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Vinorelbine, Epirubicin and Fluorouracil as First-Line Therapy in Metastatic Breast Cancer

A Phase II Trial

Inkeri Elomaa, Heikki Joensuu and Carl Blomqvist

From the Cancer Center, University Hospital of Helsinki, Finland (I. Elomaa, H. Joensuu) and the Department of Oncology, University of Uppsala, Sweden (C. Blomqvist)

Correspondence to: Inkeri Elomaa, Cancer Center, University Hospital of Helsinki, Finland, P.O. Box 180, FI-00029 HUCH, Finland. Tel: +358 9 4716 0257. Fax: +358 9 4717 4201. E-mail: inkeri.elomaa@hus.fi

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A phase II study was conducted to assess the toxicity and response rate of vinorelbine (NavelbineR) combined with epirubicin and fluorouracil (NEF) in metastatic breast cancer. Vinorelbine was delivered at a dose of 25 mg/m^2 on days 1 and 8, epirubicin at 60 mg/m^2 on day 1 and fluorouracil at 600 mg/m^2 on day 1, at 3-week intervals. Forty consecutive ambulant patients with breast cancer with measurable metastases were treated with a total of 310 cycles (median 8) as first-line therapy. The objective response rate was 83% (95% CI 71–95) (6/40 CR 15%, 27/40 PR 68%). In 3 patients, CNS metastases were detected during NEF therapy those who had a partial response in their visceral metastases. Median time to progression was 13 months (95% CI 7–19) and estimated median survival time was 32 months. The main dose-limiting adverse effect, grade III–IV haematological toxicity, was reported in 92% of patients. One patient died of neutropenic sepsis. Grade III infections requiring hospitalization were observed in 8 patients (20%). Half of the patients complained of mild constipation, nausea or stomatitis, which were easily managed. Almost all patients had grade III alopecia. One patient with previous adjuvant anthracycline therapy (CEF × 9 two years earlier) developed fatal grade IV cardiac failure associated with pulmonary emboli 2 months after completion of NEF therapy (PR with 6 cycles). In line with the observations of others conducting phase II first-line trials combining vinorelbine and epirubicin, it is concluded that the NEF regimen is effective in metastatic breast cancer. Haematological toxicity, however, requires dose reductions in many patients. Furthermore, careful monitoring of cardiac function is necessary, particularly in patients who received prior adjuvant anthracycline therapy.

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Vinorelbine is one of the new agents with single-agent activity equivalent to that of many standard cytotoxic agents, including doxorubicin, epirubicin and taxanes, with a response rate in first-line treatment of 40–60% (1–3). Many phase II trials have demonstrated reasonable results in terms of efficacy, with an objective response rate of over 70% and a median survival time of over 20 months when vinorelbine is combined with an anthracycline (2, 4–11). Since fluorouracil, like anthracyclines, potentiates the antitumour activity of vinorelbine (12–17), we tested the tolerability and efficacy of the three-drug regimen, vinorelbine-epirubicin-fluorouracil.

MATERIAL AND METHODS

A phase II study was conducted between March 2000 and November 2001 at the Cancer Center, University of Helsinki. Forty consecutive ambulant patients (ECOG of 0–2), <75 years of age, with histologically confirmed measurable metastastic breast cancer, were included in the study in order to estimate the response rate with approximately 30%:s accuracy ($\pm$15%). Patients treated with adjuvant chemotherapy more than 12 months earlier were included, as well as women treated with hormonal therapy, but patients who had received prior chemotherapy for metastatic disease were not eligible. The characteristics of patients, previous treatments and metastatic sites are listed in Table 1. The design and doses of the vinorelbine (NavelbineR) combined with epirubicin and fluorouracil (NEF) regimen are presented in Table 2. Treatment cycles were repeated every 3 weeks.

Haematological and non-haematological toxicities were registered on the days of treatment and nadir values on days 11–15. If patients experienced dose-limiting toxicities, which were defined as WHO grade III neutropenia associated with infection greater than grade II and/or constipation greater than grade II, the vinorelbine dose was reduced by 20% and the epirubicin dose by 50%. Similarly, the

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Table 1

Pretreatment characteristics

Age[#]	53 [32–69]
Surface area[#]	1.75 [1.5–2.0]
Postmenopausal	34 (85)
ER positive	25 (63)
PR positive	22 (55)
N positive	24 (60)
Previous treatments	
Adjuvant	
CMF	14 (35)
CEF	7 (18)
AE	14 (35)
None	14 (35)
Metastases AI	12 (30)
Metastastic organs involved	
1	14 (35)
2	14 (35)
3	8 (20)
4	4 (10)
Bone	21 (53)
Lung	14 (35)
Liver	29 (73)
Viscera	33 (83)
Soft tissue	15 (38)

[#]Median [range], number of patients (%).
Abbreviations: AE = antioestrogens; AI = aromatase inhibitors.

fluorouracil dose was reduced by 25% in the case of stomatitis, mucositis or diarrhoea greater than grade II. Treatment was delayed if necessary until recovery to a neutrophil count $> 0.5 \times 109$/L and/or a platelet count $> 50 \times 109$/L. All patients underwent a 12-lead ECG and heart/chest x-ray before they entered the study. If there were any cardiac symptoms, an echocardiograph had to be performed. Only patients without any significant vascular or heart disease, e.g. uncontrolled hypertension, documented myocardial infarction, congestive heart disease, unstable angina or ventriculat/atrial arrhytmias, were included.

Response to treatment was assessed according to the UICC criteria for every 3 cycles, with repetition of the clinical, laboratory, or radiologic assessments (x-rays, ultrasound, computed tomography, or MRI) done at baseline. Treatment was recommended to be continued until progressive disease (PD) stage or until the total epirubicin dose of 1 000 mg/m^2 had been reached, but treatment could be discontinued earlier on clinical judgement and/or at the patient's request, if there were serious side effects. If the maximum epirubicin dose and/or objective response had been reached, treatment was continued with hormonal treatment in oestrogen receptor-positive postmenopausal patients. In the case of PD, taxanes were recommended. Time to progression (TTP) and overall survival (OS) were estimated using the Kaplan–Meier method. The study was approved by the local ethics committee.

RESULTS

Tolerability and toxicity

The medium dose intensity (mg/m^2) per course was 80% and per time 72% of that planned for vinorelbine and epirubicin. A total of 310 cycles (median, 8 per patient) were given. None of the patients received more than 850 mg/m^2 epirubicin. The number of cycles per patient and haematological nadir values are presented in Table 2.

The main dose-limiting adverse effect was grade III–IV haematological toxicity, which was seen in 92% of the patients. Grade III infection requiring hospitalization and antimicrobic therapy occurred in 8 patients (20%); all of these patients recovered. One patient died from septic shock (grade IV infection). Grade III alopecia was seen in almost all patients. Nausea, stomatitis, constipation and local irritation at the infusion site were generally mild and were seen in half of the patients (Table 3). Therapy was interrupted because of these symptoms in 3 patients, at

Table 2

Design of the NEF regimen, dose intensity, number of cycles and nadir values

Doses (mg/m^2) in a 3-week cycle	Vinorelbine	Epirubicin	Fluorouracil	
Day 1	25	60	600	
Day 8	25	–	–	
Dose intensity (median %) per				
Course	80	80	88	
Time	72	73	78	
No. of cycles given to patients				
	1–6 cycles	7–9 cycles	10–12 cycles	
	14 (35%)	18 (45%)	8 (20%)	
Haematological nadir values, median and range				
	Hb	Leucocytes	Neutrophils	Platelets
	104	1,4	0,2	174
	(70–137)	(0.7–4.7)	(0.10–2.3)	(65–353)

Table 3

Haematological and non-haematological toxicity (percent of patients)

WHO	0	1	2	3	4
Haemat.	0	3 (8)	0	4 (10)	33 (83)
Alop.	1 (3)	0	0	12 (30)	27 (68)
Cardiac	0	0	0	1 (3)	1 (3)
Constip.	12 (30)	23 (58)	4 (10)	1 (3)	0
Infect.	26 (65)	2 (5)	3 (8)	8 (20)	1 (3)
LI[#]	21 (53)	18 (45)	1 (3)	0	0
Nausea	14 (35)	19 (48)	6 (15)	1 (3)	0
Neurot.[#]	36 (90)	3 (8)	1 (3)	0	0
Pain[#]	28 (70)	9 (23)	1 (3)	0	0
Stomat.	15 (38)	22 (55)	1 (3)	2 (5)	0

Abbreviations: [#]LI = Local irritation; neurot = paresthesia; pain = abdominal colics and myalgia.

their own request, (Table 4). Their therapy was continued with aromatase inhibitors.

Two patients developed heart failure after completion of NEF, both with an objective response (Table 4). Both patients had received CEF as adjuvant therapy—the first patient received 9 courses (cumulative epirubicin dose 528 mg/m^2) 2 years earlier and the second patient 8 courses (cumulative epirubicin dose 482 mg/m^2) 7 years earlier.

In the first patient, grade IV cardiac toxicity occurred 2 months after completion of 6 NEF courses (cumulative epirubicin dose of 798 mg/m^2) and was associated with deep venous thrombosis and pulmonary emboli. The patient died of congestive heart failure with a left ventricular ejection fraction of 25% (echocardiography). The patient had received radiation from tangential opposing fields to the remaining breast after sector resection of a left-sided breast cancer (photons 6 MeV, 50 Gy/2 Gy) on completion of systemic adjuvant therapy. The myocardium dose was estimated to be <1 Gy. The second patient developed grade III heart toxicity with a left ventricular ejection fraction of 25%. Her cardiomyopathy occurred 2 months after discontinuation of 8 NEF courses (cumulative epirubicin dose of 849 mg/m^2) simultaneously with a non-leucopenic pulmonary infection. The patient was treated with ACE inhibitors, beta-blockers and diuretics, resulting in recovery of myocardial function. The patient had bilateral breast cancers operated on by mastectomy and irradiated after completion of adjuvant CEF cycles, 50 Gy/2 Gy to the fields to both thoracic walls (electrons 6 MeV) and to lymph nodes in the parasternal (electrons 9 MeV), axillary and supraclavicular regions (photons 6 MeV). The estimated myocardium dose was <1 Gy.

Table 4

Treatment interruptions and complications

Causes of interruption	
Grade II n+v+s+c	1 patient (6 cycles—PR)
Grade III n+v+s	1 patient (4 cycles—PR)
Grade III constip	1 patient (6 cycles—PR)
Complications	
Infection	
Grade IV	1 patient (1 cycle—NE[#])
Heart failure	
Grade IV	1 patient (cumul. epi* 798 mg/m^2—PR[##]) 9 × CEF (528 mg/m^2); 6 × NEF (270 mg/m^2)

n+v+s+c = Nausea+vomitus+stomatitis+constipation.
[#]The patients died of neutropenic sepsis.
[##]The patient died of heart failure with an ejection fraction of 25% two months after completion of NEF therapy.
*CEF as adjuvant therapy.

Treatment response, time to progression and survival

The overall response rate was 83% (6/40 CR (complete response) 15%; 27/40 PR (partial response) 68%)(95% CI 71–95) (Table 5). One patient was non-evaluable, because she died of neutropenic sepsis after the first NEF cycle. The response rates to NEF were similar in patients with and without prior adjuvant CEF. Three patients had a PR in visceral metastases, but developed CNS metastases during NEF therapy; in two of these patients meningeal metastases were detected after the 5th and the 9th cycles, respectively; in one of them brain metastases were found after 4 cycles. The median time to progression was 13 months (95% CI 7–19%) for all patients and for those with no change (NC) (6/40) 12 months (95% CI 7–19). Median survival time was 32 months (it was not possible to estimate the CI because of the short follow-up) (Figs. 1 and 2).

DISCUSSION

While breast cancer is generally sensitive to initial treatment, resistance almost always develops in metastatic disease. The efficacy of treatment deteriorates rapidly with more lines of therapy. Efforts have therefore been made to give first-line treatment that will maximize tumour response, but with acceptable toxicity. According to the present results, the NEF regimen seems to fulfil both these requirements.

The NEF combination was clearly active with an objective response rate of 83% (95% CI 71–95%), which is in line with other phase II trials using vinorelbine and anthracycline (ORR 67–78%) (2, 4–10) or after combining them with cyclophosphamide (11).

The only trial in which vinorelbine and epirubicin were combined with fluorouracil delivered fractionated doses of N 25 mg/m^2, E 35–40 mg/m^2 and F 350 mg/m^2 on days 1 and 8 every 3 weeks (17). In this trial the response rate was 70% (CR 14%, PR 56%), and the median TTP and OS rates (7 and 14 months, respectively) were shorter than those in our study (13 and 32 months, respectively). The less intensive pretreatment and endocrine therapy given after

Table 5

Treatment response

Response rate	OR (95% CI)	CR	PR	NC	NE
% All patients	83 (71–95)	15	68	15	2
n = 40	33	6	27	6	1
% After prior adjuvant CEF	71	14	58	14	14
n = 7	5	1	4	1	1
% After no adjuvant CEF	85	15		5	–
n = 33	28	5	23	5	–

Abbreviations: OR = overall response; CR = complete response; PR = partial response; NC = no change; NE = not evaluable.

discontinuation in our study may have contributed to our more favourable results. However, the fractionated NEF combination was better tolerated than our NEF regimen and no fatal toxicities occurred in the fractionated NEF.

The main dose-limiting adverse effect was grade III or IV haematological toxicity, which occurred in the majority of the patients. Although neutropenia was generally rapidly reversible, 20% of the patients had to be hospitalized for neutropenic fevers. One of our patients died from septic shock (grade IV infection). The fractionated NEF caused grade III or IV neutropenia in only 15% of patients (17). Neutropenia has been a major problem in the two-drug combination studies with anthracyclines and vinorelbine as well (6, 7, 9, 10). In the study by Spielmann et al. (4) in which vinorelbine was given 25 mg/m^2 on days 1 and 8 and doxorubicin 50 mg on day 1 at 4-week intervals, grade III or IV neutropenia was observed in 41% of patients. Fifty-six percent (50/89) of the patients developed fever and four patients experienced neutropenic sepsis, two of them being fatal. In a randomized study by Norris et al. (1), grade III or IV granulocytopenia occurred in 88% and neutropenic fever in 15% of the patients in the vinorelbine (25 mg/m^2 on days 1 and 8)+doxorubicin (50 mg/m^2 on day 1) group, whereas the corresponding figures were 86% and 10% in the doxorubin (70 mg/m^2 on day 1) arm. There were no fatal cases of neutropenic fevers.

Cardiotoxicity grade I–II was observed in 0–23% and grade III–IV in 0–7% of patients when anthracycline was combined with vinorelbine (1, 4, 8, 9, 18–22). Cardiotoxicity was fatal in 3 patients (2%) in phase II trials (4) but in none of the patients in phase III trials in the vinorelbine-anthracycline arm (1, 19–22). In our study, 2 patients experienced cardiac damage, which was of grade IV and fatal in the first patient and grade III but manageable in the second patient. Both patients had previously received CEF as adjuvant therapy (the first patient receiving 9 cycles; the second patient 8 cycles). In addition to adjuvant anthracycline, predisposing factors to a cardiac failure were pulmonary emboli in the first patient and pulmonary infection in the second patient. Since cardiotoxicity was not found in association with single-agent vinorelbine in phase I and II studies elsewhere (3, 4) and since the toxicity occurred after several cycles, as in the above-mentioned study (4), it would seem that cardiotoxicity is related to the cumulative epirubicin dose. The maximum epirubicin dose $<1\,000$ mg/m^2 recommended in the present trial was not exceeded (798 and 849 mg/m^2, resp.), but this dose seems to be too high, particularly in patients who have had previous

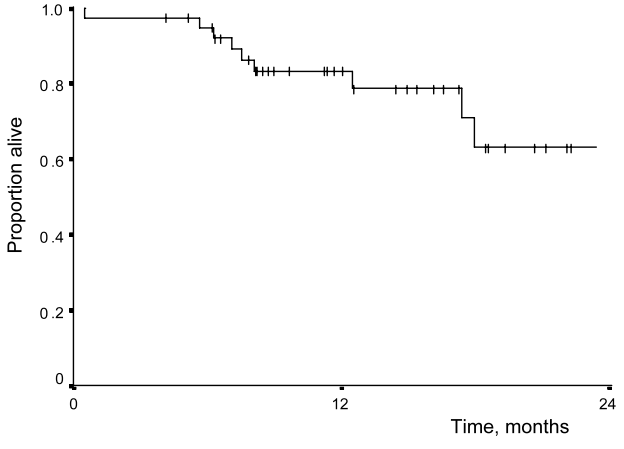

Fig. 1. Estimated median overall survival.

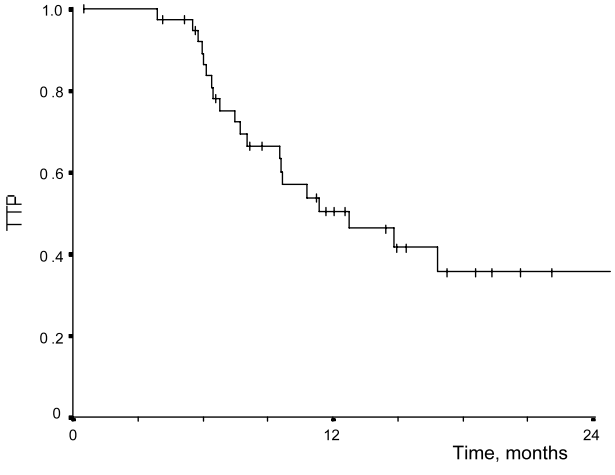

Fig. 2. Time to progression.

anthracycline as adjuvant therapy. The part played by locoregional radiation in our two cases of cardiotoxicity was probably minimal (23). Monitoring of left ventricular ejection fraction either by echocardiography or radionuclide ventriculography might be one way of avoiding the cardiotoxicity of NEF.

Other toxic effects (constipation, abdominal colics, local vein irritation, nausea and stomatitis) were mild and manageable.

Although our results are encouraging, the role of vinorelbine in the treatment of breast cancer still needs to be defined. Three randomized phase III trials have failed to demonstrate any superiority of vinorelbine-anthracycline combinations when compared to CAF (cyclophosphamide, Adriamycin, fluorouracil in response rate, TTP and median OS (1, 19, 20). In a fourth randomized trial where vinorelbine and mitoxantrone was compared with CAF, no difference was found in the response rates (21). The combination of vinorelbine and fluorouracil has been compared to single-agent docetaxel in a randomized trial, where the response rates were 44% and 54% and the median response durations were 6 and 8 months, respectively (22).

The findings of the present study, as well as those of other phase II studies may be questioned, as it is quite possible that patients with measurable disease represent a non-random subset of metastatic breast cancer with different toxicity profiles and outcomes. Many women with immediately life-threatening unmeasurable metastatic breast cancer, e.g. patients with ascites, pleural effusions, diffuse lung or liver involvement, are presently excluded from most chemotherapy trials. The generally higher response rates and longer OS times of phase II studies compared to phase III studies may thus partly be a result of the inclusion of patients with measurable metastases and better outcomes.

We conclude that in our study the NEF regimen was active in achieving response rates, TTP and median OS similar to or better than those of other phase II first-line regimens using vinorelbine and anthracyclines. The most severe adverse effect was neutropenia, which caused a decrease in the dose intensity per course and per time of both vinorelbine and doxorubicin. Two patients died of toxicity, one from neutropenic sepsis and one from cardiac failure. Repeated monitoring of cardiac function is necessary in patients who have received previous adjuvant anthracycline therapy.

REFERENCES

1. Norris B, Pritchard KI, James K, et al. Phase III Comparative study of vinorelbine combined with doxorubicin versus doxorubicin alone in disseminated metastatic/recurrent breast cancer: National Cancer Institute of Canada Clinical Trials Group Study MA8. J Clin Oncol 2000; 18: 2385–94.
2. Gregory RK, Smith IE. Vinorelbine—a clinical review. Br J Cancer 2000; 82: 1907–13.
3. Spielmann M, Zelek L. Vinorelbine. In: Nabholtz J-M, Tonkin K, Aapro MS, Buzdar AU, BCIRG, eds. Breast cancer management. UK: Martin Dunitz Ltd, 2000: 87–97.
4. Spielmann M, Dorval T, Turpin F, et al. Phase II trial of vinorelbine/doxorubicin as first-line therapy of advanced breast cancer. J Clin Oncol 1994; 12: 1764–70.
5. Blomqvist C, Hietanen P, Teerenhovi L, Rissanen P. Vinorelbine and epirubicin in mtetastatic breast cancer. A dose finding study. Eur J Cancer 1995; 31A: 2406–8.
6. Garcia Lopez MJ, Morales S, Conzalez R, et al. Vinorelbine plus adriamycin as first line chemotherapy for advanced breast cancer. Ann Oncol 2000; 11(Suppl 4): 41.
7. Lopez Veva JM, Valladares M, Calvo L, et al. Phase II study with vinorelbine-epirubicin as first line treatment in metastatic breast cancer. Ann Oncol 2000; 11(Suppl 4): 41.
8. Pawlicki M, Rolski J, Siedlecki P, et al. A phase II study of i.v. fractionated vinorelbine and doxorubicin combination in previously untreated advanced breast carcinoma. Ann Oncol 2000; 11(Suppl 4): 40.
9. Piquet D, Fechter E, Buser K. Vinorelbine and fractionated dose of doxorubicin in advanced breast cancer: the Swiss experience. Ann Oncol 2000; 11(Suppl 4): 33.
10. Vici P, Colucci G, Gebbia V, et al. Epirubicin and vinorelbine as first-line chemotherapy in advanced breast cancer. (GOIM–Gruppo Oncologico Italia Meridionale). Ann Oncol 2000; 11(Suppl 4): 33.
11. Esteban E, de Sande G, Puertas J, et al. A phase II trial of cyclophosphamide, epirubicin and vinorelbine in the treatment of advanced breast cancer. Breast Cancer Res Treat 2000; 62: 127–33.
12. Dieras V, Extra JM, Bellisant E, et al. Efficacy and tolerance of vinorelbine and fluorouracil combination as first-line chemotherapy of advanced breast cancer: results of a phase II study using a sequential group method. J Clin Oncol 1996; 14: 3097–104.
13. Zambetti M, Demicheli R, De Candis D, et al. Five-day infusion fluorouracil plus vinorelbine i.v. in metastatic pretreated breast cancer patients. Breast Cancer Res Treat 1997; 44: 255–60.
14. Nole F, de Braud F, Aapro M, et al. Phase I–II study of vinorelbine in combination with 5-fluorouracil and folinic acid as first-line chemotherapy in metastatic breast cancer: a regimen with a low subjective toxic burden. Ann Oncol 1997; 8: 865–70.
15. Goss PE, Fine S, Gelmon K, et al. Phase I studies of fluorouracil, doxorubicin and vinorelbine without (FAN) and with (SUPER-FAN) folinic acid in patients with advanced breast cancer. Cancer Chemother Pharmacol 1997; 41: 53–60.
16. Kornek GV, Haider K, Kwasny W, et al. Effective treatment of advanced breast cancer with vinorelbine, 5-fluorouracil and l-leucovorin plus human granulocyte colony-stimulating factor. Br J Cancer 1998; 78: 673–8.
17. Gueler N, Yucel I, ôzet A, et al. Vinorelbine, epirubicin and 5-fluorouracil combination in the first-line treatment of metastatic breast carcinoma (TOG-009 protocol). Ann Oncol 2000; 11(Suppl 4): 33.
18. Blomqvist C, Elomaa I, Rissanen P, et al. Influence of treatment schedule on toxicity and efficacy of cyclophosphamide, epirubicin, and fluorouracil in metastatic breast cancer: a randomized trial comparing weekly and every-4-week administration. J Clin Oncol 1993; 11: 467–73.

19. Blajman C, Balbiani L, Block J, et al. A prospective, randomized phase III trial comparing combination chemotherapy with cyclophopshamide, doxorubicin, and 5-fluorouracil with vinorelbine plus doxorubicin in the treatment of advanced breast carcinoma. Cancer 1999; 85: 1091–7.
20. Ejlertsen B, Mouridsen HT, Langkjer ST, et al. Epirubicin and vinorelbine versus single agent epirubicin as first line chemotherapy in metastatic breast cancer. Eur J Cancer 2002; 38(Suppl 3): 111.
21. Namer M, Soler-Michel P, Turpin F, et al. Prospective randomized study comparing mitoxantrone (M) and vinorelbine (V) with fluorouracil (F), epirubicin (E) or Adriamycin (A) and cyclophosphamide (C) in patients with metastatic breast cancer. Eur J Cancer 2001; 37: 1132–40.
22. Bonneterre J, Roche H, Monnier A, et al. Taxotere (TXT) versus 5-fluorouracil+Navelbine (FUN) as second-line chemotherapy (CT) in patients (pts) with metastatic breast cancer (MBC) (preliminary results). Proc Am Soc Clin Oncol 1997; 16: A564.
23. Whelan TJ, Julian J, Wright J, et al. Does locoregional radiation therapy improve survival in breast cancer? A Meta-analysis. J Clin Oncol 2000; 18: 1220–9.