Breast Cancer Research and Treatment (2005) 90: 169–185

Review

Primary docetaxel chemotherapy in patients with breast cancer: impact on response and survival

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Key words: breast cancer, docetaxel, primary chemotherapy

Summary

Primary chemotherapy achieves high clinical response rates and facilitates breast conservation in many patients with large and locally advanced breast cancer. It may also serve to indicate responsiveness to chemotherapeutic agents. A pathological complete response to primary chemotherapy is a primary predictor and surrogate marker of long-term outcome, but occurs in only approximately 15% of patients. Docetaxel is of particular interest in this setting. Primary docetaxel chemotherapy has single-agent activity in both dose-dense and traditional schedules, with acceptable tolerability. Furthermore, concomitant docetaxel–anthracycline schedules have shown promise in Phase II trials, achieving clinical overall response rates (ORRs) of 77–96%, pathological complete responses of up to 24%, and breast conservation in up to 89% of patients.

Two Phase III studies have shown that pathological complete response is significantly improved with the addition of docetaxel to anthracycline-based therapy versus the latter alone: the Aberdeen study achieved a rate of 34% versus 16%, respectively ($p = 0.04$), and the NSABP-B27 study a rate of 26% versus 14%, respectively ($p < 0.001$). The Aberdeen study has suggested that the addition of docetaxel may yield a survival benefit at 5 years ($p = 0.04$). The Phase II GEPAR-D*U*O study hints at a benefit for sequential over concomitant docetaxel-based therapy, with improvements in both clinical response (ORR 87% versus 77%, respectively) and pathological complete response (23% versus 12%, respectively). Non-anthracycline docetaxel-based primary regimens have shown early promise. As we continue to define the optimal regimen, a growing body of evidence supports the use of docetaxel in primary chemotherapeutic regimens for breast cancer.

Introduction

Primary chemotherapy is chemotherapy administered prior to loco-regional treatment, and has also been termed neoadjuvant, induction or preoperative chemotherapy. Primary chemotherapy was first used in locally advanced breast cancer (LABC) some 30 years ago, and has since become the standard of care in the management of patients with inflammatory breast cancer and LABC. The approach is also being used increasingly in patients with operable breast cancer, with the main aim of reducing the requirement for mastectomy and thus increasing breast-conservation rates.

The aims of primary chemotherapy in operable breast cancer have included decreasing the size of the primary tumour and hopefully reducing and/or eliminating metastatic disease before appropriate surgery is undertaken [1–3]. The rationale was that eliminating distant occult metastases should improve survival. Furthermore, by downstaging the primary tumour it was assumed that the possibility of breast-conserving surgery rather than mastectomy would be increased in those patients with large primary tumours. It has also been suggested that primary chemotherapy will allow the assessment of tumour response, which in turn indicates the usefulness of the therapy in terms of long-term outcome. In particular, previous studies have indicated that a pathological complete response indicates improved long-term survival [4–6]. Moreover, the rapid individual evaluation of a regimen is likely to be facilitated by the use of appropriate molecular and biological markers, enabling the tailoring of therapy to a specific patient and tumour.

It is has been shown that primary chemotherapy can achieve a high clinical response rate in terms of reduction in the size of the primary breast tumour, but no significant survival advantages have been shown until recently. The primary approach also facilitates breast conservation in patients with large tumours. Although the need for mastectomy is reduced, it is not eliminated and breast-conserving surgery may hold a slightly increased risk of local recurrence in certain groups of patients, but without any adverse effect on survival.

Among a number of new treatment approaches, the taxanes docetaxel and paclitaxel are being studied in the primary setting. Recently reported Phase III data have indicated that docetaxel-based primary chemotherapy may significantly increase overall survival [7, 8]. This

study builds on the efficacy of docetaxel in patients with metastatic breast cancer, where docetaxel is acknowledged to be one of the most active agents both as first-line therapy and in the management of anthracycline-refractory tumours [9–11].

Our review considers current progress in primary breast cancer therapy, specifically evaluating the evidence for docetaxel-based regimens. Our aim has been to comprehensively assess docetaxel studies published in full during the past 6 years (1997 to present) that included more than 25 patients. In addition, several studies currently available only in abstract form are also considered.

Primary versus adjuvant chemotherapy

At least five randomised trials comparing primary and traditional adjuvant treatments have been published, and are summarised in Table 1 [2, 4, 12–16]. The main trial endpoints have included disease recurrence, survival and the type of surgery undergone (breast conservation or mastectomy). Despite the heterogeneous design of these trials in terms of the variability of the tumour sizes studied and the therapeutic regimens evaluated, there are some common themes that have emerged from these studies.

In these trials, primary chemotherapy was shown to achieve significant clinical responses, with clinical overall response rates (ORR) in the range of 69–82%. This reduction in the clinical size of the primary tumour resulted in more patients (63–89%) undergoing breast-conserving surgery than for patients who received adjuvant chemotherapy. Importantly, there was no increase in surgical complications in patients receiving primary chemotherapy.

In the largest and perhaps the most important of the trials, the National Surgical Adjuvant Breast and Bowel Project (NSABP)-B18, 1495 patients with tumours staged as T0–3, N0–1 and without detectable metastases were randomized to receive either doxorubicin–cyclophosphamide (AC) followed by surgery, or surgery followed by AC [4]. A clinical ORR of 79% and complete response (CR) rate of 36% were reported. Breast-conserving surgery was possible in 68% of primary patients compared with 60% of those receiving adjuvant chemotherapy ($p = 0.002$). In particular, primary chemotherapy permitted breast conservation more frequently in patients with larger tumours $\geq$3 cm (primary 38%, adjuvant 31%). Similar results were seen in the other trials, which involved far fewer patients [2, 12, 14].

A major concern has been whether there is an increased risk of local recurrence in those patients receiving primary chemotherapy and breast-conserving surgery thereafter. Importantly, none of these trials has shown a significant difference in local recurrence between the two treatment approaches [2, 4, 12–16]. However, these data should be analyzed critically, as there are lessons to be learned. In NSABP-B18, the rate of breast tumour recurrence at the 5-year follow-up was similar in both groups (8% in the primary chemotherapy group and 6% in those receiving adjuvant therapy) [4]. However, in the 27% of women who were initially scheduled for mastectomy, but who had sufficient reduction in tumour size after primary chemotherapy to allow breast conservation, the local recurrence rate was 15%. In contrast, in those who were initially scheduled for breast conservation and who subsequently received it, the local recurrence rate was less than one-half of that observed above, at 7% ($p = 0.04$).

It is also important to note that there was a trend towards higher recurrence in younger women ($\leq$49 years) (13% primary chemotherapy, 8% adjuvant chemotherapy) compared with older women (3% in both groups). Notably, only women $\geq$50 years received tamoxifen in the trial. Administration of tamoxifen to younger women, particularly those with oestrogen receptor (ER)-positive tumours, would likely have reduced the incidence of local recurrence.

The effect of primary chemotherapy on survival is still contentious. However, none of the trials showed a reduction in disease-free survival (DFS) or overall survival (OS) when patients received primary chemotherapy, which it had been suggested might occur as a result of delayed loco-regional treatment. Initial reports from three of the earlier studies suggested a small survival benefit for patients receiving primary chemotherapy [2, 14, 15]. However, in at least two studies the survival advantage was not sustained over the longer follow-up period of 10 years [13, 16].

It is difficult to make any definitive conclusions from these studies because of their heterogeneity, particularly in terms of the tumour sizes included, which ranged from very small to advanced. The NSABP-B18 trial showed no difference in survival: in both groups the 5-year OS and DFS were 80 and 67%, respectively [4]. However, with more prolonged follow-up of this trial, a recent sub-group analysis has suggested that premenopausal women who received primary chemotherapy had better survival rates than those who received chemotherapy in the adjuvant setting [17].

An important finding from the NSABP-B18 trial was that patients with a complete pathological response to primary chemotherapy had a significantly increased 5-year OS of 87% (DFS 84%) [4]. A strong association between breast tumour response to primary chemotherapy and the eradication of tumour from lymph nodes was also observed [4].

The consensus emerging from these trials is that primary chemotherapy with traditional combinations and schedules neither improves nor reduces longer-term survival compared with the adjuvant approach when all patients are considered. However, there is an indication that premenopausal patients may benefit with a prolonged survival [17]. In contrast, the need for mastectomy can be significantly reduced, but not altogether eliminated, with primary chemotherapy, although there may be a slightly increased risk of local recurrence after

Table 1. Primary versus adjuvant breast cancer therapy – randomised trials

Study reference	Patients enrolled	Median follow-up (months)	Disease stage	Regimen	Clinical response (%)			Pathological CR (%)	OS (%)	DFS (%)	BCT (%)
					OR	CR	PR				
IBBGS Mauriac et al. [2, 13]	272	124	T2–3, N0–1, M0	*Primary*: EVM × 3 → MTV × 3 → L-Rx	NR	33	NR	NR	NS	NS	63
				Adjuvant: S → EVM × 3 →MTV × 3 [ER−, N+]	–	–	–	–	NS	NS	0
NSABP-B18 Fisher et al. [4]	1523	>60	T1–3, N0–1, M0	*Primary*: AC × 4 → S	79	36	43	13	80	67	68
				Adjuvant: S → AC × 4	–	–	–	–	80	67	60
Royal Marsden Makris et al. [12]	309	48	T0–4, N0–1, M0	*Primary*: 2MT × 4 → LRx → 2M-T × 4	83	22	61	7	NS	84	89
				Adjuvant: LRx → 2MT × 8	–	–	–	–	NS	82	78
Institut Curie S6-trial Scholl et al. [14, 16]	414	54	T2–3, N0–1, M0	*Primary*: FAC × 4 → RT ± S	82	30	52	NR	NS	NS	82
				Adjuvant: RT ± S → FAC × 4	85	41	44	NR	NS	NS	77
Petrov Research Institute Semiglazov et al. [15]	271	53	T1–3, N0–2, M0	*Primary*: TMF × 1–2 → RT → S → TMF × 4–5	69	12	57	29	86	81	0
				Adjuvant: RT → S → TMF × 4–5	57	6	51	19	78	72	0

Abbreviations: AC = doxorubicin–cyclophosphamide; BCT = breast-conserving treatment; CR = complete response; DFS = disease-free survival; ER = oestrogen receptor; EVM = epirubicin–vincristine–methotrexate; FAC = 5-fluorouracil–doxorubicin–cyclophosphamide; IBBGS = Institut Bergonie Bordeaux Groupe Sein; LRx = local treatment; M = metastasis; MTV = mitomycin–thiotepa–vindesine; 2MT = mitoxantrone–methotrexate–tamoxifen; N = node; NR = not reported; NS = not statistically significant; NSABP = National Surgical Adjuvant Breast and Bowel Project; OR = overall response; OS = overall survival; PR = partial response; RT = radiotherapy; S = surgery; T = tumour; TMF = thiotepa–methotrexate–5-fluorouracil.

breast-conserving surgery for large tumours that have been downstaged by primary chemotherapy [4].

Further advantages of primary chemotherapy include the early initiation of systemic therapy in a population of patients who carry a high risk of metastatic relapse, and the rapid assessment of patient response to a chemotherapeutic regimen – with the therapeutic effect evaluated at an early stage during pathological examination, prior to surgery being undertaken for the locoregional disease. Primary chemotherapy may also allow testing of the relevance of clinical and pathological responses, and biological markers in predicting long-term treatment outcome. The continuing aim of the primary approach is to establish such surrogate predictive markers, leading the way to tailored therapy depending on the characteristics of a particular tumour.

Potential predictive factors to indicate eventual outcome

Although overall clinical tumour response may be an important predictor of outcome for primary chemotherapy, pathological response provides a better measure. For example, Fisher et al. [4] reported a 5-year DFS of 76% for patients achieving a clinical CR versus 64% for partial responders and 60% for non-responders. However, of even greater importance than clinical response as a predictive factor is the pathological response [18]. For example, in the NSABP-B18 trial, patients with a complete pathological response had a significantly improved 5-year DFS rate of 83.6% compared with patients who had a clinical CR but residual invasive cells on pathological examination (71.1%), or patients with a clinical partial response (63.5%) or no clinical response (60.3%) ($p = 0.0001$) [4].

Despite excellent clinical responses, complete pathological responses are less common in patients receiving primary chemotherapy, which hinders further study (Table 1). Furthermore, comparisons of pathological responses between trials are difficult because of the heterogeneity of the different study populations and the lack of a standard method for pathological assessment of any residual tumour following primary chemotherapy. Several systems are in use and the grade of pathological response has only been fully detailed in recent trials [18]. A technique for assessing the magnitude of the pathological response and its validation in terms of correlation with the eventual survival of patients has recently been published [6].

It would be advantageous if the eventual response to primary chemotherapy could be predicted at a very early stage in the treatment schedule. Positron emission tomography (PET) might allow this, as the technique detects biochemical and physiological changes occurring in the tissues – metabolic changes that can occur early after chemotherapy. In patients with breast cancer, initial studies have shown that these early changes, detectable even after only one pulse of chemotherapy, may predict the eventual pathological response [19, 20]. PET is able to predict the eventual histopathological response with 88% accuracy, if carried out after the first cycle of chemotherapy, and this increases to 91% after the second cycle [19]. A third important prognostic factor is persistent pathological axillary node involvement with tumour after completion of primary chemotherapy, which is associated with poor outcome. Again, a difficulty here is the lack of a single standardised classification system for assessing lymph node status and the response of any residual tumour within them following completion of chemotherapy [21].

Biological markers expressed by malignant cells may have predictive value for response to primary chemotherapy in patients with breast cancer. In a study of 158 patients with operable breast cancer receiving primary chemotherapy (and hormone therapy) comprising mitoxantrone, methotrexate and tamoxifen, key biological markers were measured before and after chemotherapy [22]. Tumours expressing ER, progesterone receptor and *bcl-2*, together with an absence of c-*erb*-b2 (*HER-2/neu*) and decreased Ki67 antibodies in the first 3 weeks, significantly predicted the subsequent objective response. Indeed, it is generally accepted that ER-negative status is a good predictor of response to chemotherapy [13]. Low *mib-1* expression and high *mdm-2* expression may also predict better treatment response [23]. Furthermore, a clear correlation between a high proliferation rate (S-phase fraction $> 5\%$) and response to primary chemotherapy has been described [16], although other studies have failed to demonstrate this association [13, 22]. Finally, an increased apoptotic index shortly after chemotherapy may predict good response [24]. Further studies are needed to determine which markers are the best predictors of response to chemotherapy and which are most appropriate for different chemotherapeutic agents.

Novel primary regimens in breast cancer: docetaxel

As discussed above, traditional combination chemotherapy regimens for the primary management of breast cancer remain sub-optimal, with a minority of patients achieving a complete pathological response. Furthermore, the effects on disease-free interval and OS are contentious (the limitations of the studies that have evaluated this are discussed above) [2, 4, 12–16]. Nevertheless, the primary chemotherapeutic approach is promising and improvements will require not only the incorporation of new chemotherapy agents but also optimisation of treatment schedules.

A number of newer agents are being assessed in primary chemotherapeutic regimens for patients with breast cancer. These comprise the taxanes (docetaxel and paclitaxel), capecitabine and the platinums, as well as non-chemotherapeutic approaches incorporating trastuzumab, tamoxifen and third-generation aromatase inhibitors (letrozole, anastrozole and exemestane). However, this review focuses specifically on the role of

docetaxel as primary chemotherapy for patients with breast cancer.

Efforts are ongoing to develop new treatment options, and to optimise both these and current treatment regimens, for primary chemotherapy. Sequential chemotherapy is one approach of interest. It is expected that sequential regimens might maximise the dose intensity of each single agent, while avoiding overlapping toxicity due to the simultaneous administration of active drugs. Another approach is the use of rapidly cycling 'dose-dense' schedules, based on the premise that success is predicted by decreasing the period available for tumour cell regrowth between treatments. A benefit deriving from such schedules is the shortened duration of chemotherapy administration.

Whether patients should receive surgery, radiotherapy or a combination of these modalities after completion of primary chemotherapy, and the associated timing of such treatment, remains undefined. It would appear, however, that local recurrence is higher in patients receiving lumpectomy alone compared with those receiving radiotherapy and surgery [25]. Perhaps this is not surprising given that less than 20% of patients receiving conventional primary chemotherapeutic regimens achieve a complete pathological response. Thus, approximately 80% of patients will have residual tumour and, based on current knowledge, surgery is essential. However, the newer imaging techniques, such as PET and magnetic resonance imaging (MRI), may allow the identification of patients with a complete pathological response, and surgery may thus be unnecessary for selected patients.

Docetaxel in the treatment of breast cancer

Docetaxel and anthracyclines are widely acknowledged as the most potent agents available against breast cancer cells. Docetaxel and the other taxane, paclitaxel, are mitotic spindle poisons sharing similar mechanisms of action and certain pharmacological characteristics, but interestingly, they also display significant differences [26]. For example, docetaxel has a greater affinity for tubulin, a longer plasma half-life and longer intracellular retention than paclitaxel [26, 27]. Predictable myelotoxicity is the major toxicity with docetaxel, whilst significant neuropathy is associated with paclitaxel [27].

It is important to remember that the most concerning complication of anthracycline-based combination regiments is chronic heart failure (CHF), which has implications for the use of taxanes. Although epirubicin can be used instead of doxorubicin (it is less cardiotoxic but equally effective) [28], docetaxel has no significant effect on the plasma disposition of anthracycline. This explains the lower cardiotoxicity of docetaxel–anthracycline combinations compared with those including paclitaxel [29].

Docetaxel's efficacy has previously been demonstrated in both metastatic disease and anthracycline-resistant tumours [9–11]. Docetaxel is the only agent with proven single-agent superiority over doxorubicin, demonstrated in a Phase III trial in patients with metastatic breast cancer [9]. Docetaxel 100 mg/m^2 was shown to achieve an improved ORR (48% versus 33%; $p = 0.008$), time to progression (TTP) and time to treatment failure compared with patients receiving doxorubicin 75 mg/m^2. Docetaxel was also more active than doxorubicin in patients with adverse prognostic factors, such as resistance to prior chemotherapy. Furthermore, a comparison of safety factors favoured docetaxel, and quality of life assessments were comparable for the two regimens.

Given the differing activity and toxicity profiles for docetaxel and anthracycline, and their relative non-cross-resistance, there is a clear rationale for combining them in the treatment of patients with breast cancer. Indeed, in a Phase III study of first-line chemotherapy for 429 patients with metastatic breast cancer, doxorubicin–docetaxel (AT) achieved a 17% increase in TTP and a response rate of 59% versus 47% for AC [10].

Docetaxel-based primary chemotherapy in patients with operable breast cancer: an overview of the evidence

The role of docetaxel as one of the most active agents currently available for the treatment of patients with metastatic breast cancer, together with the benefits shown for docetaxel–anthracyline combinations, led to the investigation of docetaxel-based primary chemotherapeutic regimens. Below we provide a comprehensive overview of the data published to date, including the first Phase III studies.

Docetaxel Phase II monotherapy studies

Several studies have shown that single-agent docetaxel administered in weekly (36–40 mg/m^2) and 3-weekly doses (100 mg/m^2) is both active and well tolerated [30–33] (Table 2). These studies have demonstrated high clinical response rates, with ORRs of 68–85% (CR 19–29%) and complete pathological response rates as high as 20–36%. Furthermore, up to 72% of patients treated with docetaxel as primary chemotherapy subsequently go on to have breast-conserving surgery [30].

Two Phase II studies have considered dose-dense docetaxel monotherapy schedules [31, 32]. In the study by Estévez et al. [32], patients with stage II–III BC received weekly docetaxel (40 mg/m^2) prior to surgery. In 56 patients, a clinical ORR of 68% (CR 29%) was achieved, with a complete pathological response rate of 16%. In a second study detailed in abstract form at present, docetaxel 36 mg/m^2 given as a weekly schedule achieved a clinical ORR of 67% (CR 19%) and a complete pathological response rate of only 5% in 36 patients who had a poor prognosis [31]. Both of these weekly docetaxel regimens were well tolerated. Bines et al. [31] observed no grade 3–4 haematological toxicity, while Estévez et al. [32] reported only 4% grade 3–4 neutropenia but no febrile neutropenia.

Table 2. Single-agent docetaxel primary chemotherapy – Phase II trials

Study reference (number of patients enrolled)	Number of evaluable patients	Patient/disease characteristics	Study regimen	Clinical		Pathological CR (%)
				OR (%)	CR (%)	
Weekly regimens						
Estévez et al. [32] (n = 56)	56	Previously untreated stage IIA–IIIB BC ECOG PS 0–1	40 mg/m^2 q1w 6/8 × 2 → S	68	29	16
Bines et al. [31][a] (n = 37)	36	Previously untreated stage IIIA–B BC ECOG PS 0–1	36 mg/m^2 q1w 6/8 × 2 → S	69	22	5
Three-weekly regimens						
Amat et al. [30] (n = 88)	80	Previously untreated stage II–III BC WHO PS 0–1	100 mg/m^2 q3w × 6 → S/RT	68	19	20–36[b]
Gradishar [33] (n = 33)	33	Previously untreated stage III BC Karnofsky PS ≥ 60	100 mg/m^2 q3w × 4 → S → adjuvant AC + RT ± tamoxifen	85	18	NR

Abbreviations: AC = doxorubicin–cyclophosphamide; BC = breast cancer; CR = complete response; ECOG = Eastern Cooperative Oncology Group; NR = not reported; OR = overall response; PS = performance status; RT = radiotherapy; S = surgery; WHO = World Health Organization.

[a] Reported in abstract.

[b] Dependent on classification system applied.

Primary chemotherapy comprising 3-weekly docetaxel at a dose of 100 mg/m^2 has been evaluated in two Phase II studies where it was given over either 6 [30] or 4 cycles [33]. In the study by Amat et al. [30], a clinical ORR of 68% (CR 19%) was obtained in 80 evaluable patients with stage II and III tumours. A high complete pathological response occurred – 20% when using the Chevallier classification [34], but rising to 36% when Sataloff's classification was used [35]. The authors suggest that the high clinical and pathological response rates may be attributed to the dose of docetaxel (100 mg/m^2) and the length of treatment (6 cycles). Breast-conserving surgery was undertaken in 72% of patients. The main toxicities were, predictably, haematological (grade 3–4 neutropenia 71%, leucopenia 26%), but no grade 3 or 4 non-haematological toxicities occurred. Preliminary findings from the ongoing study by Gradishar [33] in 33 patients with stage III breast cancer have shown 3-weekly docetaxel 100 mg/m^2 results in a clinical ORR of 85% (CR 18%), with acceptable toxicity.

These results for single-agent docetaxel appear to be comparable with those that have been reported previously for traditional polychemotherapeutic regimens [2, 4, 12, 14, 15], albeit these latter were Phase III studies. The findings support the further evaluation of docetaxel-based combinations in concomitant and sequential primary schedules, with a particular focus on the effect on pathological response rates, a surrogate marker for survival and, ultimately, the actual overall survival of these patients.

Docetaxel–anthracycline concomitant regimens: Phase II studies

A number of studies of docetaxel in combination with anthracycline, either in dose-dense or traditional schedules, have shown further improved efficacy in comparison with single-agent studies. Comprehensive details on the regimens studied and outcomes achieved are provided in Table 3.

Docetaxel in combination with doxorubicin. Four Phase II studies have evaluated docetaxel in combination with doxorubicin [36–39]. In the earliest study by von Minckwitz et al. [38], a dose-dense AT schedule yielded one of the highest clinical tumour response rates reported in the literature. Patients with stage II–IIIB disease received AT either every 2 weeks or every 3 weeks for 4 cycles. Despite these patients having some adverse disease characteristics (median tumour size 4 cm and 71% with positive nodes), a high clinical ORR was achieved: 96% for the dose-dense schedule compared with 89% for patients receiving the 3-week regimen (intention to treat population). Clinically non-involved axillary nodes increased from 29% of patients at study initiation to 52% after completion of chemotherapy and before surgery was undertaken.

A significant reduction in the clinical tumour size occurred. Initially, 36% of patients were scheduled for breast-conserving surgery but this increased to being possible in 59% after completion of primary chemotherapy. The time from initial diagnosis to surgery being undertaken was only 8 weeks for those receiving the dose-dense schedule and the regimen was well tolerated. Both schedules were associated with only slight haematotoxicity, most likely because of the use of prophylactic granulocyte colony-stimulating factor (G-CSF).

These promising results led the German Adjuvant Breast Cancer Study Group (GABG) to initiate a randomised, controlled Phase IIb study of a dose-dense AT schedule, with or without tamoxifen [39]. The rationale for the inclusion of tamoxifen was data from *in vitro* studies that had demonstrated synergism between docetaxel and tamoxifen in three ER-negative cell lines: MDR- MDA-MB 231, MDR+ CEM-VBLr and MCF-7 ADRr [40].

This dose-dense primary AT regimen offered rapid efficacy, moderate toxicity and high compliance in 250 patients with operable breast cancer, 47% of whom were ER-positive and 32% ER-negative (ER status not assessed in 21% of patients). Although concurrent tamoxifen usage did not improve the primary endpoint of complete pathological response (AT + tamoxifen 9%, AT alone 10%), AT plus tamoxifen achieved a 10% increase in clinical ORR (78%, CR 13%) versus AT alone (clinical ORR 68%, CR 6%) [39]. Effective tumour downstaging resulted in a breast-conservation rate of 69% in both patient groups. Toxicity was moderate, but the incidence of grade 3–4 neutropenia was 30%, which was greater than the 2% reported in the pilot study [38]. This may be due to a shortening of the period of administration of G-CSF from 10 days down to only 6. However, febrile neutropenia remained infrequent. A low incidence of CHF (1%) was observed, possibly linked to the low cumulative dose of doxorubicin. The high level of compliance was attributed to the short treatment duration, with patients encouraged to continue after observing the clinical reduction in their tumour size.

Results of two further studies of primary AT in traditional 3-weekly schedules are available [36, 37]. Preliminary results currently published in abstract form by Valero et al. [37] show that for 70 patients with stage III–IV breast cancer, a clinical ORR of 90% (CR 4%) and a complete pathological response rate of 10% can be achieved with AT. Because of febrile neutropenia occurring in 29% of patients, prophylactic G-CSF was administered to all patients after the first 11 patients had been treated, and this reduced the risk of neutropenia. In the study by Ganem et al. [36], AT was given to 47 evaluable patients with T2 or T3 breast cancers. The combination showed promise, achieving a clinical ORR of 85% (CR 23%), complete pathological response rate of 13% and a 69% breast-conservation rate. G-CSF was administered only as secondary prevention to patients with grade 3–4 neutropenia (65%) and febrile neutropenia (17%). There was no evidence of clinical cardiotoxicity in any patients [36].

Table 3. Docetaxel-based concomitant primary chemotherapy – Phase II trials

Study reference (number of patients enrolled)	Patients evaluable for efficacy	Patient/disease characteristics	Study regimen	Clinical		Pathological CR (%)	BCT (%)	Grade 3–4 toxicities in ≥5% of patients or cycles (%)
				OR (%)	CR (%)			
Doxorubicin– docetaxel regimens								
von Minckwitz et al. [39] (n = 250)	Arm A: 123	Previously untreated BC, primary tumour ≥3 cm, N0–2, M0	Arm A: doxorubicin 50 mg/m^2 + docetaxel 75 mg/m^2 q2w × 4 → S	Arm A: 68	Arm A: 6	Arm A: 10	Arm A: 69	Arm A (% of patients): leucopenia (35); neutropenia (25); fatigue (15); appetite loss (7); diarrhoea (6)
	Arm B: 120	Karnofsky PS ≥ 70	Arm B: as for Arm A + tamoxifen 30 mg for 5 years[a] → S Prophylactic G-CSF 150 μg/m^2/d d5–10 → S	Arm B: 78	Arm B: 13	Arm B: 9	Arm B: 69	Arm B (% of patients): leucopenia (40); neutropenia (36); fatigue (19); appetite loss (11); infection (8); hot flushes (8); skin changes (6)
Ganem et al. [36] (n = 48)	47	Non-inflammatory T2– 3 M0 BC WHO PS 1	Doxorubicin 50 mg/m^2 + docetaxel 75 mg/m^2 q3w × 6 → S Secondary G-CSF	85	23	13	69	% of patients: neutropenia (65); febrile neutropenia (17); thrombocytopenia (4)
Valero et al. [37] [b] (n = 70; target = 88)	70	Stage IIB–IV BC	Doxorubicin 60 mg/m^2 + docetaxel 60 mg/m^2 q3w × 6 → S Prophylactic G-CSF 150 μg/m^2/d for 10–14 days (after first 11 patients)	90	4	10	16	% of patients: febrile neutropenia (29); fatigue (16); infection (11); mucositis (9)
von Minckwitz et al. [38] (n = 42)	Arm A: 24	Previously untreated stage II–IIIB BC	Arm A: doxorubicin 50 mg/m^2 + docetaxel 75 mg/m^2 q2w × 6 → S	Arm A: 96[c]	Arm A: 29[c]	Overall: 5	Overall: 59 [c]	% of patients: lethargy (17); appetite loss (10); stomatitis (7); skin desquamation (7)
	Arm B: 18	Karnofsky PS ≥70	Arm B: doxorubicin 50 mg/m^2 + docetaxel 75 mg/m^2 q3w × 6 → S Prophylactic G-CSF 150 μg/m^2/d d3–12	Arm B: 89[c]	Arm B: 39[c]			

Epirubicin–docetaxel regimens								
Wenzel et al. [45] (n = 20) Phase I/II	20	Primary or metastatic BC Karnofsky PS >70	Epirubicin 25–35 mg/m^2 + docetaxel 25–40 mg/m^2 q1w × 4 → S	90	10	10	85	DLT: grade 4 leucopenia at highest dose level
de Matteis et al. [41] (n = 30)	28	T2–4, ≤N2, M0, including inflammatory disease ECOG PS ≤ 2	Epirubicin 75 mg/m^2 + docetaxel 80 mg/m^2 q3w × 4 → S Secondary G-CSF (grade 4 or febrile neutropenia lasting >4 days)	77[c]	20[c]	13[c]	17[c]	% of patients: neutropenia (87); febrile neutropenia (33)
Wenzel et al. [42] (n = 66)[d]	66	Previously untreated T1–4 N+ve/-ve, M0 BC Karnofsky PS ≥70	Epirubicin 75 mg/m^2 + docetaxel 75 mg/m^2 q3w × 8 → S → ET/ CMF/RT/tamoxifen[e] Prophylactic G-CSF 30 MU/d d3–10	82	NR	15	65	% of patients: leucopenia (8)
Milla et al. [44][b] (n = 36)	29	Previously untreated stage IIIA–B BC ECOG PS ≤2	Epirubicin 120 mg/m^2 + docetaxel 100 mg/m^2 q3w × 4 Prophylactic G-CSF 150 μg/m^2/d d3–13	93	38	24	NR	% of cycles: febrile neutropenia (7); neutropenia (5)
Luporsi et al. [43][b] (n = 90)	Arm A: 25	Operable stage II–IV BC	Arm A: 5-FU 500 mg/m^2 + epirubicin 100 mg/m^2 + cyclophosphamide 500 mg/m^2 q3w × 6 → S	Arm A: 72	NR	Arm A: 24	Arm A: 69	Arm A (% of patients): neutropenia (61)

(Continued overleaf)

Table 3. (Continued)

Study reference (number of patients enrolled)	Patients evaluable for efficacy	Patient/disease characteristics	Study regimen	Clinical		Pathological CR (%)	BCT (%)	Grade 3–4 toxicities in ≥5% of patients or cycles (%)
				OR (%)	CR (%)			
	Arm B: 25		Arm B: epirubicin 100 mg/m^2 + docetaxel 75 mg/m^2 q3w × 6 → S Secondary G-CSF	Arm B: 84	NR	Arm A: 24	Arm A: 85	Arm B (% of patients): neutropenia (71)

Abbreviations: BC = breast cancer; BCT = breast-conserving treatment; CMF = cyclophosphamide–methotrexate–5-fluorouracil; CR = complete response; DLT = dose-limiting toxicity; ECOG = Eastern Cooperative Oncology Group; ET = epirubicin–docetaxel; 5-FU = 5-fluorouracil; G-CSF = granulocyte colony-stimulating factor; IV = intravenously; M = metastasis; MU = million units; N = node; NR = not reported; OR = overall response; PS = performance status; RT = radiotherapy; S = surgery; T = tumour; WHO = World Health Organization.

[a] Tamoxifen continued for 5 years after conclusion of preoperative chemotherapy only in patients with CR or PR.

[b] Reported in abstract.

[c] Intention to treat population – all other data are for the evaluable population, as originally reported by the authors.

[d] The primary analysis (n = 66) is extracted from a combined analysis (n = 104) of two Phase II trials considering palliative and primary therapy.

[e] Post-operative treatment adjusted according to disease stage.

Docetaxel in combination with epirubicin. Four Phase II studies have considered 3-weekly primary regimens incorporating epirubicin and docetaxel, with two published in full [41, 42] and two in abstract form [43, 44].

In the study by Wenzel et al. [42], 3-weekly epirubicin–doxorubicin (ET) was shown to have anti-tumour activity and acceptable toxicity in 66 patients with previously untreated breast cancer. A high clinical ORR (82%) was observed, and no disease progression was seen to occur during primary chemotherapy (median follow-up 39 months). A complete pathological response occurred in 15% of patients, but with a further 67% having a pathological partial response. Breast-conserving surgery was possible in 65% of patients. This regimen was particularly well tolerated, with leucopenia being the main grade 3–4 toxicity, occurring in 8% of patients. No patient experienced cardiotoxicity or allergic reactions. This low rate of toxicity is likely due to the use of prophylactic G-CSF. A study that evaluated ET in patients who were at a higher risk of relapse was reported by de Matteis et al. [41]. In 30 patients, one-third of whom had poor-prognosis inflammatory breast cancer, the intention to treat analyses yielded a clinical ORR of 77% (82% of the evaluable population) and a clinical CR of 20%. A complete pathological response occurred in 13% of patients (15% of the evaluable population). Overall, 44% of patients had no evidence of tumour involving the axillary lymph nodes at pathological examination; 23% of whom had palpable lymph nodes prior to chemotherapy. Although significant grade 3–4 neutropenia (87%) and neutropenic fever (33%) occurred, secondary G-CSF support allowed all patients to complete the planned treatment.

Interim results from a trial of 4 cycles of 3-weekly high-dose epiribucin 120 mg/m^2 plus docetaxel 100 mg/m^2 in patients with stage III breast cancer who had not received prior chemotherapy demonstrated a very high clinical response (ORR 93%, CR 38%) in 29 evaluable patients [44]. A high complete pathological response of 24% also occurred in these patients. Myelotoxicity was the main toxicity, with grade 3–4 neutropenia occurring in 5% of cycles and febrile neutropenia in 7%; no cardiotoxicity was reported.

The final 3-weekly study by Luporsi et al. [43] compared ET with the combination 5-fluorouracil–epirubicin–cyclophosphamide (FEC) in an 18-week regimen. Early results showed a complete pathological response rate of 24%, which was the same in both groups of patients. ET achieved a higher clinical ORR (84%) than did FEC (72%), and also a higher rate of breast-conserving surgery (85% versus 69%, respectively). In the absence of routine G-CSF prophylaxis, grade 3–4 neutropenia was higher with ET (71%) than with FEC (61%), and febrile neutropenia occurred in 10% of patients receiving ET.

A single Phase I/II trial of dose-dense weekly ET in the primary, and also palliative, treatment of patients with breast cancer has shown the regimen to be feasible, safe and highly active [45]. In this study, 20 patients

received weekly primary chemotherapy incorporating epirubicin 25–35 mg/m^2 plus docetaxel 25–40 mg/m^2 for 6 weeks, followed by 1 week's rest, without G-CSF support. A complete pathological response rate of 10% occurred and a clinical ORR of 90% was achieved. Furthermore, breast-conserving surgery was possible in 85% of patients. The maximum tolerated dose was epirubicin 35 mg/m^2 plus docetaxel 40 mg/m^2, with the dose-limiting toxicity being grade 4 leucopenia. Based on these results, the authors recommended weekly epirubicin 30 mg/m^2 and docetaxel 35 mg/m^2 for further evaluation in Phase II studies.

These findings with both AT and ET concomitant schedules compare well with the previously reported anthracycline combinations [2, 4, 14]. However, these results have yet to be confirmed in Phase III trials. Traditional concomitant regimens have been shown to be feasible with high clinical response rates and acceptable tolerability [36, 37, 41–44]. Dose-dense schedules offer rapid efficacy, mild to moderate toxicity and high patient compliance [38, 45].

The results suggest that primary chemotherapy with a docetaxel–anthracycline combination is likely to prevent mastectomy being necessary in 50–89% of patients receiving such treatment (Table 3). It is interesting to note that a relatively high complete pathological response rate of up to 24% has been achieved [43, 44]. It would appear that the predictable haematological toxicities might be prevented by the judicious administration of prophylactic G-CSF. Encouragingly, minimal cardiotoxicity was observed with regimens incorporating either doxorubicin or epirubicin.

Sequential docetaxel-based primary chemotherapy. Results from four randomised studies are very important in trying to define clearly the role of sequential docetaxel-based primary chemotherapy. Two Phase II randomised studies [46, 47] are considered below, with the designs and key findings of these studies detailed in Table 4. Thereafter, two Phase III trials, the Aberdeen study [5, 8] and the NSABP B-27 study [48], are considered.

Phase II sequential docetaxel studies. Following on from the observed complete pathological response rate of 10% with the previously described dose-intensified, 8-week AT schedule [39], the randomised Phase II GEPARDUO study has tested whether equivalent complete pathological response rates could be achieved for the 8-week schedule and a sequential 24-week schedule – AC for 4 cycles followed by docetaxel for 4 cycles – in the primary treatment of primary operable breast cancer [47, 49]. Results presented at the 2002 American Society of Clinical Oncology (ASCO) meeting showed that while both regimens were feasible, the sequential regimen achieved a significantly higher overall complete pathological response than did AT alone (23% versus 12%, respectively) [47].

This overall rate incorporated complete pathological response for tumours of the breast (16% for the sequential regimen versus 8% for AT) and for the axillary lymph glands (combined rate 14% versus 7%, respectively), in addition to further patients having only residual *in situ* carcinoma (6% versus 4%, respectively). These results led to the premature termination of study accrual because of the better results obtained with the sequential regimen. A 10% increase in clinical ORR (87% versus 77%) and a 25% increase in clinical CR (58% versus 33%) were observed in favour of the sequential schedule. Furthermore, more patients had no pathological evidence of nodal involvement with the sequential regimen (61%) compared with those receiving AT alone (55%).

Both regimens facilitated breast-conserving surgery (75% of those with the sequential schedule; 66% with the dose-intense schedule), and the level of toxicity was acceptable. Neutropenia, the major grade 3–4 toxicity, occurred in 45% of patients receiving AT plus G-CSF support and 67% of those treated with AT followed by docetaxel (without G-CSF). A higher dropout rate was observed for the sequential docetaxel group (22% versus 8%), due in part to the longer treatment period required. In both groups, the main reason for dropout was toxicity.

The randomised Phase II study by Miller et al. [46] evaluating sequential versus concomitant AT chemotherapy has shown both regimens to be highly active with acceptable tolerability, but with the sequential regimen achieving a significantly greater reduction in the tumour involvement of the axillary nodes. The treatment arms were designed to deliver the same total doses of both doxorubicin and docetaxel over a 12-week period prior to surgery (Table 4). The complete pathological response rate (defined as no invasive malignancy in breast or lymph node specimens at surgery) was 16% with sequential therapy and 10% with concomitant therapy. However, the patients in this study had a large tumour size (median 5.8 cm) and poor prognosis (57% axillary node involvement).

High clinical ORRs were achieved: 89% (CR 32%) for the sequential group and 81% (CR 10%) for the concomitant group. Patients who received sequential therapy had fewer positive lymph nodes (mean 2.17 versus 4.81; $p = 0.037$) and were more likely to undergo breast-conserving surgery (37% versus 19%) than those receiving concomitant therapy. Although substantial myelotoxicity occurred, the administration of prophylactic G-CSF limited infectious complications and allowed intensive therapy to be delivered. A high incidence (42%) of grade 3–4 hand–foot syndrome in the sequential regimen group was unexpected, and additional studies are required to elucidate the cause of this toxicity.

Phase III sequential docetaxel studies. The randomised Phase III Aberdeen study was, to the best of our knowledge, the first randomised trial comparing the efficacy of docetaxel with an anthracycline-based regi-

Table 4. Docetaxel-based sequential primary chemotherapy – randomised Phase II trials

Study reference (number of patients enrolled)	Patients evaluable for efficacy	Patient/disease characteristics	Study regimen	Clinical		Pathological CR (%)	BCT (%)	Grade 3–4 toxicities in ≥5% of patients or cycles (%)
				OR (%)	CR (%)			
GEPAR-D*UO* trial	Pathological CR, BCT, nodal disease:	Operable T2–3, N0–2, M0 BC	Arm A: doxorubicin 60 mg/m^2; + cyclophosphamide 600 mg/m^2; q3w × 4 → docetaxel 100 mg/m^2; q3w x 4 → S	Arm A: 87	Arm A: 58	Arm A: 23	Arm A: 75	Arm A (% of patients): neutropenia (67); nausea (13); hot flushes (12); constipation (9); skin changes (6); nail changes (5)
von Minckwitz et al. [47][a] (n = 913)	Arm A: 442 Arm B: 443	Karnofsky PS ≥70	Arm B: doxorubicin 50 mg/m^2; + docetaxel 75 mg/m^2; q2w x 4 + → S					
	Clinical response: ArmA: 429 Arm B: 421		Tamoxifen 20 mg for 5 years	Arm B: 77	Arm B: 33	Arm B: 12	Arm B: 66	Arm B (% of patients): neutropenia (45), nausea (10); hot flushes (8); diarrhoea (8)
			Prophylactic G-CSF 5 ìg/kg d5–10 (Arm B)					
Hoosier Oncology Group	Arm A: 19	Previously untreated stage II–III non-inflammatory BC	Arm A: doxorubicin 75 mg/m^2; q2wx 3 → docetaxel 100 mg/m^2; q2w x 3 → S	Arm A: 89	Arm A: 32	Arm A: 16	Arm A: 37	% of patients: leucopenia (48); granulocytopenia (74),anaemia (63), hand–footsyndrome (42); diarrhoea (26)
Miller et al. [46] (n = 40)	Arm B: 21	WHO PS 1	Arm B: doxorubicin 56 mg/m^2; + docetaxel 75 mg/m^2; q3w x 4 → S	Arm B: 81	Arm B: 10	Arm B: 10	Arm B: 19	% of patients: leucopenia (81); granulocytopenia (86); anaemia (43); diarrhoea (28)
			Prophylactic G-CSF 5 μg/kg d2–12					

[a] Reported in abstract.

Abbreviations: BC = breast cancer; BCT = breast-conserving treatment; CR = complete response; G-CSF = granulocyte colony-stimulating factor; M = metastasis; N = node; OR = overall response; PS = performance status; T = tumour; S = surgery; WHO = World Health Organization.

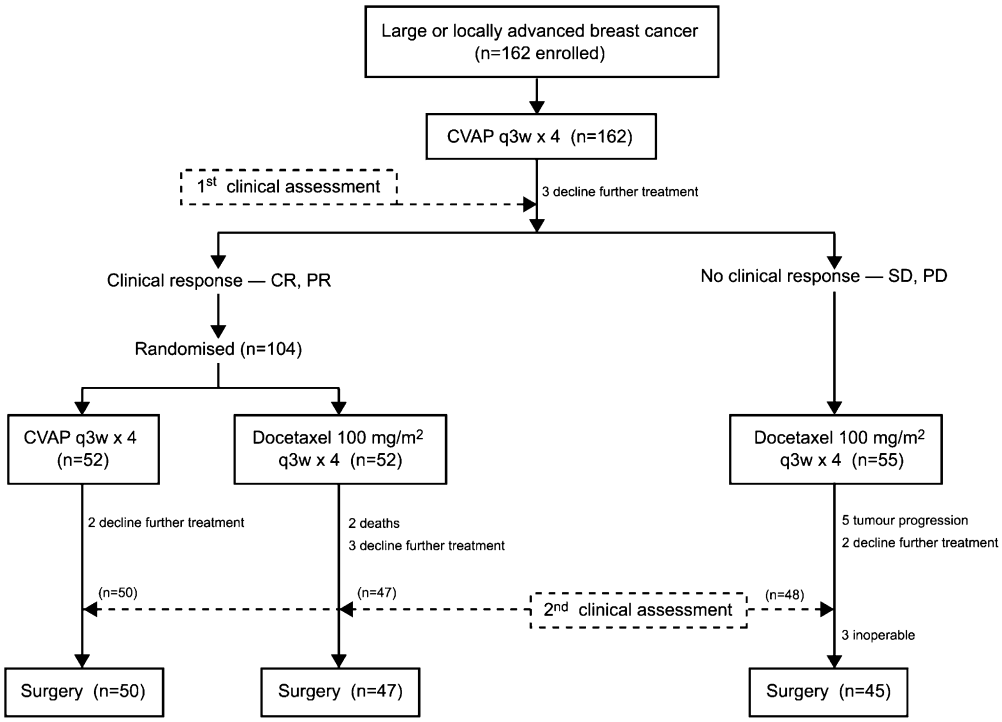
men in the primary setting [5, 8]. The study enrolled 162 patients with large tumours or LABC. The protocol and profile are comprehensively detailed in Figure 1. The primary endpoints for this study were the clinical and pathological responses.

The Aberdeen study showed a clinical ORR of 66% for all patients after an initial 4 cycles of cyclophosphamide, vincristine, doxorubicin and prednisolone (CVAP) chemotherapy. Patients who demonstrated a clinical response to CVAP were then randomized to either 4 further cycles of CVAP or 4 cycles of docetaxel. In these responding patients, sequential docetaxel resulted in a significantly higher clinical response compared with those receiving an additional 4 cycles of CVAP (clinical ORR 94% versus 66%, respectively; $p = 0.001$). The Miller and Payne classification for assessing histological response to chemotherapy was used, in which pathological response (i.e. grade 5 on a 5-point scale) is defined as 'no invasive cells identifiable in sections from the site of the previous tumour', was used [6]. It was shown that sequential docetaxel significantly improved the complete pathological response rate when compared with the findings for the CVAP group (34% versus 16%, respectively; $p = 0.04$).

A better clinical response after completion of the chemotherapy regimen predicted a better pathological response ($p < 0.05$). Residual tumour in the axillary lymph nodes was found in 33% of patients receiving 8 cycles of CVAP and in 38% of patients receiving the further 4 cycles of docetaxel. Sequential docetaxel chemotherapy was shown to significantly reduce the rate of mastectomy compared with those receiving only CVAP (67% versus 48%, respectively; $p < 0.01$). In patients who did not initially respond to anthracycline-based therapy and who were therefore given 4 cycles of docetaxel as 'rescue' therapy, a 55% clinical ORR, but only a 2% complete pathological response rate, was obtained with subsequent docetaxel. Residual tumour in the axillary lymph nodes was found in 44% of these patients.

Five-year survival data for the Aberdeen study have recently been presented at the 2003 San Antonio Breast Cancer Symposium (SABCS) and the survival benefit for sequential docetaxel after CVAP persists, which is in keeping with the pathological responses reported previously [7]. At a median follow-up of 65 months, the overall survival rate was almost 95% in patients receiving docetaxel versus 78% in the CVAP group ($p = 0.04$). Although the 5-year survival data have yet to be reported in full, it has previously been shown that the 3-year DFS rate was also significantly improved with administration of docetaxel (90%) versus CVAP (77%; $p = 0.03$) [8]. Progression-free survival at a median follow-up of 104 weeks (range 13–187 weeks) is shown in Figure 2 [50]. It is important to note that although this result is interesting, the study was not statistically designed to evaluate survival and these results must be interpreted with caution.

Leucopenia and granulocytopenia were the major toxicities; patients who received 4 cycles of CVAP followed by 4 cycles of docetaxel experienced significantly less grade 3–4 leucopenia ($p = 0.029$) and granulocytopenia ($p = 0.006$) than those receiving 8 cycles of CVAP.



Abbreviations: CVAP = cyclophosphamide 1000 mg/m^2 + vincristine 1.5 mg/m^2 (max 2 mg) + doxorubicin 50 mg/m^2 + prednisolone 40 mg/day for 5 days; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease

Figure 1. Aberdeen study protocol and profile (reprinted with permission from the American Society of Clinical Oncology [5]).

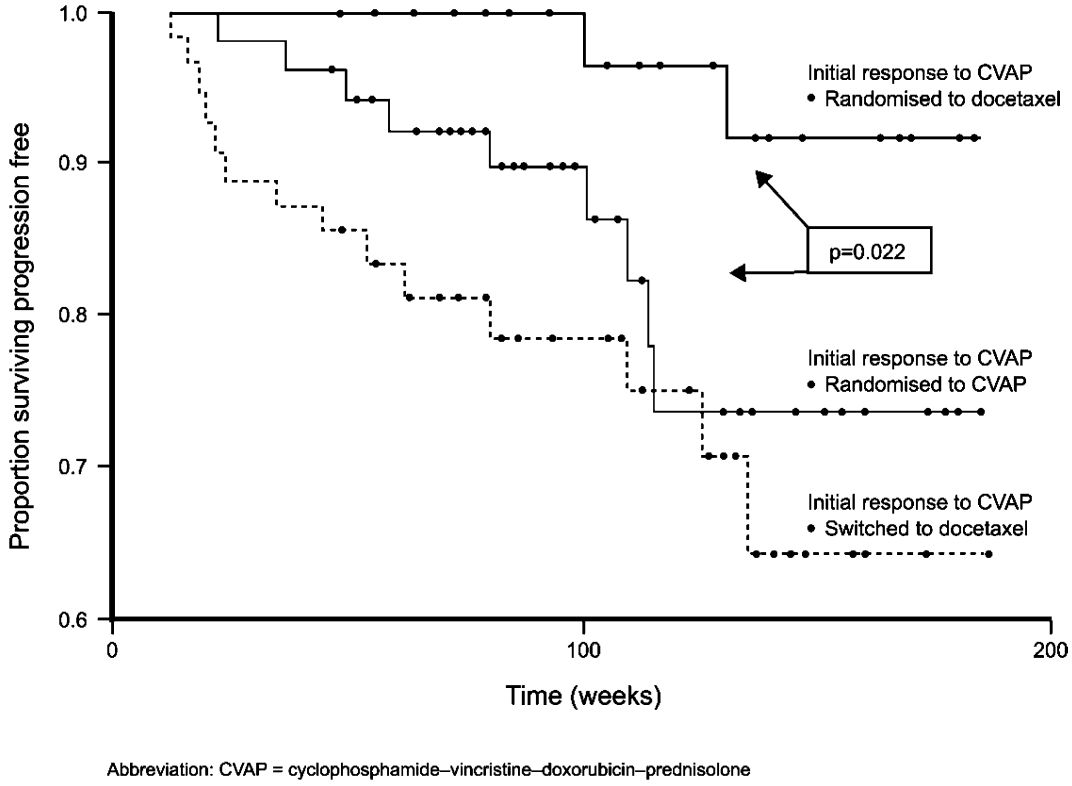


Figure 2. Progression-free survival at a median follow-up of 104 weeks in the Aberdeen study (reprinted with permission from Hutcheon et al. [50]).

Patients in the sequential docetaxel group consequently required less dose reduction in response to toxicity.

These results are very encouraging, with the Aberdeen study being the first to demonstrate significantly increased 5-year survival rates with docetaxel-based primary chemotherapy. However, it is acknowledged that whilst these results are interesting and promising, survival was not a primary endpoint of the study when it was designed and the numbers of patients involved are relatively small.

The large-scale, randomised Phase III NSABP-B27 trial was designed to take the results of NSABP-B18 a step further and evaluate the role of sequential docetaxel administered either preoperatively or postoperatively, following 4 cycles of primary AC [48]. In total, 2411 patients with operable breast cancer (median tumour size 4.5 cm) were included. The study protocol and profile are summarised in Figure 3.

The clinical response was significantly improved with sequential AC plus docetaxel compared with AC alone, with a clinical ORR of 91% versus 86%, respectively ($p < 0.001$), and a complete CR of 64% versus 40%, respectively ($p < 0.001$), being achieved. Furthermore, docetaxel administration precipitated a dramatic increase in the complete pathological response rate (an 87% increase in relative terms) compared with AC alone (26% versus 14%, respectively; $p < 0.001$), and provided a 16% increase in the incidence of lack of involvement of the axillary nodes with tumour (58% versus 51%, respectively; $p < 0.001$).

Pathological breast tumour response was a significant predictor of pathological node status. Overall, ER-negative tumours had a higher response rate than ER-positive tumours (17% versus 8%, respectively), in line with previously published studies. However, patients with both ER-negative and ER-positive tumours achieved significantly higher complete pathological response rates with the addition of docetaxel compared with AC alone. The frequency of breast-conserving surgery was similar between the groups receiving AC plus docetaxel and AC alone.

The improved responses achieved with docetaxel were, however, at the expense of some increased toxicity. Grade 4 toxicity was observed in 10% of patients during treatment with AC and 23% of patients during administration of docetaxel. Febrile neutropenia accounted for most of the difference in grade 4 toxicity between the groups, occurring in 21% of patients receiving docetaxel versus 7% of those receiving AC alone. However, no significant increase in neutropenic infection was observed with docetaxel usage. Non-haematological toxicities were generally mild in both groups (<1% grade 4). In total, 81% of patients completed docetaxel therapy to the planned schedule.

Longer-term data are required to confirm whether the increased pathological response rates in the breast and axilla that can be achieved with docetaxel administration will translate into improved survival, as has been demonstrated in the smaller Aberdeen study [7, 8].

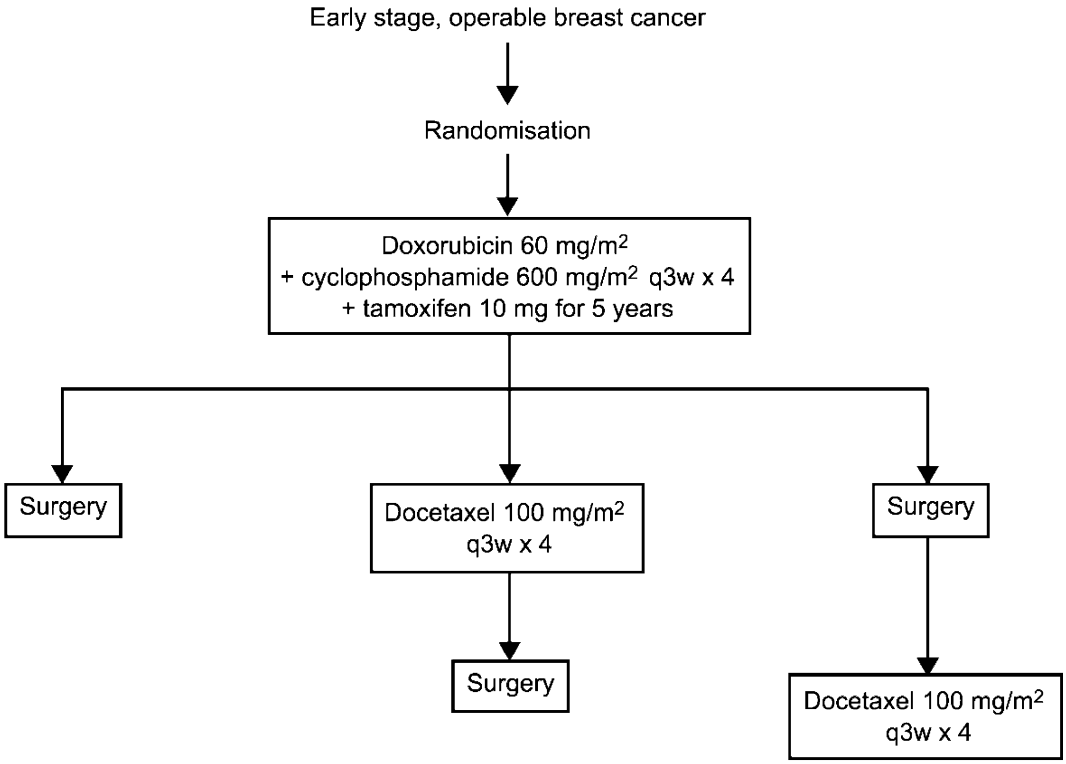


Figure 3. NSABP-B27 study protocol.

Non-anthracycline primary regimens incorporating docetaxel

With the advent of new therapeutic agents and new approaches, non-anthracycline-based primary chemotherapeutic regimens have come into focus. Two studies (published in abstract form to date) demonstrate the potential for docetaxel-based non-anthracycline combinations. A Phase II study of 3-weekly docetaxel plus cisplatin, both at 70 mg/m^2, in 25 patients with LABC demonstrated a particularly high clinical ORR of 96% (CR 52%) and a complete pathological response rate of 20% [51]. A second novel primary regimen comprising docetaxel–cisplatin–trastuzumab was assessed in 33 patients with LABC that was overexpressing *HER-2/neu* [52]. A complete pathological response rate of 22% was documented, together with an exceptionally high rate of lack of involvement of the axillary glands with tumour (56%), and both regimens were well tolerated [51, 52]. The authors suggest that these results may point to a different mode of action when trastuzumab is added to chemotherapy, but further studies are required to understand these relationships and interactions more fully.

Conclusions

The primary chemotherapeutic approach in patients with breast cancer is useful for studying innovative therapies, with the taxane docetaxel of particular interest in this setting. Docetaxel has demonstrated single-agent activity both in dose-dense and traditional schedules, with acceptable tolerability. Furthermore, docetaxel–anthracycline concomitant schedules have shown promise in the Phase II setting, although Phase III studies are needed to confirm whether the good complete pathological response rates achieved will translate into improved overall patient survival.

The randomised Phase II GEPAR-D*U*O study [47] and, more specifically, the Phase III Aberdeen study [5, 8] and Phase III NSABP-B27 study [48] suggest that sequential therapy with docetaxel is superior to anthracycline-based therapy as a means of inducing complete pathological response, a surrogate marker for overall survival. Furthermore, the Aberdeen study has for the first time demonstrated a significant 5-year survival advantage for patients receiving sequential docetaxel therapy.

These data suggest that the continued administration of anthracyclines to patients who show an initial response may no longer be appropriate, with sequential docetaxel being a more effective approach. The GEPAR-D*U*O trial suggests that there might be a benefit for sequential versus concomitant therapy, with significant improvement of complete pathological response rates, although this finding has yet to be confirmed in a Phase III setting.

The question as to whether inclusion of anthracycline is essential in primary chemotherapeutic regimens also requires further study. Even while we wait for additional studies to define the optimal regimen, the findings to date suggest that docetaxel should be considered in the management of all patients receiving primary chemotherapy for large and locally advanced breast cancer.

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