Vinorelbine and Cisplatin (CIVIC Regimen) for the Treatment of Metastatic Breast Carcinoma after Failure of Anthracycline- and/or Paclitaxel-Containing Regimens

Isabelle Ray-Coquard, M.D.
Pierre Biron, M.D.
Thomas Bachelot, M.D.
Jean-Paul Guastalla, M.D.
Gilles Catimel, M.D.
Yacine Merrouche, M.D.
Jean-Pierre Droz, M.D.
Franck Chauvin, M.D., Ph.D.
Jean-Yves Blay, M.D., Ph.D.

Centre Léon Bérard, Lyon, France.

Presented in part in poster form at the 8th European Cancer Conference, Paris, France, October 1995.

The authors thank Pierre-Emmanuel Colle for language assistance.

Address for reprints: I. Ray-Coquard, M.D., Centre Léon Bérard, 28 rue Laënnec, 69008 Lyon, France. E-mail: ray@lyon.fnclcc.fr

Received April 16, 1997; revision received June 27, 1997; accepted June 27, 1997.

BACKGROUND. A pilot study of a new chemotherapy, the CIVIC regimen, was performed in 58 patients with metastatic breast carcinoma previously treated with chemotherapy with or without hormonal therapy (n = 41). Cisplatin, 20 mg/m^2/day, was given (Days 1–5) every 21 days during a 1-hour intravenous (i.v.) infusion, and vinorelbine (VNB) was delivered at a dose of 6 mg i.v. bolus followed by VNB, 6 mg/m^2/day, in continuous i.v. infusion (Days 1–5) every 21 days.

METHODS. Fifty-eight patients were included in this trial between June 1992 and March 1994 (median age, 46.5 years; range, 28–69 years). The number of previous chemotherapy in the adjuvant or metastatic phase were: 1 in 9 patients, 2 in 33 patients, and $\geq$ 3 in 16 patients. Forty-four and 12 patients, respectively, were previously treated in metastatic phase with regimens containing anthracyclines and paclitaxel. Overall, 210 cycles were given (median, 3 cycles; range, 1–6 cycles).

RESULTS. Among the 58 patients assessable for tumor response to the CIVIC regimen, 24 patients (41%) (95% confidence interval, 28–54) achieved an objective response (complete response or partial response) with 2 complete response (3%) and 22 partial response (38%). The median time to response was 11 weeks (range, 4–16 weeks). The median survival time from the initiation of the CIVIC regimen was 9.2 months (range, 0–45 months). The response rate was 43% (19 of 44 patients) in patients refractory to anthracyclines and 58% (7 of 12 patients) in patients with disease progression after treatment with anthracyclines and paclitaxel. Myelosuppression was the most frequent side effect. World Health Organization Grade 3 neutropenia occurred in 8 of 58 patients (14%) and in 41 of 210 cycles (20%), Grade 4 neutropenia occurred in 37 of 58 patients (64%) and in 63 of 210 cycles (30%), and Grade 3 and 4 thrombopenia occurred in 7 of 58 patients (12%) and in 9 of 210 cycles (4%). Grade 2 peripheral neuropathy was observed in 6 of 58 patients (10%) and in 12 of 210 cycles (6%), and Grade 3 peripheral neuropathy was observed in 3 of 58 patients (5%) and in 4 of 210 cycles (2%). The risk of Grade 2–3 neuropathy was significantly higher after the fourth chemotherapy cycle (14 of 23 patients vs. 3 of 35 patients: $P = 0.00002$).

CONCLUSIONS. The CIVIC regimen is effective and has acceptable tolerance in patients with metastatic breast carcinoma refractory to previous anthracycline- and/or paclitaxel-containing chemotherapy. Four cycles were found to provide the best toxicity-efficacy ratio. ***Cancer* 1998;82:134–40.**

© 1998 American Cancer Society.

KEYWORDS: metastatic breast carcinoma, vinorelbine, cisplatin, chemotherapy.

Metastatic breast carcinoma is most often not curable with available treatments. The most commonly used cytotoxic chemother-

apy regimens contain cyclophosphamide, methotrexate, fluorouracil, and anthracyclines.[1] First-line combination chemotherapy induces an objective response in approximately two-thirds of patients previously unexposed to chemotherapy, but the median duration of response is less than 1 year.[2,3] The response rate for second-line chemotherapy in patients previously untreated with doxorubicin is approximately 35% (range, 17–54% in 17 studies); this figure is 21% (range, 0–40% in 11 separate studies) for patients already exposed to doxorubicin (median duration of response, 2–8 months).[4]

Vinorelbine (VNB) is a semisynthetic vinca alkaloid. In first-line chemotherapy for metastatic breast carcinoma, response rates for VNB range from 40–50% (mean, 44%).[5–7] Phase II trials of combination VNB plus doxorubicin as first-line chemotherapy yield higher response rates (74%)[8] but induce significant toxicities (paralytic ileus, cardiotoxicity, severe infections). Response rates of 61.6% and 51% have been reported with the combination of VNB and fluorouracil[9] or VNB and mitoxantrone[10] for metastatic disease. Toussaint et al.[11] reported an overall response rate of 36% with continuous infusion of VNB in advanced breast carcinoma in relapse or first-line therapy. In second-line chemotherapy regimens including vinca alkaloids, the response rates ranged from 16–43%.[12] Continuous infusion of vinca alkaloids has been reported to have a significant dose-dependent antitumor activity against breast carcinoma,[13] with an overall response rate of 40% for previously treated patients.[14] Vinorelbine exerts synergistic antitumoral activity with cisplatin (CDDP) in animals models.[15] Theses observations prompted us to study the efficacy of VNB continuous infusion in combination with CDDP in patients with metastatic breast carcinoma in whom previous anthracycline therapy had failed.

PATIENTS AND METHODS

Patient Selection

Women with a histologically confirmed diagnosis of breast carcinoma and evidence of metastatic disease were selected for this protocol. Eligibility criteria included the following: life expectancy longer than 2 months, at least one measurable lesion, and adequate bone marrow (granulocytes $> 1000/\mu L$; platelets $> 100.000/\mu L$), liver, and renal (creatinemia $< 150\ \mu mol/L$) functions. Ineligibility criteria included central nervous system metastases, a unique lesion that could allow treatment by surgery, or previous irradiation. All patients were previously treated in adjuvant and/or metastatic phase with chemotherapy regimens containing anthracyclines. An additional patient who did not receive anthracyclines because of left ventricular ejection failure was treated with the CIVIC regimen outside the protocol and did not respond after two cycles.

Pretreatment and Follow-Up Evaluation

Clinical staging was performed for all patients and included history and physical examination with tumor measurement. Complete blood cell counts with differential and platelet counts were performed once a week, and a biochemical profile was assessed before each cycle. Imaging procedures included chest radiograph, bone scintigraphy, and either liver ultrasonography or computed tomography. Imaging procedures were repeated every two or three cycles, more often when necessary.

Treatment Plan

The CIVIC regimen consisted of VNB, 6 mg bolus diluted in 100 ml normal saline, in 15-minute intravenous (i.v.) infusion, followed by VNB, 6 mg/m^2 diluted in 250 ml normal saline, in 24-hour i.v. infusion (Days 1–5). Cisplatin was given at 20 mg/m^2 diluted in 250 ml normal saline in 1-hour i.v. infusion (Days 1–5). The regimen was repeated every 21 days until evidence of progressive disease or severe toxicity was noted and for a maximum of six courses.

Response Criteria

All patients were considered as assessable for response. Standard criteria for response were used. Objective response (OR) included either complete response (CR) or partial response (PR). Complete response was defined as a 100% disappearance of all known tumor sites and normalization of all abnormal laboratory parameters for 1 month or more (World Health Organization criteria[16]). Partial response was defined as a 50% or greater reduction in the sum of the product of the two longest perpendicular diameters of all measurable lesions for 1 month or more. Stable disease (SD) was defined as less than a 50% reduction or 25% increase in the sum of the product of the two longest perpendicular diameters of all measurable lesions. Progressive disease (PD) was defined as a 25% or greater increase in the sum of the product of the two longest perpendicular diameters of one measurable lesion (even with regression of other lesions) or with the appearance of new lesions. For nonmeasurable lesions (lytic bone metastases), the only responses accepted were CR, SD, and PD. Duration of response for the whole cohort was not assessed, because 18 patients received consolidation with high dose chemotherapy (HDCT) and hematopoietic stem cell treatment.

Toxicity and Dosage Modification Guidelines

Toxicity evaluations were based on World Health Organization criteria.[16] No dosage modifications were adopted for Grades 1 or 2 hematologic toxicity. Whenever a febrile Grade 4 neutropenia was observed, treatment was administered with a 20% reduction of the dose (CIVIC regimen given from Day 1–4). If any other toxicity (neurologic, renal, or gastrointestinal) was observed either in combination with hematologic toxicity or by itself and of Grade 3, doses of both VNB and CDDP were decreased by 40% (CIVIC regimen given from Days 1–3). Reduction by shortening the duration of continuous infusion rather than by reducing the daily dose was realized for practical considerations.

Statistical Analysis

Statistical analyses were performed using Pearson chi-square test or Fisher's exact test when appropriate. Survival was considered from the beginning of therapy and was assessed by means of the Kaplan–Meier product-limit method.[17] The Mantel–Cox test was used to determine survival rates.[18]

RESULTS

Between June 1992 and March 1994, 58 women with metastatic breast carcinoma previously treated with anthracyclines and/or paclitaxel received the CIVIC regimen. The characteristics of the patients are listed in Table 1. Eighty-five percent of patients had previously received one or more chemotherapy in metastatic phase before the CIVIC regimen. All patients received anthracyclines either in adjuvant phase only (14 of 58 patients) or in metastatic phase (44 of 58 patients). Forty-five patients had received previous hormonal therapy. Fifty-eight patients were assessable for response and for toxicity and received an average of three cycles of treatment (range, 1–6 cycles). Overall, 210 cycles were administered.

TABLE 1
Patient Characteristics

	No. (%)
Entered on study	58 (100)
Age (yrs)	
Median	46.5
Range	28–69
Menopausal status	
Premenopausal	40 (69)
Postmenopausal	14 (24)
ND	4 (7)
Estrogen receptors	
Positive	15 (26)
Negative	15 (26)
ND	28 (48)
pTNM classification at initial diagnostic (UICC[19])	
T1T2	38 (64)
T3T4	14 (24)
M1	6 (12)
N+	40 (68)
N−	13 (22)
Disease free interval after initial treatment (mo)	
Median	37.5
Range	3–347
Metastatic sites	
Liver	36 (31)
Bone	36 (31)
Lung	20 (18)
Cutaneous	11 (8)
Lymph nodes	8 (7)
Other	6 (5)
No. of involved metastatic sites	
1	18 (30)
2	20 (35)
≥3	20 (35)
Hormonal therapy	
In adjuvant phase	24 (41)
In metastatic phase	41 (71)
Previous chemotherapy (adjuvant and/or metastatic phase)	58 (100)
Previous adjuvant chemotherapy	41 (71)
No. of previous chemotherapy in metastatic phase	
0	9 (16)
1	33 (58)
2	13 (22)
≥3	3 (5)
Previous anthracyclines in metastatic phase	44 (76)
Previous paclitaxel in metastatic phase	12 (21)
Previous anthracyclines and paclitaxel in metastatic phase	12 (21)

ND: not determined; M1: metastatic disease; N+: involved nodes; N−: not involved node.

Response Rates and Survival

Of 58 patients, 24 (41%; 95% confidence interval, 28–54) experienced OR; 2 patients (3%) achieved CR—1 after the first cycle (liver sites) and 1 after the third cycle (node sites). Twenty-two women achieved PR (38%). Stable disease was observed in 12 patients (21%), and PD was observed in 22 patients (38%). There was one early death due to PD at Day 2 of the first cycle. The median time to response was 11 weeks (range, 4–16 weeks), and all responses occurred before the fourth cycle. Nineteen of 44 patients (43%) who received previous doxorubicin-containing chemotherapy in metastatic phase achieved OR. Seven of 12 patients (58%) who had received previous paclitaxel-containing chemotherapy in metastatic phase achieved OR. The median overall survival time for these 12 patients was 5.6 months (range, 1–11 months). Among 12 patients who received the CIVIC regimen after failure of anthracyclines and paclitaxel, 7 had PD during anthracycline therapy and during paclitaxel therapy. Five of these experienced OR on the CIVIC regimen. Responses according to patient characteristics are shown in Table 2. Response rates did not differ sig-

TABLE 2
Responses According to Patient Characteristics (n = 58)

		CR + PR (OR)		SD + PD		
	No.	No.	%	No.	%	*P* value
Metastatic sites						0.18
Lung	20	9	45	11	55	
Cutaneous	11	5	45	6	55	
Liver	36	15	42	21	56	
Bone	36	6	17	30	83	
No. of involved metastatic sites						0.33
1	18	6	33	12	67	
2	20	8	40	12	60	
≥3	20	10	50	10	50	
No. of chemotherapy regimens in metastatic phase						0.75
First line	9	3	33	7	67	
Second line	33	13	39	20	61	
≥3	16	8	50	8	50	
Previous anthracyclines						
Adjuvant phase only	14	5	36	9	64	0.62
Metastatic phase	44	19	43	25	57	0.62
Previous paclitaxel	12	7	58	5	42	0.20
Previous vinca alkaloids[a]	13	6	46	7	54	0.73

CR: complete response; PR: partial response; OR: objective response; SD: stable disease; PD: progressive disease.
[a] Vinblastine, bolus vinorelbine, or vindesine.

TABLE 3
Toxicity of the CIVIC Regimen in 58 Evaluable Patients and 210 Evaluable Cycles

		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	ND
Characteristics	No.	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Hematologic							
Hemoglobin							
Cycles	210	53 (25)	78 (37)	42 (20)	19 (9)	3 (1)	15 (7)
Patients	58	7 (12)	15 (26)	17 (29)	15 (26)	3 (5)	1 (2)
Granulocytes							
Cycles	210	45 (21)	29 (14)	17 (8)	41 (20)	63 (30)	15 (7)
Patients	58	7 (12)	4 (7)	2 (3)	8 (14)	37 (64)	0 (0)
Platelets							
Cycles	210	122 (58)	43 (21)	19 (9)	6 (3)	3 (1)	17 (8)
Patients	58	24 (41)	14 (24)	12 (21)	5 (9)	2 (3)	1 (2)
Peripheral neurotoxicity							
Neuropathy							
Cycles	210	151 (72)	40 (19)	12 (6)	4 (2)	0 (0)	3 (1)
Patients	58	41 (71)	8 (14)	6 (10)	3 (5)	0 (0)	0 (0)
Gastrointestinal							
Nausea/vomiting							
Cycles	210	27 (13)	71 (34)	95 (45)	9 (4)	0 (0)	8 (4)
Patients	58	5 (8)	6 (10)	37 (64)	8 (14)	0 (0)	2 (3)
Renal							
Cycles	210	208 (98)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Patients	58	56 (98)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)

ND: not determined.

nificantly according to the number of previous lines of treatment and the number of chemotherapy in metastatic phase. No correlation was found between response rate and estrogen receptor status ($P = 0.54$), age ($P = 0.6$), sites of metastases ($P = 0.18$), number of sites (1 versus ≥ 2) ($P = 0.33$), previous hormonal therapy ($P = 0.54$), and anthracyclines ($P = 0.62$), paclitaxel ($P = 0.20$), or vinca-alkaloid–containing chemotherapy in the metastatic phase (vinblastine or vindesine or bolus VNB) ($P = 0.73$).

The median survival duration (from initiation of the CIVIC regimen) for all patients was 9.2 months (range, 0–45 months). Eighteen patients (of whom 56% responded to the CIVIC regimen) received HDCT and peripheric blood stem cell or marrow support as consolidation therapy. The median survival was 20.8 months for patients who received HDCT and 7.8 months for other patients.

Dose Reduction, Tolerance, and Toxicity

Two-hundred ten cycles were administered and evaluated. The median number of treatments with the CIVIC regimen for each patient was 3 (range, 1–6 treatments). Dose reduction was performed in 31 cycles (15%); for 11 cycles (5%) the dose was decreased by 20%, and for 20 cycles (10%) the dose was decreased by 40%. In 97% of cases (30 of 31 cycles), the dose reduction was due to hematotoxicity.

Leukopenia occurred in 51 patients (88%), with Grade 3 or 4 leukopenia occurring in 45 patients (14% and 64%, respectively). A correlation between the number of cycles ($\leq$4 cycles or $>$ 4 cycles) and Grade 3 and 4 leukopenia (28 of 35 patients vs. 23 of 23 patients; $P = 0.02$) was observed. Thrombopenia was rarely severe and occurred (Grade 3 or 4) in 7 patients (12%); 3 cycles required platelet transfusion but no bleeding episodes were observed. Grade 2 or 3 anemia occurred in 32 patients (55%), and Grade 4 anemia was observed in 3 patients (5%) and required red blood cell transfusion. Peripheral neurotoxicity was observed in 17 patients (29%). Grade 1 occurred in 8 patients (14%). Six patients (10%) experienced Grade 2 toxicity, and 3 patients (5%) experienced Grade 3 toxicity at the end of treatment. A correlation between the number of administered cycles and the risk of peripheral neurotoxicity was observed; the risk of Grade 2–3 neuropathy was significantly higher after the fourth cycle (14 of 23 patients vs. 3 of 35 patients; $P = 0.00002$). Grade 3 nausea and vomiting was observed in 8 patients (14%). All patients received a prophylactic antiemetic therapy with 5HT3 inhibitors. Renal Grade 2 toxicity was observed in 2 patients. Grade 1 or 2 alopecia was observed in all patients. It is important to note that 43% (25 of 58) patients received anthracycline and/or paclitaxel chemotherapy immediately ($\leq$ 2 months) before the initiation of the CIVIC regimen, with both drugs being responsible for alopecia.

DISCUSSION

In this study, we report on the efficacy of the CIVIC regimen in patients with progressive metastatic breast carcinoma after first-line chemotherapy with anthracyclines in metastatic phase. The antitumor activity of second-line chemotherapy regimens for metastatic breast carcinoma varies considerably; responses rates ranging from 3–45% have been reported in the literature.[20,21] For patients with PD after anthracycline therapy in metastatic phase, a mean response rate of 21% in second-line therapy was reported.[4,22]

Vinorelbine has been reported to have a high efficacy and a favorable toxicity profile in first-line therapy of patients with advanced breast carcinoma.[5,6,23] In second-line therapy, weekly VNB has been reported to yield a 32% response rate (15 of 47 patients), with a median time to treatment failure of 18 weeks.[24] These results compare favorably with the response rates achieved in anthracycline-refractory metastatic breast carcinoma with other vinca alkaloids alone[25,26] or in combination with CDDP.[27] The encouraging results with VNB as a single agent in Phase II studies[24,28] in metastatic breast carcinoma, and the synergistic activity of CDDP with VNB,[15] prompted us to study the combination of these two agents in patients with anthracycline-refractory metastatic breast carcinoma. Continuous infusions of vinca alkaloids have been reported, although inconsistently, to yield high response rates in metastatic breast carcinoma.[13,27,29] Therefore, this mode of administration was chosen for VNB in this regimen.

The combination of continuous VNB and bolus CDDP was found efficient in this cohort of heavily pretreated patients, yielding an OR rate of 41% among 58 patients. This compares favorably with the 20–25% response rate reported in previous studies for patients with anthracycline-resistant disease.[4,22] In addition, the response rate achieved with the CIVIC regimen is in the range of those achieved with taxanes in similar clinical situations: paclitaxel and docetaxel have been reported to provide response rates of 48% and 53%, respectively.[30,31] Importantly, the CIVIC regimen was found to yield a high response rate in a small subgroup of patients with metastatic breast carcinoma failing to respond to both anthracycline and paclitaxel therapy. Seven of 12 patients (58%) who had received previous paclitaxel-containing chemotherapy in metastatic phase achieved OR, including 5 of 7 patients who had PD during anthracycline and paclitaxel therapy. Although this observation should be confirmed in a

larger cohort of patients, these results compare favorably with the response rate of 12% reported with docetaxel among 26 patients in the same situation.[32] No predictive factors for response were found in this study, including the proportion of patients previously treated with hormonal therapy or chemotherapy, expression of estrogen receptor, median disease free interval between initial treatment and relapse, tumor size at diagnosis, and negative or metastatic nodes. The response rate was not influenced by the previous number of chemotherapy lines, indicating that the CIVIC regimen is efficient even in a cohort of heavily pretreated patients.

The toxicity of the CIVIC regimen was moderate to high but manageable. Leukopenia (50% Grade 3 and 4 on 210 cycles) was the dose-limiting side effect. Neurotoxicity was generally mild and was Grade 0 in 71% of patients. A Grade 2–3 neurotoxicity was observed in 9 patients (15%). All objective responses were observed before four cycles, whereas the hematologic and neurologic toxicities were significantly higher after the fourth cycle.

The median overall survival rate of the whole population was 9.2 months. Eighteen patients of this cohort received consolidation therapy with cyclophosphamide and thiotepa, according to the protocol reported by Kennedy et al.,[33] after four or more courses of the CIVIC regimen. The median survival time for patients receiving HDCT (20.8 months) was superior to that of patients who did not receive HDCT (8 months). However, no definitive conclusions regarding the role of consolidation with HDCT after the CIVIC regimen can be drawn from the series because (1) this treatment was not randomized protectively and (2) a majority of patients treated with HDCT responded to the CIVIC regimen. Finally, the median survival of patients not receiving HDCT is 8 months, which is in the upper range of those published in second-line treatment in metastatic phase.[4]

These results suggest that the CIVIC regimen is efficient for the treatment of metastatic breast carcinoma refractory or in relapse to previous anthracycline- and/or paclitaxel-containing chemotherapy. Neutropenia is the dose-limiting toxicity, and because most responses were obtained after two cycles, a fourth cycle is optimal in terms of response rate and toxicity.

REFERENCES

1. Bonadonna G, Valagussa P, Rossi A, Tancini G, Brambilla C, Zambeti M, et al. Ten-year experience with CMF-based adjuvant chemotherapy in resectable breast cancer. *Breast Cancer Res Treat* 1985;5:95–115.
2. Henderson IC, Canellos GP. Cancer of the breast, the past decade (Part I). *N Engl J Med* 1980;302:17–30.
3. Henderson IC, Canellos GP. Cancer of the breast, the past decade (Part II). *N Engl J Med* 1980;302:78–90.
4. Henderson IC, Harris JR, Kinne DW, Hellman S. Cancer of breast. In: De Vita VT, Hellman S, Rosenberg SA, editors. Cancer: principles and practice of oncology. 4th ed. Philadelphia: JB Lippincott, 1989:1197–268.
5. Cannobio L, Boccardo F, Pastorino G, Brema F, Martini C, Resasco M, et al. Phase II study of navelbine in advanced breast cancer. *Semin Oncol* 1989;16:33–6.
6. Fumoleau P, Delgado FM, Delrozier T, Monnier A, Gil Delgado MA, Kerbrat P, et al. Phase II trial of weekly intravenous vinorelbine in first line advanced breast cancer chemotherapy. *J Clin Oncol* 1993;11:1245–52.
7. Marty M, Extra JM, Dieras V, Giacchetti S, Ohana S, Espie M. A review of the antitumour activity of vinorelbine in breast cancer. *Drugs* 1992;44:29–35.
8. Spielmann M, Dorval T, Turpin F, Jouve M, Rouëssé J, Turz T, et al. Phase II study with navelbine/doxorubicin as first line therapy of advanced breast cancer. *J Clin Oncol* 1994;12:1764–70.
9. Dieras V, Extra JM, Bellissant E, Espie M, Morvan F, Pierga JY, 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.
10. Ferrero JM, Pivot X, Namer M, Wendling JL, Frenay M, François E, et al. Combination of mitoxantrone-vinorelbine as first-line chemotherapy for metastatic breast cancer. *Bull Cancer* 1995;82:202–7.
11. Toussaint C, Izzo J, Spielmann M, Merle S, May-Levin F, Armand JP, et al. Phase I/II trial of continuous infusion vinorelbine for advanced breast cancer. *J Clin Oncol* 1994;12:2102–12.
12. Hortobagyi GN. Futures directions for vinorelbine (navelbine). *Semin Oncol* 1995;22:80–6.
13. Franschini G, Yap HY, Hortobagyi GN, Buzdar AU, Blumenschein G. Five-day continuous infusion vinblastine in the treatment of breast cancer. *Cancer* 1985;56:225–9.
14. Tannir N, Yap HY, Hortobagyi GH, Hug V, Buzdar AU, Blumenschein GR. Sequential continuous infusion with doxorubicin and vinblastine: an effective chemotherapy combination for patients with advanced breast cancer previously treated with cyclophosphamide, methotrexate, 5-FU, vincristine, and prednisone. *Cancer Treat Rep* 1984;68:1039–41.
15. Cros S, Wright M, Morimoto M, Lataste H, Couzinier JP, Krikorian A. Experimental activity of navelbine. *Semin Oncol* 1989;16:15–20.
16. Perry MC. Appendix: WHO toxicity guidelines. In: Perry MC, editor. The chemotherapy sources book. Baltimore: Williams & Wilkins, 1992:1132–44.
17. Kaplan EC, Meier P. Non parametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:437–81.
18. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959;22:719–48.
19. Hermanek P, Solin LH, editors. UICC TNM classification of malignant tumours. 4th ed. 2nd rev. Berlin: Springer-Verlag, 1992.
20. Henderson IC, Allegra JC, Woodcock T, Vollf S, Bryan S, Cartwright K, et al. Randomized clinical trial comparing mitoxantrone with doxorubicin in previously treated patients with metastatic breast cancer. *J Clin Oncol* 1989;7:560–71.

21. Swain SM, Lippman ME, Egan EF, Drake JC, Steinberg SM, Allegra CJ. Fluorouracil and high-dose leucovorin in previously treated patients with metastatic breast cancer. *J Clin Oncol* 1989;7:890–9.
22. Porkka K, Blomqvist C, Rissanen P, Elomaa I, Pyrhönen S. Salvage therapies in women who fail to respond to first-line treatment with fluorouracil, epirubicin, and cyclophosphamide for advanced breast cancer. *J Clin Oncol* 1994;12:1639–47.
23. Mathe G, Rezentein P. Phase I pharmacological study of a new vinca-alkaloid: navelbine. *Cancer Lett* 1985;27:285–93.
24. Weber BL, Vogel C, Jones S, Harvey H, Hutchins L, Bigley J, et al. Intravenous vinorelbine as first-line and second-line therapy in advanced breast cancer. *J Clin Oncol* 1995; 13:2722–30.
25. Holland JF, Sharlan C, Gailiani S, Krant MJ, Olson KB, Horton J, et al. Vincristine treatment of advanced cancer: a cooperative study of 392 cases. *Cancer Res* 1973;33:1258–64.
26. Smith IE, Powls T. Vindesine in the treatment of breast cancer. *Cancer Chemother Pharmacol* 1979;2:261–2.
27. Franschini G, Holmes FA, Buzdar AU, Hug V, Hortobagyi GN. Cisplatin in combination with continuous infusion vinblastine for refractory breast cancer. *Am J Clin Oncol* 1988;11:448–50.
28. Romero A, Rabinovish MG, Vallejo CT, Perez JE, Rodriguez R, Cuevas MA, et al. Vinorelbine as first-line chemotherapy for metastatic breast carcinoma. *J Clin Oncol* 1994;12:336–41.
29. Shah MK, Creech RH, Catalano R, St. Marie K. Phase II study of vinblastine infusion in the treatment of refractory advanced breast cancer. *Proc Am Soc Clin Oncol* 1982;280:73.
30. Wilson WH, Berg SL, Bryant G, Wittes RE, Bates S, Fojo A, et al. Paclitaxel in doxorubicin-refractory or mitoxantrone-refractory breast cancer: a phase I/II trial of 96-hour infusion. *J Clin Oncol* 1994;12:1621–9.
31. Valero V, Burris HA, Jones SE, Booser DJ, Ravdin P, Mennel R, et al. Multicenter pilot study of taxotere in Taxol-resistant metastatic breast cancer (MBC). *Proc Am Soc Clin Oncol* 1996;15:95.
32. Valero V, Holmes FA, Walters RS, Theriault RL, Esparza L, Franschini G, et al. Phase II trial of docetaxel: a new, highly effective antineoplastic agent in the management of patients with anthracycline-resistant metastatic breast cancer. *J Clin Oncol* 1995;13:2886–94.
33. Kennedy MJ, Beveridge RA, Rowley SD, Gordon GB, Abeloff MD, Davidson NE. High-dose chemotherapy with reinfusion of purged autologous bone marrow following dose-intense induction as initial therapy for metastatic breast. *J Natl Cancer Inst* 1991;83:920–6.