for docetaxel. As with the majority of chemotherapeutic agents, asthenia, alopecia, and mouth ulcers are common with both agents.

Regimens combining a taxane with doxorubicin, the two most potent agents in breast cancer, are of particular interest. The agents' different activity and toxicity profiles, and their relative non-cross-resistance, support their combination. However, the taxanes differ with respect to their pharmacokinetic interactions with anthracyclines. Docetaxel has no significant effect on the plasma disposition of anthracycline, explaining the higher cardiotoxicity of paclitaxel–anthracycline *versus* docetaxel-based regimens (39). In addition, docetaxel is the only agent to demonstrate single-agent superiority over doxorubicin in a Phase III MBC trial (40). To date, the largest study combining a taxane and anthracycline is the Phase III study of Nabholz *et al.* (41), involving 429 chemotherapy naïve MBC patients. In this trial, doxorubicin–docetaxel was shown to significantly improve both the overall response rate (ORR) and time to progression compared with AC, although no difference in OS was observed.

The taxanes also differ with respect to their efficacy:toxicity ratio in relation to dose and schedule. In breast cancer, the recommended dosing for paclitaxel is 175 mg/m² as a 3-h i.v. infusion every 3 weeks, whereas docetaxel is recommended at 60–100 mg/m² as a 1-h i.v. infusion every 3 weeks. When administered in combination with an anthracycline, the recommended dose for docetaxel is 75 mg/m². The use of the taxanes in a weekly schedule is currently receiving attention. The rationale behind this approach is to optimize dose intensity and avoid tumor regrowth between cycles, with the benefit of potentially improved tolerability through use of doses well below the maximum tolerated dose. Preliminary results from a Phase II randomized trial of single-agent docetaxel in MBC have demonstrated similar efficacy for patients receiving either weekly or 3-weekly treatment (42). Both schedules were well tolerated, although the toxicity profiles differed. The recently completed Eastern Cooperative Oncology Group (ECOG) 1199 Phase III trial of AC followed by docetaxel or paclitaxel given weekly or

3-weekly in patients with ALN-positive breast cancer, will help clarify the optimal scheduling for taxanes in the management of early breast cancer.

The aim of this article is to provide a comprehensive review of both taxanes as NC for operable and inoperable breast cancer, with the inclusion of trials that considered any or all of stage I, II or III breast cancer. We have focused on peer-reviewed Phase II and III clinical trial publications following the criteria: English language; indexed on MEDLINE/Index Medicus, EMBASE/Excerpta Medica, and/or CANCELIT; ≥ 30 patients. Selected reports currently in abstract form are also included, but are clearly identified as preliminary. Data from well-designed, randomized controlled trials remain "level 1 evidence" (43) and, based on a critical appraisal of these data, recommendations for application to clinical practice are provided.

Docetaxel As Neoadjuvant Therapy in Breast Cancer

Docetaxel Monotherapy

To date, three Phase II studies of single-agent docetaxel in the neoadjuvant treatment of breast cancer have been published: two of a 3-weekly regimen (44, 45) and one of weekly docetaxel (46).

In a preliminary analysis of the study by Gradishar (45), 33 stage III breast cancer patients received four cycles of neoadjuvant docetaxel, 100 mg/m² every 3 weeks, and achieved an ORR of 85% [18% clinical complete response (CR)]. Amat *et al.* (44) investigated neoadjuvant docetaxel, 100 mg/m² every 3 weeks, but over six rather than four cycles. In 80 evaluable women with stage II–III breast cancer, an ORR of 68% (19% CR) occurred. A pCR was observed in 20% of patients by Chevallier's classification, and in 36% of patients by Sataloff's classification. In both studies, the major toxicity was hematological.

The Spanish Breast Cancer Research Group (GEICAM; Ref. 46) recently published the first Phase II trial of weekly neoadjuvant docetaxel in 56 patients with stage II–III breast cancer. Docetaxel, 40 mg/m², was administered weekly over 6 consecutive weeks followed by 2 weeks' rest (one cycle), with two cycles administered before surgery. The ORR in the intent-to-treat (ITT) population was 68% (29% CR). A pCR with no evidence of tumor in the breast and lymph nodes was confirmed in 16% of patients, including two patients (4%) with carcinoma *in situ*. The weekly regimen was very well tolerated.

These encouraging Phase II findings for single-agent docetaxel have precipitated the assessment of neoadjuvant docetaxel-based combination regimens in the treatment of breast cancer, with the aim of improving pathological and clinical response and, ultimately, survival.

Should Docetaxel Be Combined with an Anthracycline in the Neoadjuvant Treatment of Breast Cancer?

Several nonrandomized Phase II trials have evaluated the concomitant administration of anthracycline plus docetaxel NC in breast cancer (summarized in Table 3; Refs. 47–52). The majority of these trials considered 3-weekly regimens of docetaxel at a range of doses (60–80 mg/m²), together with either

doxorubicin (50–60 mg/m²) or epirubicin (70–75 mg/m²). The study of von Minckwitz *et al.* (51) compared a weekly dose-dense *versus* 3-weekly traditional doxorubicin-docetaxel schedule. Although the number of patients treated in these trials was small, encouraging results have been obtained, including ORRs in the range of 77–96% and pCRs as high as 23%.

Randomized trials that have compared an anthracycline-based regimen with concomitant docetaxel–anthracycline include the Phase III studies of Evans *et al.* (53) and Vinholes *et al.* (54) and the Phase II trial of Luporsi *et al.* (55; Table 3). To date, only very preliminary results for the first evaluable patients have been reported for these trials, with no statistically significant differences between the study arms identified thus far. The Phase II randomized trial of von Minckwitz *et al.* (56), which studied the effect of adding hormonal therapy to a neoadjuvant doxorubicin–docetaxel regimen, has been published in full and is considered in detail below.

How Do Dose-Dense and Traditional Anthracycline–Docetaxel Regimens Compare? von Minckwitz *et al.* (51) evaluated the efficacy and toxicity of concomitant docetaxel plus anthracycline in either a dose-dense or a traditional administration schedule (Table 3). Forty-two chemotherapy-naïve patients with stage II–IIIB breast cancer (median tumor size, 4 cm; 71% node positive) received doxorubicin 50 mg/m² plus docetaxel, 75 mg/m², either every 2 weeks ($n = 24$) or every 3 weeks ($n = 18$) for four cycles. Granulocyte colony-stimulating factor was routinely administered for both arms. The ORR was 93% for all patients (CR, 33%); 96% for the 2-weekly schedule *versus* 89% for the 3-weekly schedule. Only two patients (5%) had a pCR. No grade 4 toxicity was reported, and grade 3 hematological and nonhematological toxicities were infrequent. Overall, the 3-weekly schedule was associated with less toxicity than the 2-weekly schedule. Although the small patient population and nonrandomized nature of the trial do not allow for a conclusion to be drawn regarding the superiority of one schedule over the other, it is notable that concomitant doxorubicin plus docetaxel was well tolerated and yielded among the highest clinical tumor response scores reported in the literature, notwithstanding the unfavorable baseline patient characteristics.

Should Hormonal Therapy Be Added to a Neoadjuvant Docetaxel-Containing Regimen? Building on the results of the 1999 trial discussed above, von Minckwitz *et al.* (56) investigated the addition of tamoxifen to a dose-dense doxorubicin–docetaxel NC regimen in chemotherapy-naïve breast cancer patients (Table 3). The addition of tamoxifen was based on preclinical findings of synergism between docetaxel and tamoxifen in estrogen receptor (ER)-negative cell lines (57). In this Phase IIb study, patients (median tumor size, 4 cm; 49% node positive) were randomized to receive doxorubicin 50 mg/m² plus docetaxel 75 mg/m² every 2 weeks for four cycles, either with ($n = 122$) or without ($n = 128$) concurrent tamoxifen, independent of ER status. Granulocyte colony-stimulating factor support was routinely administered. A 10% pCR (the primary end point) was obtained, with no difference observed between the groups. Only nodal status was of significant predictive value for achieving a pCR in both univariate and multivariate analyses. The clinical tumor response rates were similar between the groups (ORR, 68% without tamoxifen; 78%, with tamoxifen), and breast conservation rates were identical at 69%.

Table 3 Trials of concomitant anthracycline plus docetaxel in the neoadjuvant management of breast cancer

Study reference	No. of patients	Disease stage	Neoadjuvant schedule dose, (mg/m ²)	ORR ^a (%)	CR (%)	pCR (%)
Phase II studies						
de Mattels <i>et al.</i> (48)	30	T2–4, ≤N ₂ , M ₀ , inflammatory	ET (75/80) q3w × 4 cycles	77	20	13
Baltali <i>et al.</i> (47) ^b	63	IIIA–B	FET (500/70/80) q3w × 4 cycles	95 ^c	25 ^c	23 ^c
Wenzel <i>et al.</i> (52)	66	T1–4, N+ve/–ve, M ₀	ET (75/75) q3w × 8 cycles	82	NR	15
Tubiana-Hulin <i>et al.</i> (49) ^b	48	Non-inflammatory T2–3, M ₀	AT (50/75) q3w × 6 cycles	84 ^c	15 ^c	13 ^c
Valero <i>et al.</i> (50) ^{b,d}	70	IIB–IV	AT (60/60) q3w × 6 cycles	90	4	10
von Minckwitz <i>et al.</i> (51)	42	II–IIIB	AT (50/75) q2w × 4 cycles AT (50/75) q3w × 4 cycles	96 89	29 39	5 ^e
Randomized studies						
Evans <i>et al.</i> (53) ^{b,d}	362	II–III, inflammatory	AT (50/75) q3w × 6 cycles AC (60/600) q3w × 6 cycles	88 ^c 78 ^c	NR NR	8 ^c 12 ^d
Vinholes <i>et al.</i> (54) ^{b,d}	407	IIIA–B	AT (50/75) q3w × 4 cycles FAC (500/50/500) q3w × 4 cycles	62 ^c 55 ^c	NR NR	NR NR
von Minckwitz <i>et al.</i> (56)	250	T ≥3 cm, N _{0–2} , M ₀	AT (50/75) q2w × 4 cycles AT (50/75) q2w × 4 cycles + Tm	68 ^c 78 ^c	6 ^c 13 ^c	10 ^c 9 ^c
Phase II						
Luporsi <i>et al.</i> (55) ^{b,d}	90	T2–4	ET (100/75) q3w × 6 cycles FEC (500/100/500) q3w × 6 cycles	84 ^c 72 ^c	NR	24 ^c 24 ^c

^a ORR, overall response rate; CR, complete response rate; pCR, pathological complete response; Tu, tumor; N, node; M, metastasis; E, epirubicin; T, docetaxel; q3w, every 3 weeks; F, 5-fluorouracil; NR, not reported; A, doxorubicin; q2w, every two weeks; C, cyclophosphamide; Tm, tamoxifen.

^b Interim results.

^c Evaluable population (all other data for the intent-to-treat population).

^d Reported in abstract.

^e Overall population.

Toxicity was moderate, and treatment compliance was high. Grade 3–4 neutropenia occurred in 30% of patients, and there was a trend toward more frequent hematological toxicity (leukopenia, thrombocytopenia, neutropenia) and severe infection (possibly related to the higher rate of grade 3–4 neutropenia) in patients receiving tamoxifen. These findings suggest that the simultaneous application of tamoxifen does not significantly impact the effectiveness of doxorubicin–docetaxel therapy.

In contrast, recent preliminary results from the Intergroup trial 0100 (Southwest Oncology Group 8814) suggest that delaying the administration of tamoxifen until after adjuvant chemotherapy results in a DFS advantage compared with the concurrent application of chemohormonal therapy (58). These data are consistent with the hypothesis that tamoxifen may antagonize certain chemotherapy agents. On the basis of the current evidence (57, 58), the combination of tamoxifen with docetaxel-based NC is not to be advised.

What Is the Potential for Docetaxel-Based Non-Anthracycline Concomitant Regimens? Several small Phase II trials (published in abstract form) have addressed the efficacy of nonanthracycline combination regimens with docetaxel (59–61).

Three small studies have assessed docetaxel in combination with platinum (60–62). Preliminary results from the first study by Hurley *et al.* (60), showed that 3-weekly docetaxel 70 mg/m² plus cisplatin 70 mg/m² was highly active in the treatment of 57 patients with LABC (ORRs, 96%; pCR in the breast and ALNs, 20%). Thereafter, a novel neoadjuvant regimen incorporating trastuzumab plus docetaxel–cisplatin was assessed in 34 patients with *HER-2/neu*-overexpressing LABC (61). A high pCR rate (21%) in the breast was documented,

together with exceptionally high ALN clearance (54%), supporting the preclinical evidence that docetaxel and cisplatin are synergistic with trastuzumab (62). Both regimens were well tolerated (60, 61).

Estévez *et al.* (59) recently reported preliminary data on a dose-dense schedule incorporating docetaxel 65 mg/m² plus gemcitabine 2500 mg/m² every 2 weeks for six cycles in 30 stage II–III breast cancer patients, with a median tumor size of 7 cm. Although a good clinical tumor response rate was reported (ORR 75%; CR 32%), only 1 patient of the first 17 achieved a pCR in the breast at the time of definitive surgery. Breast-conserving therapy (BCT) was, however, possible in 58% of patients and toxicities were manageable.

Although the small patient populations and preliminary nature of these data must be stressed, the results suggest high antitumor activity with both neoadjuvant docetaxel–cisplatin and docetaxel–gemcitabine, together with good tolerability.

How Best to Administer Docetaxel Plus Anthracycline? Concomitant Versus Sequential Schedules

Results from two randomized Phase II trials (63, 64) and two randomized Phase III trials (65, 18) have defined a lead role for the sequential addition of docetaxel to conventional AC neoadjuvant regimens (summarized in Table 4).

The Phase II randomized German preoperative adriamycin–docetaxel study compared a dose-dense concomitant doxorubicin–docetaxel regimen with the sequential addition of docetaxel to AC, with final results presented at the San Antonio Breast Cancer Symposium (SABCS) meeting in 2002 (63). A total of 913 patients (median tumor size, 4 cm; 40% node positive) were randomized to

Table 4 Trials of sequential docetaxel after anthracycline-based chemotherapy in the neoadjuvant management of breast cancer

Study reference	No. of patients	Disease stage	Schedule (dose, mg/m ²)	ORR ^a (%)	CR (%)	pCR (%)
Phase III randomized studies						
Smith <i>et al.</i> (18)	162	II–III	CVAP (1000/50/1.5/40 ^b) q3w × 4 cycles	66	14	
Responders randomized						
CVAP (1000/50/1.5/40) q3w × 4 cycles → S or T (100) q3w × 4 cycles → S				94	62	34
				66	34	16
Non-responders: T (100) q3w × 4 cycles → S				47	11	2
NSABP Study Group, Bear <i>et al.</i> (65)	2500	I–III	AC (60/600) q3w × 4 cycles → S	85 ^c	40 ^c	14 ^c
			AC (60/600) q3w × 4 cycles → T (100) q3w × 4 → S	91 ^c	64 ^c	26 ^c
			AC (60/600) q3w × 4 cycles → S → T (100) q3w × 4 cycles	86	40	13 ^c
Phase II randomized studies						
Jackisch <i>et al.</i> (63) ^d	913	Tu2–3, N _{0–2} , M ₀	AC (60/600) q3w × 4 cycles → T (100) q3w × 4 cycles + Tm → S	87 ^c	58 ^c	23 ^c
			AT (50/75) q2w × 4 cycles + Tm → S	77 ^c	33 ^c	12 ^c
Miller <i>et al.</i> (64)	40	II–III	A (75) q2w × 3 cycles → T (100) q2w × 3 cycles → S	89	32	16
			AT (56/75) q3w × 4 cycles → S	81	10	10

^a ORR, overall response rate; CR, complete response; pCR, pathological complete response; C, cyclophosphamide; V, vincristine; A, doxorubicin; P, prednisolone; q3w, every 3 weeks; →, followed by; S, surgery; T, docetaxel; Tu, tumor; N, node; M, metastatic; Tm, tamoxifen; q2w, every 2 weeks.

^b mg.

^c Evaluable population, all other data are for the intent-to-treat population.

^d Reported in abstract.

receive either doxorubicin 50 mg/m² plus docetaxel 75 mg/m² every 2 weeks for four cycles or doxorubicin 60 mg/m² plus cyclophosphamide 600 mg/m² every 3 weeks for four cycles, followed by 3-weekly docetaxel 100 mg/m² for four cycles. Compared with concomitant doxorubicin–docetaxel, sequential docetaxel provided an improved pCR (the primary end point) for tumors of the breast (16% versus 8%, respectively) and an improved combined pCR for breast tumors plus ALN clearance (14% versus 7%, respectively; $P < 0.01$). An additional 6 and 4%, respectively, of patients showed *in situ* carcinoma only, yielding an overall pCR of 22% for sequential therapy versus 12% for doxorubicin–docetaxel alone. These results precipitated the early termination of accrual to this trial in favor of sequential docetaxel. Clinical tumor response was also increased in favor of the sequential regimen (Table 4), and both regimens facilitated breast conservation (76% with an 8% difference in favor of sequential therapy). Both regimens demonstrated acceptable toxicity.

In 1999, the Hoosier Oncology Group reported on a small randomized Phase II study comparing concomitant doxorubicin–docetaxel versus a sequential regimen in chemotherapy naïve stage II–III breast cancer patients (64). Forty patients (median tumor size, 5.7 cm; 57% node positive) were randomized either to doxorubicin 75 mg/m² every 2 weeks for three cycles followed by docetaxel 100 mg/m² every 2 weeks for three cycles or to doxorubicin 56 mg/m² plus docetaxel 75 mg/m² every 3 weeks for four cycles (the arms were designed to deliver the same total dose over 12 weeks). Clinical tumor response was similar between the groups (Table 4), with an overall pCR of 13% achieved, including 1 patient with residual carcinoma *in situ*. Patients who received sequential therapy had

fewer positive lymph nodes and were more likely to undergo BCT than those who received concomitant therapy. The major toxicity was myelosuppression in both groups, which was more frequently observed in the concomitant arm. Unexpectedly, patients receiving sequential therapy developed grade 3–4 hand–foot syndrome more often (42%), compared with no occurrences in the concomitant arm. This was likely due to the dose intensification of docetaxel administered on a 2-weekly schedule.

Level 1 Evidence: Sequential Therapy with Docetaxel.

Two randomized Phase III trials [the Aberdeen study (18, 66) and the NSABP study B-27 (65)] have evaluated the role of sequential docetaxel in the neoadjuvant management of breast cancer, both of which have been reported in full (Table 4).

NSABP B-27 is the largest ever trial evaluating the role of sequential docetaxel in addition to neoadjuvant AC in the treatment of stage I–III breast cancer (65). Patients ($n = 2411$) were randomized to one of three treatment groups: four cycles of neoadjuvant doxorubicin, 60 mg/m², plus cyclophosphamide, 600 mg/m², every 3 weeks; four cycles of neoadjuvant AC followed by 4 cycles of docetaxel, 100 mg/m², every 3 weeks; and four cycles of neoadjuvant AC followed by surgery and then four cycles of docetaxel 100 mg/m² every 3 weeks. The study end points included DFS and OS. Patients' characteristics were well balanced between the three arms (mean tumor size 4.5%; 70% node negative).

Compared with neoadjuvant AC alone, AC followed by sequential docetaxel significantly improved the clinical ORR (86 versus 91%; $P < 0.001$) and CR (40 versus 64%; $P < 0.001$), in addition to the pCR in the breast (14 versus 26%; $P < 0.001$) and the proportion of node-negative patients (51 versus

58%; $P < 0.001$). Notably, the addition of docetaxel resulted in statistically significant improvements in pCR in both ER-positive and ER-negative patients. Toxicities were somewhat higher in the group receiving sequential docetaxel than in those receiving AC alone (grade 4 toxicity, 23 *versus* 10%, respectively; Ref. 65).

The randomized comparative Phase III Aberdeen study assessed the benefit of sequential docetaxel after an anthracycline-based regimen in the neoadjuvant setting (18). The trial included stage II-III breast cancer patients, all of whom initially received four cycles of NC with CVAP (cyclophosphamide 1000 mg/m², doxorubicin 50 mg/m², vincristine 1.5 mg/m², and prednisolone 40 mg) every 3 weeks. Thereafter, patients in whom a complete or partial clinical response was recorded were randomized to receive either an additional four cycles of CVAP or four cycles of docetaxel 100 mg/m² every 3 weeks. Nonresponders to CVAP received four cycles of 3-weekly docetaxel 100 mg/m². After the completion of the additional cycles and before definitive surgery, clinical response was again assessed.

In total, 162 patients enrolled into the study received CVAP NC and achieved an ORR of 66% (14% CR). After randomization, 50 patients received additional CVAP and 47 patients sequential docetaxel. Patients receiving docetaxel achieved a significantly improved ORR compared with patients receiving CVAP alone: 94% (62% CR) *versus* 66% (34% CR), respectively ($P = 0.001$). In those patients who failed to respond to CVAP ($n = 55$), NC docetaxel rescue therapy provided an ORR of 47% (11% CR).

After completion of the eight chemotherapy cycles, pathological response of the primary breast tumor was assessed in 142 patients according to the Miller and Payne classification (Ref. 16; Table 1). Patients receiving docetaxel achieved a significantly higher pCR (34%) than those receiving further CVAP (16%; $P < 0.04$), although the incidence of ALN clearance was similar between the groups (15% for docetaxel *versus* 14% for CVAP). Furthermore, the docetaxel group had an increased rate of BCT (67%) *versus* patients administered CVAP alone (48%). In nonrandomized patients receiving docetaxel, 44% achieved a pathological response, but only 2% a pCR. It is relevant that, after achieving the best clinical response with CVAP, the pathological response increased with the addition of a non-cross-resistant agent rather than continued CVAP. Hypothetically, this may also be applicable to adjuvant therapy, which would suggest that patients receive a different adjuvant regimen from that administered preoperatively. This hypothesis would require testing.

Hematological toxicity was the major toxicity. Patients who received eight cycles of CVAP experienced a significantly greater incidence of grade 3–4 leukopenia and granulocytopenia *versus* patients receiving sequential docetaxel.

Although the study was not primarily designed to identify a survival difference statistically, at a median follow-up of 3 years, survival was significantly increased in patients who had received sequential docetaxel ($P = 0.05$; Ref. 66). Indeed, 90% of patients who had received docetaxel were alive compared with 71% of patients who had received the anthracycline-based regimen only.

Of additional interest was an apparent predictive significance of the tumor (T) classification of tumors in this study:

initial CVAP responses were more common in patients with less advanced T-stage disease. Those administered docetaxel after an initially successful four cycles of CVAP achieved greater dose intensity than those receiving a total of eight cycles of CVAP. It is possible that this may have accounted at least in part for differences in tumor response between regimens.

The interpretation of sequential trials is also potentially confounded by differences in the duration of NC, and it might be argued that additional treatment could account for the differences in response rates in the NSABP-B27 trial irrespective of the agents used (65). However, data on longer *versus* shorter durations of therapy are conflicting, and the Aberdeen study showed improved response rates with the addition of a docetaxel even when the treatment duration did not differ (18, 66).

When we consider these Phase II and III data, it would appear that the sequential administration of docetaxel after anthracycline-based neoadjuvant therapy provides increased benefit, including improved pathological and clinical response, and acceptable tolerability, compared with the concomitant approach. However, additional confirmatory Phase III data are required, with the final B-27 trial results eagerly awaited (65). Notwithstanding the encouraging 3-year survival data from the Aberdeen study (66), mature 5-year data will ultimately confirm whether the observed improvements in response translate to a survival benefit.

Paclitaxel As Neoadjuvant Therapy in Breast Cancer

Paclitaxel Monotherapy

To date, there has been only one peer-reviewed publication considering paclitaxel monotherapy in the neoadjuvant treatment of breast cancer (67). In this Phase III trial of 174 patients with stage II-III disease (38% node positive), 87 were assigned to receive NC that included four cycles of either 3-weekly paclitaxel 250 mg/m² or 3-weekly FAC at standard doses. After NC, all of the patients received local therapy and an additional four cycles of FAC.

The NC regimens demonstrated similar activity, with FAC achieving an ORR of 79% (24% CR) and paclitaxel an ORR of 80% (26% CR). There was a trend toward a higher pCR with FAC (16%) *versus* paclitaxel (8%), and a higher proportion of patients receiving neoadjuvant FAC had less residual disease in the breast and axilla compared with the paclitaxel arm. To date, only 2-year DFS rates are available and these are similar for the two arms (89% FAC, 94% paclitaxel). The major toxicity was hematological in both arms.

We hypothesize that the alternate use of these non-cross-resistant regimens may improve treatment outcome; for example, FAC after paclitaxel may compensate for the lower pCR associated with paclitaxel. The ongoing Phase III study by Green *et al.* (68) seeks to assess such alternating schedules and is discussed below.

Should Paclitaxel Be Combined with an Anthracycline in the Neoadjuvant Treatment of Breast Cancer?

Several Phase II studies, including randomized trials, have assessed concomitant paclitaxel plus anthracycline NC in breast cancer (Refs. 69–77; summarized in Table 5). Although the

Table 5 Trials of concomitant paclitaxel plus anthracycline in the neoadjuvant management of breast cancer

Study reference	No. of patients	Disease stage	Neoadjuvant schedule dose, (mg/m ²)	ORR ^a (%)	CR (%)	pCR (%)
Phase II studies						
Gogas <i>et al.</i> (70)	35	Tu ₀₋₄ , N ₀₋₃	AP (35/175) q3w × 6 cycles	71	17	8
Sanchez-Rovira <i>et al.</i> (74, 75) ^{b,c}	45	Tu ₂₋₄ , N ₀₋₂ , M ₀	GAP (2000–2500/35–40/135–140) ^d	98	42	18
Sousa (77) ^{b,c}	49	IIIA–B	ECP (90/600/175) q3w × 4 cycles	84 ^e	NR	33 ^e
Bellino <i>et al.</i> (69)	48	Tu >3 cm, T ₄	EP (90/200) q3w × 4 cycles	NR	NR	12 ^e
Molitemi <i>et al.</i> (72) ^b	73	II–III	EP (90/200) q3w × 4 cycles	88 ^e	25 ^e	7 ^e
Randomized studies						
Semiglazov <i>et al.</i> (76) ^{b,c}	103	Tu ₂₋₄ , N ₀₋₂ , M ₀	AP (60/200) q3w × 4 cycles	84	33	25
Phase III			FAC (600/60/600) q3w × 4 cycles	73	11	10
Pouillart <i>et al.</i> (73) ^{b,c}	247	Tu ₂₋₃ , N ₀₋₁ , M ₀	AP (60/200) q3w × 4 cycles	83	14	16
Phase II			AC (60/600) q3w × 4 cycles	66	9	10
Fumoleau <i>et al.</i> (71) ^{b,c}	232	Tu ₂₋₃ , N ₀₋₁ , M ₀	AP (60/200) q3w × 4 cycles	82 ^e	20 ^e	17 ^e
Phase II			AP (60/200) q3w × 6 cycles	86 ^e	32 ^e	28 ^e

^a ORR, overall response rate; CR, complete response; pCR, pathological complete response; Tu, tumor; N, node; M, metastatic; GAP, gemcitabine, adriamycin, and paclitaxel; P, paclitaxel; q3w, every 3 weeks; G, gemcitabine; E, epirubicin; C, cyclophosphamide; NR, not reported; F, 5-fluorouracil.

^b Interim results.

^c Reported in abstract.

^d Because of unacceptable toxicity, GAP doses were reduced and growth factor support included.

^e Evaluable population, all other data are for the intent-to-treat population.

majority of these studies have yet to be fully published in peer-reviewed journals, encouraging clinical tumor response (ORR, 66–98%) and pathological response (pCR, 7–33%) rates have been observed.

Semiglazov *et al.* (76) have compared paclitaxel plus anthracycline with FAC in a randomized Phase II trial in locally advanced breast cancer. In total, 103 patients received four cycles of either doxorubicin 60 mg/m² plus paclitaxel 200 mg/m² every 3 weeks or standard FAC (5-fluorouracil 600 mg/m², doxorubicin 60 mg/m², and cyclophosphamide 600 mg/m²) every 3 weeks. A preliminary analysis identified a trend toward a higher clinical response rate with doxorubicin–paclitaxel (84%) versus FAC (73%). In addition, a statistically improved pCR was observed in the paclitaxel arm compared with FAC (25 versus 10%, respectively; $P = 0.003$). BCT was possible in 35% of patients receiving doxorubicin–paclitaxel and 29% receiving FAC. No toxicity data were reported.

A second randomized Phase II trial has compared 4 versus 6 cycles of neoadjuvant doxorubicin 60 mg/m² and paclitaxel 200 mg/m² every 3 weeks in patients with operable breast cancer (71). The preliminary report in abstract form detailed that 232 patients had been randomized, although data were analyzed for only 191 patients (61% node positive). A higher pCR (Sataloff classification) was observed in patients receiving the extra treatment cycles (24%) versus those receiving only four cycles (17%), although statistical data were not reported. There was also a trend toward an increased CR with 6 (ORR 86%; CR 32%) versus four treatment cycles (ORR 82%; CR 20%), and both arms had similar and acceptable toxicity profiles.

In the third and final randomized Phase II study, a preliminary analysis has suggested increased benefit with doxorubicin 60 mg/m² plus paclitaxel 200 mg/m² over doxorubicin 60 mg/m² plus cyclophosphamide 600 mg/m², with both schedules administered 3-weekly for four cycles (73). At the time of a planned interim analysis in the first evaluable patients, 2 pCRs

were observed with AC versus 10 pCRs with doxorubicin–paclitaxel, such that accrual was stopped for AC in favor of doxorubicin–paclitaxel. In the 247 patients finally enrolled (67 AC, 180 doxorubicin–paclitaxel), a 16% pCR was observed with doxorubicin–paclitaxel versus 10% with AC. Clinical response similarly improved with doxorubicin–paclitaxel (ORR 83%) versus AC (ORR 66%), and BCT was possible in 56% of patients receiving doxorubicin–paclitaxel but in only 45% of those receiving AC. Notably, increased cardiac toxicity was not observed with doxorubicin–paclitaxel.

Should Radiation Therapy be Administered Concomitantly with Neoadjuvant Paclitaxel? A Phase I/II trial by Formenti *et al.* (78) in 44 stage IIB–III LABC patients has investigated the safety and efficacy of neoadjuvant treatment with twice-weekly paclitaxel 30 mg/m² for 8–10 weeks plus concurrent radiation (45 Gy at 1.8 Gy/fraction) followed by surgery and adjuvant doxorubicin-based chemotherapy. Paclitaxel plus concurrent radiation was shown to be highly feasible achieving an ORR of 91% and pCR of 18%. In addition, the regimen was generally well tolerated, with the major toxicities being grade 3 skin desquamation (7%), hypersensitivity (2%), and stomatitis (2%). Additional studies comparing neoadjuvant chemoradiation with chemotherapy in LABC are required to confirm these encouraging results.

What Is the Potential for Paclitaxel-Based Non-Anthracycline Concomitant Regimens? Two separate Phase II trials have considered the potential of paclitaxel in combination with either platinum (79) or trastuzumab (80) in the neoadjuvant breast cancer setting, with both studies published in full.

In the first of these studies, Ezzat *et al.* (79) showed paclitaxel–cisplatin to be active and tolerable in the neoadjuvant treatment of patients with stage IIB–IIIB noninflammatory breast cancer. Seventy-two patients were administered paclitaxel 135 mg/m² plus cisplatin 75 mg/m² every 3 weeks for three or four cycles before surgery and subsequently six cycles

Table 6 Trials of sequential chemotherapy including paclitaxel and anthracycline in the neoadjuvant management of breast cancer

Study reference	No. of patients	Disease stage	Schedule (dose, mg/m ²)	ORR ^a (%)	CR (%) ^b	pCR (%) ^b
Phase III randomized studies						
Gianni <i>et al.</i> (27) ^{c,d}	892	Operable BC (Tu > 2 cm)	AP (60/200) q3w × 4 cycles CMeF → S S → AP (60/200) q3w × 4 cycles CMeF	81	52	23
Green <i>et al.</i> (68) ^e	258	Tu ₁₋₃ , N ₀₋₁ , M ₀	S → A (75) q3w × 4 cycles CMeF P (225) q3w × 4 cycles FAC × 4 cycles LT ALN -ve: P (80) q1w × 12 cycles FAC × 4 cycles LT ALN +ve: P (150) q1w × 12 cycles FAC × 4 cycles LT	NR	NR	NR
Untch <i>et al.</i> (81) ^{c,d}	631	Tu > 3 cm, inflammatory disease	EP (150/250) q3w × 4 cycles LT → CMeF (500/40/6000) E (150) q2w × 3 cycles P (250) q2w × 3 cycles LT → CMeF (500/40/6000)	NR	NR	10
				NR	NR	18

^a ORR, overall response rate; CR, complete response; pCR, pathological complete response; BC, breast cancer; Tu, tumor; P, paclitaxel; q3w, every 3 weeks; C, cyclophosphamide; Me, methotrexate; F, 5-fluorouracil; →, followed by; NR, not reported; N, node; M, metastatic; LT, local therapy; ALN -ve, axillary lymph node-negative; q1w, every week; ALN +ve, axillary lymph node-positive; E, epirubicin; q2w, every 2 weeks.

of FAC at standard doses. An ORR of 90% (CR 18%) was achieved, with a pCR in 22% of patients. Despite the high clinical tumor response, BCT was low at 24%. Toxicity was acceptable, with good hematological tolerance and manageable neurotoxicity (20% grade-1–2 events). At a median follow-up of 22 months, 81% of the patients were alive and disease-free. Furthermore, no patient with a pCR had relapsed.

In the trial conducted by Burstein *et al.* (80), the authors sought to define the pCR achievable with paclitaxel–trastuzumab in patients with stage II–III HER2-positive breast cancer, and to assess the utility of serological assays for HER2. Notably, trastuzumab in combination with chemotherapy is well established in the treatment of women with HER2-overexpressing MBC. Trastuzumab was administered weekly for 12 weeks (loading dose of 4 mg/kg, and 2 mg/kg thereafter) together with paclitaxel 175 mg/m² every 3 weeks for four cycles. NC was followed by surgery and subsequent adjuvant chemotherapy. The population entered into the trial was relatively heterogeneous, with inflammatory breast cancer and ipsilateral supraclavicular lymph node metastasis allowed. At baseline, the 40 patients enrolled had a median tumor size of 5 cm and 80% were HER2 3+ (strong, complete membrane staining in >10% of tumor cells, using HercepTest [Dako, Carpinteria, CA]). Preoperative paclitaxel–trastuzumab achieved an ORR of 75% and a pCR of 18%, including three patients (8%) with carcinoma *in situ*. Although HER2 3+ tumors were more likely to show a clinical response than 2+ (weak to moderate, complete membrane staining in >10% tumor cells) tumors (84 *versus* 38%, respectively), no significant difference in pCR was observed between the subsets (19 *versus* 13%, respectively). At a median follow-up of 25 months, no patient with either a CR or pCR had relapsed. In general, the toxicity reflected the known side effects of the respective treatments. Cardiac toxicity is an ongoing concern relating to the use of trastuzumab. However, in the present trial, no symptomatic heart failure occurred and only five patients (13%) had a grade 1–2 decline in left ejection ventricular fraction during NC. Notably, in seven patients with baseline-elevated HER2 extracellular domain levels and for

whom serial data were available, the serum HER2 extracellular domain levels declined in all cases and normalized in the five patients showing a clinical response, suggesting that HER2 extracellular domain levels changes may correlate with response to paclitaxel–trastuzumab chemotherapy.

The high levels of pathological and clinical responses and the acceptable tolerability observed with neoadjuvant paclitaxel–cisplatin and paclitaxel–trastuzumab in the Phase II setting justifies further investigation in randomized controlled trials.

How Best to Administer Paclitaxel Plus Anthracycline? Concomitant Versus Sequential Schedules

Level 1 Evidence: Sequential Therapy with Paclitaxel.

Two ongoing Phase III studies are assessing sequential neoadjuvant schedules incorporating paclitaxel either before (68) or after anthracycline-based therapy (81), whereas a third Phase III study are considering a sequential schedule with doxorubicin–paclitaxel followed by cyclophosphamide–methotrexate–5-fluorouracil (CMF; Ref. 27). For all of these studies, results have been published only in abstract form (summarized in Table 6).

The innovative Phase III trial of Green *et al.* (68) has compared 3-weekly *versus* weekly paclitaxel schedules followed by sequential FAC for four cycles, with final results presented at the 2002 American Society of Clinical Oncology (ASCO) meeting. In total, 258 patients with stage I–III breast cancer were randomized to receive either four cycles of standard 3-weekly paclitaxel 225 mg/m² or weekly paclitaxel at various doses based on initial ALN status: ALN-positive patients received 150 mg/m² weekly for 3 weeks followed by a 1-week break (1 cycle), whereas ALN-negative patients received 80 mg/m² weekly for 12 weeks. A similar pCR rate was shown for ALN-negative (29%) and ALN-positive (28%) patients receiving weekly paclitaxel, and these rates were significantly improved compared with patients receiving 3-weekly treatment (pCR 14%; *P* < 0.01). The authors recommend weekly paclitaxel 80 mg/m² followed by FAC for further study, based on the

finding of similar activity but reduced toxicity with the paclitaxel 80 mg/m² compared with the other doses studied.

Preliminary results from the Phase III trial of Untch *et al.* (81) suggest that the sequential administration of paclitaxel after anthracycline is superior to concomitant administration. In this study, patients received either epirubicin 90 mg/m² plus paclitaxel 175 mg/m² every 3 weeks for four cycles or epirubicin 150 mg/m² every 2 weeks for two cycles followed by sequential paclitaxel 250 mg/m² every 2 weeks (with granulocyte colony-stimulating factor support) for three cycles. After subsequent surgery, all of the patients also received three cycles of adjuvant CMF every 4 weeks. At the time of reporting, 631 patients with breast tumors >3 cm or inflammatory disease had been randomized, with response and safety data available for 475 patients. Compared with concomitant epirubicin–paclitaxel, the dose-dense sequential regimen achieved a significantly improved pCR rate (18 *versus* 10%, respectively; *P* = 0.03), and allowed significantly more BCT (66 *versus* 55%, respectively; *P* = 0.016). The major grade 3–4 toxicity was thrombocytopenia (7% for the concomitant schedule *versus* 2% for the sequential schedule).

The third of the Phase III studies includes the European Cooperative Trial in Operable Breast Cancer (ECTO), in which a dosage of 3-weekly neoadjuvant doxorubicin 60 mg/m² plus paclitaxel 200 mg/m² for 4 cycles followed by sequential CMF every 4 weeks for 4 cycles demonstrated a promisingly high pCR and ALN clearance rate in women with operable breast cancer (tumor >2 cm; Ref. 27). This neoadjuvant study arm is to be compared with two adjuvant chemotherapy regimens: either the same regimen administered after surgery or doxorubicin alone followed by CMF (Table 6). Although DFS and OS comprise the study end points, only preliminary response and BCT data are available. In total, 892 patients have been randomized, with 270 receiving NC. A high ORR (81%; 52% CR) was associated with NC, as well as a significantly superior BCT rate (71%), compared with patients who did not receive NC (35%), regardless of tumor size at baseline. Absence of invasive breast cancer was observed in 23% of patients after NC and was associated with negative ALN in 87%. The only factor predictive of pCR was negative ER status (by multivariate analysis).

Although peer-reviewed publications of the final results of these three Phase III trials are awaited, the data available suggest that the sequential administration of paclitaxel and an anthracycline-based regimen is beneficial, with the potential to improve pCR. However, it remains to be conclusively defined whether paclitaxel is best administered as a weekly or a 3-weekly schedule. It is also unclear whether paclitaxel should be administered before or after anthracycline-based chemotherapy. To date, both approaches have shown benefit (68, 81) and the direct comparison of different scheduling in a Phase III trial is warranted.

Conclusions

The evidence suggests that taxane-based NC is an effective alternative to surgery followed by adjuvant chemotherapy in both early and locally advanced breast cancer, with both docetaxel and paclitaxel having demonstrated single-agent activity and acceptable tolerability. In addition, the rate of BCT appears to be improved with such NC, and potential breast conservation

should be offered to all patients with breast cancer, regardless of initial tumor size.

The taxanes and anthracyclines represent the most potent drugs for use in breast cancer, and their combination for NC is of particular interest. Indeed, the concomitant administration of these agents has shown promise in the Phase II setting, although only the final peer-reviewed results of several ongoing Phase III studies will definitively confirm whether the high pCR rates achieved translate into improved survival. Notably, pCR as a surrogate marker of survival should remain the key objective for NC, and efforts must be made to define a universal measure of pathological response. In our opinion, the Miller and Payne classification system (16) is the most complete and should be used universally and consistently in the grading of pCR in clinical trials. Microarray studies are required to yield potentially useful information about the expression of several gene clusters that may identify patient groups at either high risk or low risk of achieving pCR. It remains unclear, however, whether patients treated preoperatively with taxane-based therapy should also receive postoperative adjuvant chemotherapy to improve survival, and the decision to administer adjuvant chemotherapy in addition to NC is currently left to the discretion of the investigator. In contrast, it is accepted practice to treat patients with residual tumor at surgery with a non-cross-resistant chemotherapy regimen.

Findings from both docetaxel- and paclitaxel-based randomized studies suggest that the sequential administration of taxane- and anthracycline-based therapy may provide improved outcomes *versus* the outcome with concomitant administration. Although the majority of these findings include only early results published in abstract form, the fully published Phase III Aberdeen study has shown sequential docetaxel to be a more effective approach than continuing anthracycline in patients who show an initial response to therapy (18). In addition, encouraging data from this study have suggested a significant 3-year survival advantage with sequential docetaxel therapy (66). However, the relatively small number of patients (*n* = 162) included in this trial must be taken into account. Results of the large-scale NSABP-B27 trial (*n* = 2441) also confirm that sequential docetaxel after neoadjuvant AC significantly increases the pCR rate *versus* the rate with AC alone (26 *versus* 14%, respectively; *P* < 0.001). In addition, a 16% increase in the rate of negative ALNs, was observed as was a significantly improved clinical response (65). However, only longer-term follow-up data will show whether the improved pCR in the breast and ALNs will translate to a survival advantage. The apparent superiority of a sequential anthracycline–taxane regimen is exclusively limited to docetaxel. To date, no similar randomized trials incorporating paclitaxel *versus* a non-taxane-based comparator have been fully published.

Full publication of the ongoing Phase II and Phase III randomized trials is required to define the optimal taxane-based NC regimen. In the interim, the currently published data suggest that a taxane should be considered in the management of all patients receiving NC for operable and inoperable breast cancer.

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