Cancer Chemother Pharmacol (2003) 52: 147–152
DOI 10.1007/s00280-003-0632-x

ORIGINAL ARTICLE

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Gemcitabine and vinorelbine as second-line treatment in patients with metastatic breast cancer: a phase II study

Received: 13 December 2002 / Accepted: 25 March 2003 / Published online: 23 May 2003

Abstract *Background*: To evaluate the feasibility and activity of gemcitabine and vinorelbine as a second/third-line approach in patients with advanced breast cancer. *Methods*: Entered into the study were 51 consecutive patients. All had been previously treated with anthracyclines. Of these 51 patients, 36 had experienced failure or relapse after one chemotherapy line for advanced disease, and 15 after two chemotherapy lines. The dominant sites of involvement were brain in 4 patients (7.8%), liver in 22 (43.2%), lung in 10 (19.6%), bone in 10 (19.6), and soft-tissue in 5 (9.8%). Treatment consisted of vinorelbine 25 mg/m^2 and gemcitabine 1000 mg/m^2 administered on days 1 and 8 every 21 days. *Results*: The scheme was well tolerated. Grade 3/4 neutropenia was observed in 11% of patients. Grade 3 nausea and vomiting occurred in 6%, and grade 2 neurotoxicity in 6%. No patients experienced grade 3/4 alopecia. The median relative dose intensity was 94.6% (49.7–100%) and 90.0% (23.1–100%) for vinorelbine and gemcitabine, respectively. Two patients (3.9%) were not evaluable for disease response, 4 (7.8%) attained a clinical complete response, 13 (25.5%) a partial response (for an overall response rate of 33.3%, 95% coefficient interval 20.0–46.0%), 23 (45.2%) showed stable disease, and 9 (17.6%) progressed. The median time to progression of responding patients was 10.8 months, and the median overall survival of the entire population was 17.8 months. *Conclusions*: Vinorelbine and gemcitabine is a manageable scheme with moderate activity in pretreated patients with advanced breast cancer.

Keywords Gemcitabine · Vinorelbine · Second-line treatment · Metastatic breast cancer · Phase II

Introduction

Breast cancer is the leading cause of death from cancer among women in Italy [1]. The treatment of metastatic disease still remains a challenge since there is no known treatment that appears to substantially prolong survival. The main goals of therapy are the palliation of symptoms and increasing the duration of high-quality of life [2]. The response rate of second-line combination chemotherapy in advanced breast cancer is between 20% and 40% on average, irrespective of the drugs and schedule employed, while the median response duration ranges from 2 to 8 months [3, 4].

Vinorelbine (VNB) is a semisynthetic vinca alkaloid that inhibits microtubule polymerization. Due to its lower effect on axonal microtubules, it is substantially less neurotoxic than native vinca alkaloids [5], and has non-cumulative granulocytopenia as the main dose-limiting toxicity. VNB has been largely used in breast cancer patients either alone or in combination regimens [6]. Used as a single agent in previously treated metastatic patients, the drug yields response rates of 15% to 30% [7, 8, 9].

Gemcitabine (GEM, difluorodeoxycytidine) is an analog of the pyrimidine nucleotide deoxycytidine and undergoes metabolism to an active antitumor agent after entering the cell. It is initially deaminated to difluorodeoxycytidine monophosphate (dFdc-5-monophosphate, dFdCMP) and further phosphorylated to difluorodeoxycytidine triphosphate (dFdCTP) which is actively incorporated into DNA where it produces chain

This work is presented on behalf of the Piemonte Oncology Network.

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termination [10, 11]. GEM also promotes its own intracellular accumulation and inhibits ribonucleotide reductase, an enzyme producing the deoxynucleotides required for DNA synthesis. Bone marrow suppression with neutropenia and thrombocytopenia are generally dose-limiting.

GEM has demonstrated single-agent response rates of approximately 20% in advanced breast cancer [12, 13]. This drug has a number of potential advantages as a second-line approach for advanced breast cancer patients in combination with VNB: (1) at present there is no known mechanism of cross-resistance between the two agents, (2) patients generally have had no prior exposure to GEM, (3) the combination of these two chemotherapeutic drugs has been found to be active in other malignancies such as non-small-cell lung cancer [14, 15], and (4) both VNB and GEM lack complete clinical cross-resistance with other drugs commonly used as first-line therapy of breast cancer, such as taxanes and anthracyclines [16, 17]. In addition, the low toxicity profile of both drugs makes them candidates for administration in a heavily pretreated population of cancer patients. A few phase II studies have recently been reported in which the association of GEM and VNB was investigated in pretreated breast cancer patients [18, 19, 20, 21, 22, 23]. Different schedules and dose intensities have been tested and a response rate ranging from 22% to 48% has been reported.

We report here the results of a phase II study in which both GEM and VNB were administered on days 1 and 8 every 21 days as a second/third-line approach in metastatic breast cancer. The primary aim was to evaluate the response rate. Toxicity, time to progression and overall survival were the secondary aims.

Patients and methods

Eligibility criteria

Eligibility criteria were: histologically confirmed metastatic breast cancer with evidence of disease progression; age 18–70 years; previous treatment with anthracyclines in an adjuvant setting or for advanced disease; previous one or two lines of chemotherapy for advanced disease; at least one measurable tumor site (target lesion) with index lesions on physical examination, radiography, ultrasound, or computed tomography scan; ECOG performance status of 0–3; adequate bone marrow reserve (WBC count $\geq 3.5\times10^9$/l, neutrophils $\geq 2\times10^9$/l, platelets $\geq 100\times10^9$/l, hemoglobin ≥ 9 g/l); adequate organ function (bilirubin < 1.5 mg/dl, AST and ALT less than three times the upper limit of normal, and creatinine ≤ 2 mg/dl); life expectancy of at least 3 months; no severe uncontrolled comorbidity; no second malignancies; no simultaneous or previous radiotherapy on the assessable tumor target; and no prior exposure to VNB or GEM. Previous hormone therapy was permitted. Concomitant hormone therapy was not allowed. Brain or leptomeningeal involvement was not considered to be an exclusion criterion if the patient presented with another metastatic target lesion. Written informed consent was obtained before registration.

Assessment of response and toxicity

The pretreatment evaluation included medical history and physical examination, complete blood cell count, serum chemistries, liver function tests, ECG, tumor marker evaluation (CA15-3), and staging studies appropriate to define the extent of metastatic disease, which included chest radiography, abdominal ultrasound, thoracic and/or abdominal computed tomography scan, and bone scan when appropriate. Clinical monitoring and a complete blood cell count were performed once weekly; serum electrolytes, and liver function tests were performed every 3 weeks. Toxicity was evaluated according to the World Health Organization (WHO) criteria [24].

Antitumor activity was evaluated every three courses on all measurable lesions, and all patients were scheduled for at least two courses of treatment to be eligible for assessment of tumor response. In patients with tumor response or stable disease, the treatment was planned to be continued for up to six cycles; thereafter, further cycles of therapy were based on the clinician's decision. After completion of the treatment plan, the patients were monitored every 3 months.

Tumor response was classified according to WHO criteria [24] and documented by two investigations at least 4 weeks apart. A complete response was defined as a complete disappearance of all clinical, radiological, and biochemical evidence of disease for a minimum of 1 month. A partial response required a 50% or greater reduction in the sum of the products of the longest diameter and its perpendicular. Stable disease indicated a decrease of less than 50% or an increase of less than 25% in the product of the longest perpendicular diameters of measurable lesions lasting 3 months. Progressive disease was defined as the appearance of new lesions or an increase of 25% or more in the sum of the products of the longest diameter and its perpendicular, as compared with the lowest value recorded. All deaths and treatment discontinuations (for toxicity or patient refusal) were considered as treatment failures. Time to progression was calculated from the beginning of cytotoxic chemotherapy until the date of objective evidence of progressive disease. Survival was dated from the first day of treatment until death or was censored on the date of the last follow-up appointment.

Treatment plan

Treatment consisted of VNB (Navelbine; Pierre Fabre Pharma, Milan, Italy) 25 mg/m^2 and GEM (Gemzar; Eli Lilly, Rome, Italy) 1000 mg/m^2 on days 1 and 8 every 21 days. Both drugs were given by intravenous infusion diluted in 100 ml and 250 ml saline solution, respectively. On days 1 and 8 of each cycle, patients had to have an absolute neutrophil count of 1500/μl and/or a platelet count of 100,000/μl. In the event of leukopenia/thrombocytopenia, the day-1 administration was postponed for 1 or 2 weeks until acceptable blood values returned, and the day-8 administration was omitted. Patients requiring a delay of more than 2 weeks in day-1 treatment were withdrawn from the study. Drug administration was planned to be stopped for grade 4 extrahematological toxicities and for neurotoxicity of WHO grade 3 or more.

Statistical analysis

According to the optimal two-stage phase II study design of Simon [25], the sample size was assessed in order to refuse response rates $\leq 20\%$ (p0) and to provide a statistical power of 80% in assessing the activity of the regimen as a 40% response rate. The upper limit for first-stage drug rejection was 3 responses out of the first consecutive 13 patients, and the upper limit of second-stage rejection was 12 responses out of 43 patients consecutively enrolled. Response duration and survival were assessed using Kaplan-Meier survival curves. All statistical analyses were performed using the SPSS/PC for Windows program (SPSS, Chicago, Ill.).

Results

A total of 51 consecutive patients were registered in the study between January 1998 and July 2001. Demographic

and clinical characteristics are listed in Table 1. Most patients had visceral disease with prominent hepatic involvement. Among the four patients with brain metastases, two showed leptomeningeal involvement. All patients had previously received anthracycline either in an adjuvant setting or for advanced disease, and 13 patients had previously received taxanes. The GEM and VNB regimen was administered as second-line treatment in 36 patients and as third-line treatment in 15.

Response to treatment and survival

All patients included in this study were analyzed on an intention-to-treat basis. Two patients (3.9%) refused to continue the chemotherapy treatment after the first cycle and were not evaluable for disease response. Four patients (7.8%) achieved a complete response and 13 patients (25.5%) achieved a partial response, yielding a response rate of 33.3% (95% confidence interval 20–46%), and 23 patients (45.2%) had stable disease and 9 (17.6%) progressive disease. According to the previous treatment exposure, disease response was obtained in 15 out of 36 patients (41.6%) who had previously received one chemotherapy line for advanced disease, and in 2 out of 15 patients (13.3%) who had previously received two chemotherapy lines. Of the 13 patients (38.5%) with progressive disease after treatment with anthracyclines and taxanes, 5 responded to the treatment scheme. As outlined in Table 2, responses were seen in all disease sites, but particularly in soft tissue and lung. Interestingly, one patient with leptomeningeal dissemination showed a partial remission (by magnetic resonance scan) lasting 7 months. At the time of writing (March 2002) 46 treated patients (90.2%) had progressed and 32 (62.7%) had died. The median time to progression was 6.3 months overall and 10.8 months in responding patients. The corresponding median overall survival times were 17.8 and 18.5 months, respectively.

Table 1 Demographic and clinical characteristics of the patients

Total no. of patients	51
Age (years)	
Median	57
Range	28–73
Performance status	
Median	1
Range	0–3
Dominant metastatic sites	
Soft tissue	5 (9.8%)
Bone	10 (19.6%)
Lung	10 (19.6%)
Liver	22 (43.1%)
Brain	4 (7.9%)
No. of metastatic sites	
One	22 (43.1%)
Two	15 (29.4%)
Three	12 (23.5%)
Four	2 (3.9%)
Previous adjuvant treatments	
Chemotherapy	35 (66.0%)
Hormonal therapy	25 (48.0%)
Postoperative radiotherapy	20 (41.6%)
Previous treatments for advanced disease	
One chemotherapy line	36 (70.6%)
Two chemotherapy lines	15 (29.4%)
Hormone therapy	28 (54.9%)
Palliative Radiotherapy	18 (35.3%)

Treatment and toxicity

A total of 264 chemotherapy courses were administered with a median of 6 courses for each patient (range 1–8). A 1-week treatment delay occurred in 20 patients (39.2%), and a 2-week delay in 15 (29.4%). The dose of GEM was reduced in 13 patients (25.5%), and the dose of VNB was reduced in 11 (21.6%). Leukopenia was the most frequent cause for treatment delay and reduction. GEM administration was interrupted in two patients during the second cycle while VNB was continued for six cycles due to allergic reaction. The median delivered dose intensity of GEM was 600 mg/m^2 per week (range 154–667 mg/m^2) and the median delivered dose intensity of VNB was 15.8 mg/m^2 per week (range 8.3–16.7 mg/m^2). These doses amounted to 90.0% (range 23.1–100%) and 94.6% (range 49.7–100%) of the initially planned dose of the two drugs, respectively.

The major toxicities encountered are shown in Table 3. Hematological toxicity was mild. Grade 3/4

Table 2 WHO toxicity (note: for each patient, the most severe instance of toxicity was taken into account)

	Grade			
	1	2	3	4
Granulocytes	15 (29.4%)	7 (13.7%)	4 (7.8%)	2 (3.9%)
Hemoglobin	11 (21.6%)	3 (5.8%)	0	0
Platelets	2 (3.9%)	0	0	0
Nausea and vomiting	16 (31.4%)	14 (27.5%)	3 (5.9%)	0
Diarrhea	1 (1.9%)	2 (3.9%)	0	0
Stomatitis	9 (17.6%)	6 (11.8%)	0	0
Neurosensory	8 (15.7%)	3 (5.9%)	0	0
Hepatic	3 (5.9%)	0	0	0
Asthenia	6 (11.8%)	15 (29.4%)	0	0
Fever	0	2 (3.9%)	1 (1.9%)	0
Alopecia	9 (17.6%)	6 (11.8%)	0	0

Table 3 Response to therapy according to disease site

Site	Complete response	Partial response	Stable disease	Progressive disease	Not evaluable
Liver	1 (4.3%)	5 (21.7%)	10 (43.5%)	5 (21.7%)	2 (8.6%)
Bone	1 (3.4%)	2 (6.8%)	25 (86.2%)	25 (86.2%)	1 (3.4%)
Lung	2 (10.5%)	6 (31.6%)	10 (52.6%)	1 (5.2%)	0
Soft tissue	5 (22.7%)	6 (27.3%)	8 (36.4%)	2 (9%)	1 (4.5%)
Brain	0	1	2	0	1
Pericardial effusion	0	0	1	0	0

neutropenia was observed in 11% of patients. Febrile neutropenia which did not require hospitalization was observed in one patient. Hemoglobin and platelet toxicities were infrequent and mild. Gastrointestinal toxicity (nausea/vomiting and stomatitis), asthenia and neurotoxicity were the most common nonhematological toxicities. They were mild (between grade 2 and 3) in the great majority of patients. As mentioned above, two patients showed a hypersensitivity reaction to GEM requiring drug discontinuation.

Discussion

VNB is an active drug in advanced breast cancer. The activity of VNB could be enhanced by combination with GEM. Both drugs can be given by weekly administration, with the advantage of achieving a higher dose intensity than the 3-weekly schedule. In previously treated patients with metastatic breast cancer concerns are heightened regarding the tolerability of further cytotoxic agents. The goal is symptom palliation with limited toxicity [26].

In the present study, there was very good tolerability of the combination of GEM and VNB, allowing the delivery of at least 90% of the planned dose of the two drugs. These data confirm previous findings [18, 19, 20, 22, 23]. As expected, the main toxicity was on white blood cells. Severe neutropenia (grade 3/4), however, was observed in only 11% of patients and was characterized by rapid recovery. Only one patient suffered from febrile leukopenia. Thrombocytopenia was extremely rare, with only one patient having grade 1 platelet toxicity. The severity and extent of all other toxicities were within the limits for a well-tolerated combination. We can therefore state that the objective of a low-toxicity chemotherapy regimen was met. Due to the palliative nature of this regimen, GEM was administered at a lower dose than frequently prescribed in combination regimens (i.e. on days 1, 8 and 15 every 28 days) [14].

The activity of this combination was not particularly high, but was noteworthy in this population of advanced breast cancer patients whose pretreatment characteristics seemed to be predictive of a less favorable outcome. Among such patients, previous exposure to more chemotherapy lines, and visceral metastases (as well as brain involvement) have been clearly shown to be related to a poor outcome [27]. The response rate of 33% achieved in the present study is similar to that observed in two investigations [19, 22] but lower than that found in three other studies [18, 20, 23] all involving pretreated patients (Table 4). The median dose intensity in our experience was similar to that planned in two studies [19, 22] but lower than that in one study [18] and higher than that in another study [23]. A lower VNB dose and a higher GEM dose than the present study were admin-

Table 4 Gemcitabine (GEM) and vinorelbine (VNB) combination regimens. Published studies

Reference	No. of patients	Schedule	Response rate (%)	Median time to progression (months)		Planned dose intensity (mg/m^2 per week)
				Overall	Responders	
18	15	GEM 1000 mg/m^2, days 1, 15, 21; VNB 40 mg/m^2, days 1, 21; every 28 days	44	7	Not recorded	VNB 20, GEM 750
20	29	GEM 1000 mg/m^2, days 1, 8, 15; VNB 25 mg/m^2, days 1, 8; every 28 days	48	6.8	10.2	VNB12.5, GEM 750
19	31	GEM 1000 mg/m^2, days 1, 8; VNB 30 mg/m^2, days 1, 8; every 21 days	22	3.5	10	VNB 20, GEM 667
22	53	GEM 800–1400 mg/m^2, days 1, 8; VNB 15–30 mg/m^2, days 1, 8; every 21 days	24	Not recorded	12	VNB 10–20, GEM 530–930
23	51	GEM 1000 mg/m^2, days 1, 15; VNB 25 mg/m^2, days 1, 15; every 28 days	54	6.0	12	VNB 12.5, GEM 500

istered in a further investigation [20]. The results of previous studies (Table 4) seem to suggest that the activity of this combination regimen is independent of the dose intensity of both GEM and VNB, as the highest response rate was obtained in the study in which the lowest dose of both drugs per week was delivered [23].

Wide variation in outcome among different phase II studies is a well-known phenomenon, and is mainly due to patient selection. In this respect, it should be noted that response to GEM plus VNB in our study differed among the disease sites, being higher in patients with soft-tissue and lung involvement (50.0% and 42.1% response rate, respectively) and lower in patients with liver metastases (26.0% response rate). A similar trend in disease response has been observed by Stathopoulos et al. [23] who reported a 91.6% and 81.0% response rates in soft-tissue and lung metastases, respectively, and 20.0% response rate in patients with liver involvement. The difference in terms of relative number of patients with liver metastasis, 43% in our study and 20% in that of Stathopoulos et al. [23], could account at least in part for the discrepancies in treatment activity observed between the two studies. The distribution of treatment activity, which was mainly seen in patients with lung and soft tissue disease sites, could also explain the relatively long duration of response observed both in our experience and in previous studies (Table 4).

It is noteworthy that one patient with leptomeningeal involvement showed a partial response. This result is consistent with a previous observation by our group with the combination of VNB plus 5-fluorouracil [28], suggesting that VNB-containing regimens may be active in this patient subset characterized by poor prognosis.

To conclude, the results of this phase II study support and extend the results of other studies showing that GEM and VNB is an active regimen in metastatic breast cancer patients. The issue of whether GEM could increase the activity of VNB should be addressed in a phase III trial. The oral formulation of both drugs which may be available in the future could potentially further improve their feasibility in this patient population.

References

1. Verdecchia A (1996) Survival in adult Italian cancer patients (1978–1989). ITACARE Working Group. Tumori 83:39–425
2. Hortobagyi GN (1994) Multidisciplinary management of advanced primary and metastatic breast cancer. Cancer 74 [1 Suppl 1]:416–423
3. Ellis MJ, Hayes DF, Lippman ME (2000) Treatment of metastatic breast cancer. In: Harris YR, Lippman ME, Morrow M, Osborne CK (eds) Diseases of the breast. Lippincott, Philadelphia, pp 749–787
4. Cardoso F, Di Leo A, Lohrisch C, Bernard C, Ferreira F, Piccart MJ (2002) Second and subsequent lines of chemotherapy for metastatic breast cancer: what did we learn in the last two decades? Ann Oncol 13:197–207
5. Fellous A, Ohayon R, Vacassin T, Binet S, Lataste H, Krikorian A, Couzinier JP, Meininger V (1989) Biochemical effects of Navelbine on tubulin and associated proteins. Semin Oncol 16 [Suppl 4]:9–14
6. Johnson SA, Harper P, Hortobagyi GN, Pouillart P (1996) Vinorelbine: an overview. Cancer Treat Rev 22:127–142
7. Gasparini G, Caffo O, Barni S, Frontini L, Testolin A, Guglielmi RB, Ambrosini G (1994) Vinorelbine is an active antiproliferative agent in pretreated advanced breast cancer patients: a phase II study. J Clin Oncol 12:2094–2101
8. Weber BL, Vogel C, Jones S, Harvey H, Hutchins L, Bigley J, Hohneker J (1995) Intravenous vinorelbine as first-line and second-line therapy in advanced breast cancer. J Clin Oncol 13:1245–1252
9. Degardin M, Bonneterre J, Hecquet B, Pion JM, Adenis A, Horner D, Demaille A (1994) Vinorelbine (Navelbine) as salvage treatment for advanced breast cancer. Ann Oncol 5:423–426
10. Hertel LW, Kroin JS, Misner JW, Tustin JM (1988) Synthesis of 2-deoxy-2′,2′-difluoro-D-ribose and 2-deoxy-2′,2′-difluoro-D-ribofuranosyl nucleosides. J Org Chem 53:2406–2409
11. Hertel LW, Boder GB, Kroin JS, Rinzel SM, Porre G, Todd GC, Grindey GB (1990) Evaluation of the antitumor activity of gemcitabine (2′,2′-difluoro-2′-deoxycitidine). Cancer Res 50:4417–4422
12. Luftner D, Flath B, Akrivakis C, Grunewald R, Mergenthaler HG, Possiger K (1998) Gemcitabine for palliative treatment in metastatic breast cancer. J Cancer Res Clin Oncol 124:527–531
13. Seidman AD (2001) The evolving role of gemcitabine in the management of breast cancer. Oncology 60:189–198
14. Lorusso V, Carpagnano F, Frasci G, Panza N, Di Rienzo G, Cisternino ML, Napoli G, Orlando S, Cinieri S, Brunetti C, Palazzo S, De Lena M (2000) Phase I/II study of gemcitabine plus vinorelbine as first-line chemotherapy of non-small-cell lung cancer. J Clin Oncol 18:405–411
15. Krajnik G, Mohn-Staudner A, Thaler J, Greil R, Schmeikal S, Marhold F, Deutsch J, Preiss P, Malayari R, Schafer-Prokop C, Wein W, Huber H, Pirker R (2000) Vinorelbine-gemcitabine in advanced non-small cell lung cancer (NSCLC): an AASLC phase II trial. Ann Oncol 11:993–998
16. Gianni L, Munzone E, Capri G, Fulfaro F, Tarenzi E, Villani F, Spreafico C, Laffranchi A, Caraceni A, Martini C (1995) Paclitaxel by three-hour infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer: high antitumor efficacy and cardiac effects in a dose-finding and sequence-finding study. J Clin Oncol 13:2688–2699
17. Dogliotti L, Berruti A, Buniva T, Zola P, Bau MG, Farris A, Sarobba MG, Bottini A, Alquati P, Deltetto F, Gosso P, Monzeglio C, Moro G, Sussio M, Perroni D (1996) Lonidamine significantly increases the activity of epirubicin in advanced breast cancer patients: results from a multicenter prospective randomized trial. J Clin Oncol 14:1165–1172
18. Haider K, Kornek GV, Kwasny W, Weinlander G, Valencak J, Lang F, Puribauer F, Kovats E, Depisch D, Scheithauer W (1999) Treatment of advanced breast cancer with gemcitabine and vinorelbine plus human granulocyte-colony stimulating factor. Breast Cancer Res Treat 55:203–211
19. Nicolaides C, Dimopoulos MA, Samantas E, Bafaloukos D, Kalofonos C, Fountzilas G, Razi E, Kosmidis P, Pavlidis N (2000) Gemcitabine and vinorelbine as second-line treatment in patients with metastatic breast cancer progressing after first-line taxane-based chemotherapy: a phase II study conducted by the Hellenic Cooperative Oncology Group. Ann Oncol 11:873–875
20. Valenza R, Leonardi V, Gebbia V, Agostara B (2000) Gemcitabine and vinorelbine in pretreated advanced breast cancer. A pilot study. Ann Oncol 11:495–496
21. Hortobagyi G (2001) Treatment of advanced breast cancer with gemcitabine and vinorelbine. Oncology (Huntingt) 15 [Suppl 3]: 15–17
22. Mariani G, Tagliabue P, Zucchinelli P, Brambilla C, Demicheli R, Villa E, Marchiaro A, Valagussa P, Bonadonna G, Gianni L (2001) Phase I/II study of gemcitabine in association with vinorelbine for metastatic breast cancer. Breast Cancer Res Treat 70:163–169
23. Stathopoulos GP, Rigatos SK, Pergantas N, Tsavdarides D, Athanasiadis I, Malamos NA, Stathopoulos JG (2002) Phase II trial of biweekly administration of vinorelbine and gemcitabine in pretreated advanced breast cancer. J Clin Oncol 20:37–41

24. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47:207–214
25. Simon R (1989) Optimal two-stage designs for phase II clinical trials. Control Clin Trials 10:1–10
26. Porkka K, Blomqvist C, Rissanen P, Elomea I, Pyrhonen S (1994) Salvage therapies in women who fail to respond to first-line treatment with fluorouracil, epirubicin and cyclophosphamide for advanced breast cancer. J Clin Oncol 12:1639–1647
27. Buzdar AU, Asmar L, Hortobagyi GN (1997) Impact of patient characteristics on treatment outcome: anthracycline resistance. Eur J Cancer 33 [Suppl 7]:S3–S6
28. Berruti A, Sperone P, Bottini A, Gorzegno G, Lorusso V, Brunelli A, Botta M, Tampellini M, Donadio M, Mancarella S, De Lena M, Alquati P, Dogliotti L (2000) Phase II study of vinorelbine with protracted fluorouracil infusion as a second- or third-line approach for advanced breast cancer patients previously treated with anthracyclines. J Clin Oncol 18:3370–3377