Anti-Cancer Drugs 1999, **10** (suppl 1):S19–S24

Expanding options in breast cancer

John P Crown
St Vincent's Hospital, Dublin, Ireland.

In metastatic breast cancer, docetaxel is the only drug to have shown superior activity to doxorubicin [objective response rates (ORRs) 48 versus 33%] by direct comparison in a randomized trial. Importantly, this greater activity was accompanied by a lower risk of cardiotoxicity. Docetaxel has also proved superior to various combination regimens in patients who had previously failed anthracyclines. In the comparison versus mitomycin C plus vinblastine, survival was significantly prolonged in the docetaxel arm. The combination of paclitaxel with doxorubicin has achieved remarkably high rates of response. However, the combination is cardiotoxic (with the highest response rates reporting an incidence of clinical congestive heart failure in the region of 18%). In comparison, the combination of docetaxel with doxorubicin, while also highly active (ORR > 70%), is relatively non-cardiotoxic (with only one case of clinical congestive heart failure in 96 patients treated). Given that docetaxel appears to be the most active single agent in metastatic breast cancer, there is a compelling case for the drug to be evaluated in the adjuvant setting and such studies are ongoing. [© 1999 Lippincott Williams & Wilkins.]

Key words: Adjuvant, breast cancer, cardiotoxicity, combination, docetaxel.

Introduction

Breast cancer is probably the most chemosensitive of the common adult solid tumors. There is clear-cut evidence of the palliative benefit of chemotherapy in patients with metastatic disease.[1,2] It is likely that survival is prolonged by a median of around 1-year and certain patients who are apparently terminally ill are restored to reasonable health for several years. However, durable chemotherapy-induced remissions are rare to the point of being anecdotal.[3,4] There is therefore a pressing need for improvements in therapy.

Active new agents in breast cancer

A wide range of drugs are active in metastatic breast cancer. These include cisplatin, cyclophosphamide, mitoxantrone, 5-fluorouracil (5-FU) and (historically the most active single agent) doxorubicin. Recent attention has focussed on the activity of several new drugs, most notably the taxanes. Docetaxel as a first-line treatment for metastatic breast cancer has achieved response rates ranging from 52–68%, in phase II trials, and paclitaxel from 32–62%.[5,6] In the second-line setting, the response rates ranged from 2–58% for docetaxel and from 6–48% for paclitaxel.[5,6]

Comparative efficacy versus single-agent doxorubicin

Given these encouraging phase II data, it was incumbent on investigators to compare these new agents against standard therapy in randomized trials. In one important trial (the International TAX303 study), docetaxel 100 mg/m^2 was compared to doxorubicin 75 mg/m^2 in patients who had previously failed chemotherapy containing an alkylating agent.[7,8] In 53% of cases, the prior chemotherapy was for advanced disease. In this study, in which the drugs were administered at what was in effect the maximum tolerated single-agent dose, docetaxel proved substantially more active than doxorubicin (Table 1). The 48% overall response rate (ORR) observed with docetaxel was significantly greater ($p = 0.008$) than that in patients assigned to the doxorubicin arm.

There was no difference in overall survival between the two groups. This can be attributed, at least in part, to the unofficial crossover of patients

Dr Crown has received honoraria and research support from Rhône-Poulenc Rorer.

St Vincent's Hospital, Elm Park, Merrion Road, Dublin 4, Ireland.
Tel: (+353) 1 269 4533; Fax: (+353) 1 269 7949;
E-mail: john.crown@icorg.ie

Table 1. Efficacy (by intention to treat) and tolerability of docetaxel versus doxorubicin in 326 patients who had failed previous alkylating chemotherapy[5,7,8]

	Docetaxel (100 mg/m²)	Doxorubicin (75 mg/m²)
Efficacy		
No. of patients	161	165
Complete response	7%	4%
Partial response	41%	29%
Overall response rate	48%	33%*
Median time to progression	22 weeks	18 weeks**
Safety		
No. of patients	159	163
Febrile neutropenia	6%	12%
Infection	4%	2.5%
Vomiting	3%	12%
Fluid retention	5%	0%
Congestive heart failure	0%	4%
Discontinuation due to toxicity	12%	16%

*$p = 0.008$; **$p = 0.01$.

from the doxorubicin arm of the study into the docetaxel arm. However, the difference between the two drugs in time to treatment failure (median 22 weeks with docetaxel versus 18 weeks with doxorubicin) was significant at the $p = 0.01$ level on the Wilcoxon test.

Single agents have been compared with doxorubicin in three other randomized trials, two involving paclitaxel (using a short or long infusion) and one mitoxantrone.[6,9–12] Given the difference in patient populations, comparisons across trials must be treated with caution. However, it is interesting to note from the four comparative studies that docetaxel is the only agent to have shown clear superiority over doxorubicin (Figure 1).

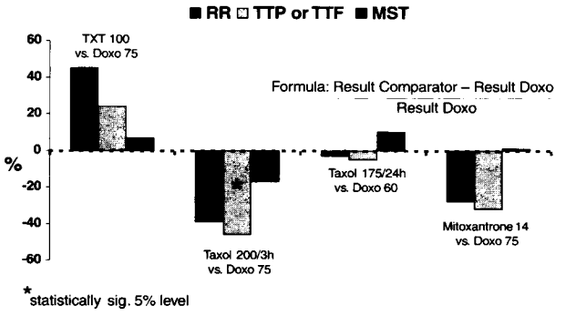

Figure 1. Phase III randomized studies with single agents versus doxorubicin: relative differences.[5–12] RR: response rate, TTP: time to progression, MST: median survival time.

Toxicity versus doxorubicin

Docetaxel also demonstrated an advantage over doxorubicin when the two single agents were compared for toxicity (Table 1).[5,7,8] The rates of febrile neutropenia, infection, vomiting and stomatitis were lower in patients randomized to docetaxel than in those administered doxorubicin. The incidence of neurotoxicity was higher in the docetaxel arm (5 versus 0%), as was the incidence of fluid retention. However, potentially of greatest importance is the risk of cardiotoxicity. None of the docetaxel patients developed clinical congestive heart failure (CHF), while CHF developed in 4% of patients receiving doxorubicin. The relative cardiotoxicity of doxorubicin is supported by data from the EORTC and Intergroup comparisons of the anthracycline versus paclitaxel.[6,9–11] With the 60 mg/m² dose of doxorubicin, 9% of 224 patients exposed developed CHF. This figure was 5% in the EORTC study in which 165 patients received 75 mg/m² doxorubicin.

Docetaxel versus combination chemotherapy in anthracycline failure

Patients who have failed anthracycline chemotherapy represent a group whose metastatic disease is very difficult to manage. In three large, prospective randomized trials, single-agent docetaxel has been compared with combination chemotherapy in these patients (Table 2).[13–18]

Single-agent 100 mg/m² docetaxel proved significantly superior to the comparator regimens of mitomycin plus vinblastine and methotrexate plus 5-FU in terms both of ORRs and median time to

Table 2. Docetaxel 100 mg/m² versus combination regimens following anthracycline failure: the results of three randomized trials[13–18]

Study	No. of patients evaluable for response (both arms)	Response rates (CR + PR) (%)		Median time to progression (weeks)	
Nabholtz[13–16]		Docetaxel	MV	Docetaxel	MV
	392	30	12	19	11
		$p < 0.0001$		$p = 0.001$	
Sjöstrom[17]		Docetaxel	MF	Docetaxel	MF
	282	42	21	27	13
		$p = 0.0001$		$p < 0.001$	
Guastella[18]		Docetaxel	NAF	Docetaxel	NAF
	176	41	39	30	25
		NS		NS	

Comparator regimens: MV, mitomycin/vinblastine; MF, methotrexate/5-flourouracil; NAF, vinorelbine/continuous infusion 5-flourouracil. CR, complete remission; PR, partial remission.

progression. In the study versus mitomycin C plus vinblastine, patients randomized to docetaxel also experienced significantly longer survival (median 11.4 versus 8.7 months; Wilcoxon $p = 0.027$). This result is impressive given the paucity of other data showing that salvage chemotherapy can alter survival. Docetaxel was equi-efficacious with the highly active regimen of continuous infusion 5-FU plus vinorelbine.

New combinations in metastatic disease

Based on the single-agent activity observed with the anthracyclines and the taxanes, it was logical to assess the feasibility of the combination of the two agents. Gianni *et al.* studied a group of patients with no prior chemotherapy (including no prior adjuvant chemotherapy) who received paclitaxel 200 mg/m² in combination with doxorubicin 60 mg/m².[19] Although the ORR of 94% was extremely high (even in these chemotherapy-naive patients), so too was the 21% incidence of CHF. Subsequently numerous studies with varying doses, schedules and sequence of administration, limiting the median cumulative dose of doxorubicin have been undertaken with the paclitaxel/doxorubicin combination in an attempt to reduce the incidence of CHF.[20,21]

Given their different toxicity profiles and evidence of non-cross resistance, the combination of docetaxel with doxorubicin was studied. In a dose-finding study in 42 patients (59% of whom had had prior adjuvant therapy), Dieras *et al.* found neutropenia to be the dose-limiting toxicity.[22–24] Grade 3/4 non-hematological toxicities were uncommon and the combinations of either 50 mg/m² doxorubicin plus 75 mg/m² docetaxel or 60 mg/m² of both drugs were recommended for further phase II studies. Importantly, although left ventricular ejection fraction decreased in a small number of patients, Dieras *et al.* found no cases of CHF, even among the 23 evaluable patients exposed to a cumulative dose of greater than 360 mg/m² doxorubicin. The ORR in this study was 71%, and 86% at the dose levels recommended for further studies. The phase II portion (docetaxel 75 mg/m² combined with doxorubicin 50 mg/m²) of this study has confirmed these results, with 0% CHF (median cumulative dose doxorubicin 401 mg/m², range: 49–606 mg/m²) and an ORR of 76%.[23,24]

Nabholtz *et al.* studied docetaxel 75 mg/m² in combination with both doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m² (the 'TAC' regimen) in 52 patients, 39% of whom had received prior adjuvant chemotherapy.[25] An ORR of 73% was reported in 48 evaluable patients. The cardiotoxicity of the triple regimen was again relatively slight, with only one case of clinical CHF reported (in a patient with a cumulative doxorubicin exposure of 400 mg/m²).

Based on these encouraging results two phase III randomized trials were undertaken. The first trial compared doxorubicin (50 mg/m²) plus docetaxel (75 mg/m²) to doxorubicin (60 mg/m²) plus cyclophosphamide (600 mg/m²) in patients with metastatic breast cancer who had not received prior chemotherapy for metastatic disease; however, prior adjuvant therapy was allowed. The second study compared docetaxel (75 mg/m²) plus doxorubicin (50 mg/m²) plus cyclophosphamide (500 mg/m²) to 5-FU (500 mg/m²) plus doxorubicin (50 mg/m²) plus cyclophosphamide (500 mg/m²). Results from these trials are awaited.

Adjuvant therapy

There is an urgent need for promising new combinations to be studied in the adjuvant setting. This applies to the range of new drugs. However, the case for the inclusion of docetaxel is particularly strong given its high level of activity in metastatic breast cancer, including anthracycline-resistant disease and the lack of cardiotoxicity observed from the combination studies with anthracyclines. The latter observation provides a powerful rationale for the joint deployment of doxorubicin and docetaxel in combination or sequential schedules.

The initial results of the CALGB trial of adjuvant therapy in node-positive disease, in which paclitaxel is administered following doxorubicin and cyclophosphamide, appear promising.[26] Although the results of a direct comparison between docetaxel and paclitaxel are still awaited, the body of available data indicate that docetaxel is at least as and possibly more active than paclitaxel in advanced disease. This suggests that benefit should also arise from use of the drug in the adjuvant setting.

With these considerations in mind, a pilot evaluation of certain candidate adjuvant therapy regimens was undertaken in patients with node-positive breast cancer. The aim was to use maximum doses of effective agents in sequence: the protocol therefore called for three cycles of doxorubicin 75 mg/m^2 to be followed by three cycles of docetaxel 100 mg/m^2 and finally three cycles of CMF. Centers in Brussels and Dublin studied both 2- and 3-week schedules for doxorubicin and docetaxel. The former schedule resulted in unacceptable mucocutaneous toxicity. The 3-week schedule, however, was safe and feasible, and has now been included in a major international trial (the 'BIG' Study). In this study, more than 2000 patients will be randomized to four arms: doxorubicin followed by CMF, doxorubicin followed by docetaxel and then CMF, doxorubicin and docetaxel administered simultaneously and followed by CMF, and doxorubicin plus cyclophosphamide followed by CMF. This trial is designed to evaluate both the contribution of docetaxel and the possibly different effects of sequential delivery versus drug combination.

High-dose chemotherapy

Following the development of autologous bone marrow transplantation (ABMT), which allowed substantial dose escalation, and the deployment of colony stimulating factors, which shortened the period of neutropenia, the use in the late 1980s and early 1990s of cytokine-mobilized peripheral blood progenitor cells dramatically reduced toxic mortality and facilitated multiple high-dose chemotherapy.

Both filgrastim and lenograstim effectively mobilize peripheral blood progenitor cells (PBPCs). However, evidence from two recent studies in which patients received both cytokines in a balanced crossover design suggests that, on a microgram for microgram basis, lenograstim mobilizes significantly more progenitors than filgrastim.[27,28] This was evident both in the mean peak CD34$^+$ cell count and in colony-forming units.

In metastatic breast cancer, the use of high-dose chemotherapy with PBPC or ABMT support as first-line treatment or (more commonly) as consolidation therapy in responders has resulted in exceptionally high complete remission rates of 50–70%. Between 10 and 25% of these complete responses appear durable. In the adjuvant therapy of patients with multiple lymph node involvement, up to 70% 5-year disease-free survival has been reported in patients treated with high-dose chemotherapy. Such results are far superior to those in historical controls. Nevertheless, there is clear potential for selection bias in the recruitment of patients to high-dose studies and hence an urgent need for the technique to be subjected to randomized trial.

In the first such trial, patients received either high- or conventional-dose chemotherapy as initial therapy for metastatic disease.[29] Those treated with high-dose chemotherapy enjoyed a significant advantage in both disease-free and overall survival. In the trial by Peters *et al.*, 98 patients who achieved complete response after intensive doxorubicin-based therapy were randomized either to immediate high-dose consolidation therapy or to an observation group, with high-dose treatment reserved for salvage therapy on relapse.[30] Disease-free survival was lengthened by high-dose chemotherapy (0.9 versus 0.3 years). However, overall survival was longer in patients assigned to observation followed by salvage transplantation (3.2 versus 1.9 years).

In the ongoing European randomized Breast cancer Dose Intensity Study (EBDIS 1), patients are being randomized to either four cycles of docetaxel plus doxorubicin followed by CMF or to docetaxel plus doxorubicin for three cycles followed by two high-dose chemotherapy cycles involving first ICE and then CPA plus thiotepa.[31] This trial should establish whether high-dose chemo-

therapy is superior to the best currently available conventional therapy and will not be subject to the potential bias involved in transplanting only those patients who are initial responders.

The potential benefit of high-dose chemotherapy is also being studied in the adjuvant setting. In the trial of Rodenhuis *et al.*, the 35 patients with high-risk operable breast cancer who underwent high-dose adjuvant therapy showed no better survival than patients randomized to conventional therapy.[32] Similarly, high-dose tandem combination chemotherapy was found not to affect disease-free or overall survival in the study by Hortobagyi *et al.*[33] In this trial, 78 patients with high-risk primary breast cancer were randomized and followed for a median of 53 months.

In the far larger Anglo-Celtic study, it is intended that 600 patients with four or more positive lymph nodes will be randomized following surgery and four cycles of doxorubicin to either eight cycles of CMF or high-dose therapy involving CPA and CPA plus thiotepa. More than 500 patients have now been enrolled into this trial. Similarly large studies are ongoing in other countries in Europe and North America. Such trials are the only means of establishing the benefit or otherwise of high-dose chemotherapy in the adjuvant or advanced settings and participation in them should be strongly encouraged.

Novel schedules

Recently, there has been considerable interest in the possible schedule-dependency of chemotherapy in breast cancer. This is reflected, for example, in trials of infusional 5-FU and weekly paclitaxel. Loeffler *et al.* have recently presented interesting preliminary data suggesting that weekly doses of 35–43 mg/m^2 docetaxel can be administered with reduced myelosuppression but undiminished activity (ORRs ~50% in second-line therapy).[34] The dose-limiting toxicity with such schedules is fatigue/asthenia. Neuropathy, however, is uncommon. Similar results of reduced toxicity with maintained efficacy were observed in the weekly schedules studies by Hainsworth *et al.* and Lück *et al.*[35–37] Further investigation of weekly docetaxel is warranted in single-agent and combination studies.

The 1990s have been an exciting decade for the advancement of breast cancer treatment. The taxanes have played an important role in this development and results from the adjuvant phase III trials are awaited to see if these agents will further enhance the curative potential of treatment in this early setting. Other areas under evaluation include high-dose chemotherapy, gene therapy and dose densification. These approaches and new agents are expanding the options for the treatment of breast cancer.

References

1. Early Breast Cancer Trialist's Collaberative Group. Systemic treatment of breast cancer by hormonal, systemic or immune therapy: 133 randomized trials involving 31 000 recurrences and 24 000 deaths among 75 000 women. *Lancet* 1992; **339**: 1.
2. Fossati R, Confalonieri C, Torri V, *et al.* Cytotoxic and hormonal treatment for metastatic breast cancer: A systematic review of published randomized trials involving 31 510 women. *J Clin Oncol* 1998; **16**: 3439–60.
3. Piccart M. Treatment of advanced breast cancer: current status. *Anti-Cancer Drugs* 1996; **7**: 5–7 (suppl 2).
4. Henderson IC. Chemotherapy for metastatic disease. In Harris JR, Hellman S, Henderson IC, Kinney DW (eds). *Breast diseases*, Philadelphia, PA: Lippincott 1993: 604–65.
5. Crown J. Evolution in the treatment of advanced breast cancer. *Semin Oncol* 1998; **25**: 12–17 (suppl 12).
6. Paridaens R. Efficacy of paclitaxel or doxorubicin used as single agents in advanced breast cancer: a literature survey. *Semin Oncol* 1998; **25**: 3–6 (suppl 12).
7. Chan S, Friedrichs K, Noel D, *et al.* A randomized phase III study of Taxotere (T) versus doxorubicin (D) in patients (pts) with metastatic breast cancer (MBC) who have failed alkylating containing regimens: preliminary results. *Proc Am Soc Clin Oncol* 1997; **16**: 144a (abstr 540).
8. Chan S, Friedrichs K, Noel D, *et al.* A phase III study of docetaxel versus doxorubicin in patients with metastatic breast cancer who have failed an alkylating containing regimen. *Breast Cancer Res Treat* 1997; **46**: 23 (abstr 1).
9. Paridaens R, Bruning P, Klinn J, *et al.* Taxol (T) versus doxorubicin (D) as first line chemotherapy (CT) in advanced breast cancer (ABC): An EORTC randomized study with crossover. *Eur J Cancer* 1997; **33**: S145 (abstr 645).
10. Paridaens R, Bruning P, Klinn J, *et al.* An EORTC crossover trial comparing single-agent Taxol (T) versus doxorubicin (D) as first- and second-line chemotherapy (CT) in advanced breast cancer (ABC). *Proc Am Soc Clin Oncol* 1997; **16**: 154a (abstr 539).
11. Sledge GW, Neuberg D, Ingle J, *et al.* Phase III trial of doxorubicin vs paclitaxel vs doxorubicin + paclitaxel as first line chemotherapy for metastatic breast cancer: an intergroup trial. *Proc Am Soc Clin Oncol* 1997; **16**: 2 (abstr 2).
12. Henderson IC, Allegra JC, Woodcock T, *et al.* Randomized clinical trial comparing mitoxantrone with doxorubicin in previously treated patients with metastatic breast cancer. *J Clin Oncol* 1989; **7**: 560–71.
13. Aapro M. Docetaxel versus doxorubicin in patients with metastatic breast cancer who have failed alkylating chemotherapy: a preliminary report of the randomized phase III trial. *Semin Oncol* 1998; **25**: 7–11 (suppl 12).
14. Nabholtz JM, Thuerlimann B, Bezwoda WR, *et al.* Taxotere (T) versus mitomycin C–vinblastine (MV) in patients (pts) with metastatic breast cancer (MBC) who have failed anthracycline (ANT) containing regimen. *Breast Cancer Res Treat* 1997; **46**: 93 (abstr 401).

15. Nabholtz JM, Thuerlimann B, Bezwoda WR, *et al.* Taxotere (T) improves survival over mitomycin C vinblastine (MV) in patients (pts) with metastatic breast cancer (MBC) who have failed anthracycline (ANT) containing regimen: final results of a phase III randomized phase study. *Proc Am Soc Clin Oncol* 1998; **17**: 101a (abstr 390).
16. Nabholtz JM, Crown J. Phase III study of single-agent docetaxel in patients with metastatic breast cancer who have progressed despite previous chemotherapy regimens: Preliminary results. *Semin Oncol* 1998; **25**: 4–9 (suppl 13).
17. Sjöström J, Mouridsen H, Pluzanska A, *et al.* Taxotere (T) versus methotrexate–5-fluorouracil (MF) in patients with advanced anthracycline-resistant breast cancer: preliminary results of a randomized phase III study by Scandanavian Breast Cancer Group. *Proc Am Soc Clin Oncol* 1998; **17**: 111a (abstract 427).
18. Monnier A, Bonneterre J, Roche H, *et al.* Phase III study: Taxotere (TXT) versus 5-fluorouracil + navelbine (FUN) in patients (pts) with metastatic breast cancer (MBC) as 2nd line chemotherapy (CT) (preliminary results). In: *23rd European Society for Medical Oncology Congress.* Athens, Greece 1998: abstr 580.
19. Gianni L, Munzone E, Capri G, *et al.* Paclitaxel by 3-hour infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer: high anti-tumor efficacy and cardiac effects in a dose-finding study. *J Clin Oncol* 1995; **13**: 2688–2699.
20. Gianni L, Dombernowsky P, Sledge G, *et al.* Cardiac function following combination therapy with Taxol (T) and doxorubicin (A) for advanced breast cancer (ABC). *Proc Am Soc Clin Oncol* 1998; **17**: 444 (abstr).
21. Sparano JA. Compilation of phase I and II trial data of docetaxel and doxorubicin in the treatment of advanced breast cancer and other malignancies. *Semin Oncol* 1998; **25**: 10–15 (suppl 13).
22. Dieras V. Docetaxel in combination with doxorubicin: A phase I dose-finding study. *Oncology* 1997; **11**: 17–20.
23. Dieras V, Misset JL, Bourgeois H, *et al.* Docetaxel (Taxotere) (T) and doxorubicin (A) as 1st line CT of metastatic breast cancer (MBC). High activity and lack of cardiotoxicity after 29 months follow-up. In: *23rd European Society for Medical Oncology Congress.* Athens, Greece 1998: abstr 79P.
24. Misset JL, Nabholtz JM, Dieras V, *et al.* Long term follow-up in metastatic breast cancer (MBC) pts treated with docetaxel (Taxotere) (T) in combination with doxorubicin (A): results of two studies. In: *23rd European Society for Medical Oncology Congress.* Athens, Greece 1998: abstr 119.
25. Nabholtz JM, Mackey JR, Smylie M, *et al.* Phase II study of Taxotere (docetaxel), doxorubicin and cyclophosphamide (TAC) in the treatment of metastatic breast cancer. *Proc Am Soc Clin Oncol* 1997; **16**: 148a (abstr 519).
26. Henderson IC, Berry D, Demetri G, *et al.* Improved disease-free survival (DFS) and overall survival (OS) from the addition o sequential paclitaxel (T) but not from escalation of doxorubicin (A) dose levels in the adjuvant chemotherapy of patients (pts) with node positive primary breast cancer. *Proc Am Soc Clin Oncol* 1998; **17**: 101a (abstr 390A).
27. Hoglund M, Smedmyr B, Bengtsson M, *et al.* Mobilization of $CD34^+$ by glycosylated and nonglycosylated G-CSF in healthy volunteers: a comparative study. *Eur J Haematol* 1997; **59**: 177–83.
28. Watts MJ, Addison I, Long SG, *et al.* Crossover study of the hematological effects and pharmacokinetic of glycosylated and non-glycosylated G-CSF in healthy volunteers. *Br J Haematol* 1998; **98**: 474–9.
29. Bezwoda WR, Seymour L, Dansey RD. High-dose chemotherapy with hematopoietic rescue as primary treatment for metastatic breast cancer: a randomized trial. *J Clin Oncol* 1995; **13**: 2483–9.
30. Peters WP, Jones RB, Vredenburgh J, *et al.* A large prospective, randomized trial of high-dose combination alkylating agents (CPB) with autologous cellular support (ABMS) as consolidation for patients with metastatic breast cancer achieving complete remission after intensive doxorubicin based induction therapy (AFM). *Proc Am Soc Clin Oncol* 1996; **15**: 121 (abstr 149).
31. Crown J, Baselga J, Leonard R, *et al.* European randomized breast cancer dose-intensity study (EBDIS): results of pilot evaluation. *Proc Am Soc Clin Oncol* 1998; **17**: 514 (abstr).
32. Rodenhuis S, Richel DJ, van der Wall E, *et al.* Randomized trial of high-dose chemotherapy and haemopoietic progenitor-cell support in operable breast cancer with extensive axillary lymph-node involvement. *Lancet* 1997; **352**: 515–21.
33. Hortobagyi GN, Buzdar AU, Champlin R, *et al.* Lack of efficacy of adjuvant high-dose (HD) tandem combination chemotherapy (CT) for high-risk primary breast cancer (HRPBC)—a randomized trial. *Proc Am Soc Clin Oncol* 1998; **17**: 471 (abstr).
34. Loeffler TM, Freund W, Hausamen TU. Activity of weekly Taxotere (TXT) in patients with metastatic breast cancer. *Proc Am Soc Clin Oncol* 1998; **17**: 113a (abstr 435).
35. Hainsworth JD, Burris HA, Erland JB, *et al.* Phase I trial of docetaxel administered by weekly infusion in patients with advanced refractory cancer. *J Clin Oncol* 1998; **16**: 2164–8.
36. Burris H. Weekly schedules of docetaxel. *Semin Oncol* 1998; **25**: 21–3 (suppl 13).
37. Lück HJ, Donnè S, Glaubitz M, *et al.* Phase I study of weekly docetaxel (Taxotere) in heavily pretreated breast cancer patients. *Eur J Cancer* 1997; **33**: S158 (abstr 703) (suppl 8).