Weekly Vinorelbine Is an Effective Palliative Regimen after Failure with Anthracyclines and Taxanes in Metastatic Breast Carcinoma

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BACKGROUND. Currently, there is no gold standard for the treatment of patients with metastatic breast carcinoma who have experienced failure with anthracyclines and taxanes. A biologic rationale suggests that the mechanism of taxane resistance could be because of an excess of depolymerized tubulin that could enhance sensitivity to vinorelbine. The objective of the study was to assess the tolerance and efficiency of weekly vinorelbine in metastatic breast carcinoma after failure with taxanes.

METHODS. Patients with measurable disease, a World Health Organization performance status of less than 3 and a life expectancy longer than 3 months were eligible. Persistent taxane-induced neuropathy higher than Grade 1 was an exclusion criterion. The initial planned dose was 30 mg/m^2/week on an outpatient basis without granulocyte colony-stimulating factor (G-CSF). Neutrophil and platelet counts of 1.0 and 80 g/L, respectively, were required before each new injection; otherwise vinorelbine was delayed for 7 days with a dose reduction of 5 mg/m^2 at the second episode. The dose also was reduced if Grade 3 or 4 toxicity occurred. If the adverse event persisted or if the delay exceeded 14 days between 2 injections given at a dose of 20 mg/m^2, vinorelbine was definitively discontinued.

RESULTS. Between November 1997 and March 1999, 40 patients with a median age of 49 (range, 39–69) were enrolled. All of them had previously received anthracyclines and taxanes. Because of the delays in neutrophil recovery, the median dose intensity did not exceed 22.5 mg/m^2/week (range, 11.25–30), and the initial planned dose of 30 mg/m^2/week appeared unfeasible without G-CSF. The starting dose therefore was 25 mg/m^2/week after the first 6 patients. Neutropenia led to fever in only three patients. Other severe toxicities were Grade 2–3 neuropathy (n = 5), Grade 2–3 ileus (n = 7), Grade 3 anemia (n = 4), and Grade 3 sepsis (n = 1). Objective responses were observed in 10 of 40 patients (25%), 7 of whom had visceral metastases and 4 who were refractory to taxanes (including 2 patients with liver involvement > 50%). The median time to failure was 6 months (range, 4–12) for responding patients. Disease stabilization was achieved in 9 patients (23%) for a median duration of 5 months (range, 4–6). The median survival duration for the whole population was 6 months (range, 2–18+).

CONCLUSIONS. Weekly vinorelbine is an active salvage therapy for metastatic breast carcinoma after failure with anthracyclines and taxanes, even in patients with taxane-refractory metastatic breast carcinoma. This confirms that vinorelbine and taxanes are not cross-resistant. ***Cancer* 2001;92:2267–72.**

KEYWORDS: metastatic breast carcinoma, chemotherapy, salvage regimen, vinorelbine.

The treatment of breast carcinoma patients with metastases after failure with taxanes remains controversial because no drug has emerged as a gold standard. Moreover, the number of trials address-

ing the issue of salvage therapy as second- or third-line management remains low, and only a few of them specifically included patients treated with taxanes.[1] The identification of active salvage agents therefore is urgently awaited.

In this setting, the administration of vinca alkaloids is supported by the biologic rationale that suggests that the mechanism of taxane resistance could be because of an excess of depolymerized tubulin that could enhance sensitivity in these compounds.[2–4] Among the vinca alkaloids currently used, vinorelbine (Pierre Fabre Médicament, Boulogne) seems to be the most promising in breast carcinoma with an objective response (OR) rate of approximately 40% when given as first-line therapy and excellent safety and feasibility,[5] making it a candidate of choice for palliative therapy in pretreated patients.

Our own experience with vinorelbine-containing regimens after failure with taxanes[6] was in favor of the use of vinorelbine; however, the combination regimen we investigated was discontinued after the inclusion of 30 patients because of its toxicity. The less toxic weekly outpatient schedule with vinorelbine alone was considered a better option for treatment with a palliative intent and therefore was chosen for this trial. We recently reviewed the advantages of weekly regimens.[7]

The conflicting results of the three trials previously published reinforced the need for further investigations on this drug after failure with taxanes. The first trial was stopped prematurely because of the absence of ORs suggesting cross-resistance between taxanes and vinorelbine and a high rate of severe toxicities.[8] The second study reported an impressive response rate of 25% in taxane-refractory patients using an intensive schedule with granulocyte colony-stimulating factor (G-CSF) support.[9] The most recent study enrolled only 20 patients with a two-weekly schedule that yielded a 35% response rate and markedly less toxicity.[10] Obviously, the dose intensity and the type of dose-limiting toxicity, namely, neutropenia or neuropathy, are critical issues when vinorelbine is administered to such patients.

PATIENTS AND METHODS

Patient Selection

Eligible patients were to have experienced treatment failure while receiving or after completing, a taxane-containing regimen for recurrent breast carcinoma. Women older than 18 years with a pathologically proven breast recurrence, a World Health Organization (WHO) performance status less than 3, and an estimated life expectancy exceeding 12 weeks were eligible for the study. Patients were required to have bi-dimensionally measurable disease located in a nonirradiated area. An interval of less than 3 weeks after radiotherapy or previous chemotherapy was not allowed. Asymptomatic central nervous system metastases, laboratory values indicating poor liver or kidney function, bone marrow involvement, and rapidly progressive visceral disease were not exclusion criteria. Patients were excluded for the following reasons: higher than Grade 1 peripheral neuropathy, hepatic encephalopathy, uncontrolled central nervous system metastases, and pregnancy. Other antineoplastic agents or concomitant radiotherapy were not allowed. All patients gave their informed consent before the initiation of treatment. All patients were enrolled in our institution.

Treatment Schedule

Pretreatment neutrophil and platelet counts of greater than 1.5 and greater than 100 g/L, respectively, were required before the initiation of treatment (except in the case of bone marrow involvement). The starting dose of vinorelbine was 30 mg/m^2/week based on the original schedule,[5] and growth factor support was not permitted throughout the study (except in the case of life-threatening neutropenic fever). Vinorelbine was given on an outpatient basis, diluted in 125 mL of normal saline or 5% glucose and infused over 30 minutes after adequate antiemetic premedication (alizapride or setron with or without steroids). A central venous access was used in all cases to prevent extravasation of vinorelbine.

Dose modifications were based on observed toxicity. A hemogram was obtained every week, and neutrophil and platelet counts of greater than 1.0 and greater than 80 g/L, respectively, were required before continuation of treatment. If this was not the case, therapy was delayed until hematologic recovery, and the dose of vinorelbine subsequently was reduced to 25 mg/m^2/week when 2 consecutive injections had to be deferred. The same rule was applicable in case of neutropenic fever or higher than Grade 2 nonhematologic toxicity, but, in case of severe neuropathy or ileus, treatment was definitively discontinued to avoid persistent detrimental effects on the patient's quality of life. If 2 consecutive injections at the planned dose of 25 mg/m^2 were unfeasible, doses could be reduced to 20 mg/m^2/week. However, if therapy was not possible at this last dose (deferral of $>$ 14 days because of delayed hematologic recovery or other toxicity, or severe neurotoxicity including ileus), the patient was withdrawn from the study.

Treatment was to be repeated as planned until disease progression, unacceptable toxicity defined as above, or discontinued at the patient's request.

Treatment Evaluation

The objective of the study was to assess the feasibility and efficiency of weekly vinorelbine administered on an outpatient basis as salvage therapy after failure with taxanes. The primary trial endpoints were the determination of an OR rate, the delivered dose intensity expressed in milligrams per square meter per week, and of the toxicity of single-agent vinorelbine in these patients with particular attention being paid to peripheral neuropathy. Secondary endpoints were time to treatment failure and survival. Before the initiation of vinorelbine, the following investigations were performed: physical examination, performance status assessment, a hemogram, hepatic chemistry, serum CA 15-3 measurement, and diagnostic imaging, as required, to document measurable disease. Symptoms and toxicities were recorded at every weekly visit, and clinical assessment was repeated every 4 weeks. Response was evaluated every 8 weeks according to WHO criteria. Time to failure and survival were calculated from the onset of therapy. Failure included death from any cause, tumor progression, and withdrawal of treatment because of toxicity. The response rate is expressed as an intent-to-treat result.

RESULTS

In total, 40 patients were entered onto this trial between November 1997 and May 1999. Their median age was 49 (range, 39–69) years. The median number of prior regimens for treatment of Stage IV disease was 2 (range, 1–7), and weekly vinorelbine was mainly used as third-line therapy (28 of 40). Twenty-nine patients had predominantly visceral disease. Patients were classified according to their chemoresistance by using the following version of the classification proposed by Piccart et al.: 1) refractory: progression as best response during either adjuvant or palliative treatment; 2) resistance: response or initially stable disease during treatment, then progression either within 3 months of completing chemotherapy for metastatic disease or within 6 months of completion of adjuvant therapy.[11] Patient characteristics are summarized in Table 1.

TABLE 1
Patient Characteristics

Characteristic	Patients (%)
Previous regimens	
Adjuvant chemotherapy	22 (55)
Metastatic disease regimens including:	
Anthracycline	33 (81)
Paclitaxel*	12 (30)
Docetaxel*	28 (70)
Previous regimens received for metastatic disease	
1–3	31 (77)
> 3	9 (23)
Resistance to previous therapy	
Anthracyclines	
Refractory	20 (50)
Resistant	6 (15)
Taxanes	
Refractory	17 (42)
Resistant	7 (17)
Metastatic sites	
Liver	22 (55) (> 50% involvement in 7 patients)
Bone	15 (37)
Skin/chest wall	10 (25)
Lung	9 (22)
Lymph nodes	5 (12)
Bone marrow	4 (10)
Pleura	3 (7)
CNS	3 (7)
Peritoneum	2 (5)
No. of metastatic sites	
1	14 (35)
2	19 (48)
3+	7 (17)
No. of involved viscera(e)	
0	11 (27)
1+	29 (73)

CNS: central nervous system.
[a] For all patients, q21d schedules were used.

Dosing and Dose Intensity

After the first 6 patients, the initial planned dose of 30 mg/m^2/week proved unfeasible because of neurotoxicity ($n = 2$), severe neutropenia with delayed recovery longer than 14 days ($n = 3$), thrombocytopenia ($n = 2$), anemia requiring transfusion ($n = 1$), and neutropenic fever ($n = 1$). As mentioned in the protocol, these patients subsequently were treated at a dose of 25 mg/m^2/week, which was also retained as the starting dose for all the patients who followed.

Of the overall population, 3 patients discontinued therapy after the first injection (Grade 3 neuropathy: $n = 1$; abdominal pain with ileus: $n = 1$; patient request: $n = 1$) and were not considered for dose intensity assessment. The median delivered dose intensity for the 37 remaining patients was 22.5 mg/m^2/week (range, 11.25–30). A median delivered dose intensity of the same magnitude was attained for the responding patients (23.5 mg/m^2/week).

Response Rate, Time to Failure, and Survival

Of the 40 patients evaluable for response, 10 (25%; 95% confidence interval, 13–41%) achieved an OR; no complete responses were obtained. Nine other patients had stable disease. Seven of the 24 patients (29%) who were refractory or resistant to taxanes achieved an OR, including 2 with liver involvement greater than 50%, and disease stabilization was ob-

TABLE 2
Response to Study Treatment According to Taxane Resistance

Response	Refractory[a] (*n* [%])	Resistant[b] (*n* [%])	Total refractory + resistant[c] (*n* [%])	Nonresistant[d] (*n* [%])	Total[e] (*n* [%])
OR	4 (24)	3 (42)	7 (29)	3 (18)	10 (25)
SD	6 (35)	1 (16)	7 (29)	2 (13)	9 (23)
PD	7 (41)	3 (42)	10 (42)	11 (69)	21 (52)

OR: objective response; SD: stable disease; PD: progressive disease.
[a] $n = 17$.
[b] $n = 7$.
[c] $n = 24$.
[d] $n = 16$.
[e] $n = 40$.

TABLE 3
Characteristics of Responding Patients

Age (yrs)	No. of previous regimens for ABC	Anthracycline resistance	Taxane resistance	Metastatic sites	Time to failure (mos)	Survival (mos)
41	1	—	—	Chest wall, lymph nodes, bone	4	10
37	2	R	R	Lymph nodes, bone	4	7
43	1	R	R	Liver,[a] bone	7	8
58	7	r	r	Skin, lung	6	9+
49	2	—	R	Liver[a]	12	18+
54	2	—	r	Liver, bone marrow	6	7
56	1	—	—	Liver	8	17+
61	1	—	—	Bone, skin, peritoneum	6	12+
66	2	r	R	Liver, brain	6	7
54	2	r	r	Liver, bone	6	8+

R: refractory; r: resistant according to the criteria proposed by Piccart et al.[11]
[a] Metastatic involvement > 50%.

tained in 7 of them (29%). In the 16 patients who were not resistant to taxanes, 3 (18%) achieved an OR and 2 (13%) disease stabilization. There was no significant difference in OR rates between these two subgroups. Responses were observed in patients who previously had received paclitaxel or docetaxel. The characteristics of responding patients are shown in Table 3.

The median time to failure was 6 months (range, 4–12) for responding patients and 5 months for patients with disease stabilization (range, 4–6). The median survival duration for the whole population was 6 months (range, 2–18+). Patients who progressed under therapy had a very poor prognosis with a median survival not exceeding 2 months (range, 1–4). For responding patients and those who had stable disease, median survival was 8.5 months (range, 7–18+) and 7 months (4–12+), respectively. No difference in time to failure or survival was found when taxane-resistant patients were compared with others.

Tolerance and Toxicity

Neutropenia was a dose-limiting toxicity, and the frequent delays in hematologic recovery account for the low dose intensity achieved. Nine patients experienced Grade 4 neutropenia, but neutropenic fever occurred in only 3 patients. Other hematologic toxicities included Grade 3–4 anemia ($n = 4$) and Grade 3–4 thrombocytopenia ($n = 2$). Platelet and erythrocyte transfusions were mandatory in one and four patients, respectively, including one patient with bone marrow involvement and another with extensive bone metastases.

Seven patients had constipation with abdominal pain or ileus (Grade 2, $n = 4$; Grade 3, $n = 3$). Five other patients had peripheral neuropathy (Grade 2, $n = 3$; Grade 3, $n = 2$). Taken together, severe peripheral or gastrointestinal neurotoxicity occurred in 12 patients (27%); in 6 of these patients a dose reduction was not conceivable and treatment had to be interrupted.

Chemotherapy was stopped for one patient for Grade 3 sepsis without neutropenia (hip prosthesis infection). No other severe side effects were reported, but persistent asthenia occurred in 19 patients, that was mainly disease-related.

DISCUSSION

Breast carcinoma is the second most common cause of cancer deaths in women in the United States and Europe. Metastatic recurrences remain distressingly common, and systemic chemotherapy is widely used in this setting with response rates attaining 70–80% if we consider the most recent taxane-based regimens.[1]

The success of alternative chemotherapy in patients with metastatic breast carcinoma who failed on taxanes has been modest, and the definition of salvage regimens increasingly is becoming a major concern because of the widespread use of taxanes as part of first-line regimens. Valero et al.[12] reported the use of standard dose docetaxel that yielded a 18% response rate in 44 patients who failed on paclitaxel, but toxicity was prohibitive. Use of weekly paclitaxel also obtained a meaningful response rate after failure with classic every 3 week schedules.[13] Among newer drugs, capecitabine appears to be promising with an OR rate of 20% and a favorable tolerance profile[14] Other agents such as gemcitabine or pemetrexed (MTA, LY231514) are potential candidates,[15,16] but to our knowledge no specific trial addressing their activity in taxane-resistant patients has been published to date with these drugs. However, an OR rate of 28% was observed in a small series of 29 patients included in a second-line Phase II trial with pemetrexed who previously had received taxanes and anthracyclines.[17]

Many clinical trials with vinorelbine as a single agent or combined with other agents have been published[5]; such regimens are feasible and as effective as other standard regimens. When given as a second-line regimen in 2 large series, vinorelbine yielded OR rates in 16%.[18,19] Among the clinical trials addressing the efficiency of salvage chemotherapy for taxane-pretreated patients, published data on single-agent vinorelbine in this setting are limited to two clinical trials with diametrically opposed results. Fazeny et al.[8] conducted a Phase II study that was discontinued after inclusion of 14 patients. They concluded that paclitaxel-pretreated patients were totally resistant to vinorelbine and should be excluded from consecutive vinorelbine-containing regimens. Neuropathy and constipation were common adverse effects and, as in our own experience, frequently led to withdrawal of vinorelbine. The vinorelbine schedule given in this study, however, was suboptimal (30 mg/m^2 every 14 days during the first 8 weeks and every 21 days thereafter), and this could explain the lack of ORs. Our own previous experience with vinorelbine-containing regimens after failure with taxanes[6] were at variance with these conclusions.

The results of the Phase I–II trial of a weekly dose-intensive schedule with G-CSF published later by Livingston et al.[9] supported our hypotheses and suggested that the biologic rationale predicting the efficiency of vinorelbine in taxane-refractory patients might be valid. Dose intensity may be a critical issue when vinorelbine is used as salvage therapy in patients with metastases. The gain in delivered dose intensity obtained in Livingston et al.'s study remains modest with a median delivered dose intensity at 27.7 mg/m^2/week (vs. 22.5 without G-CSF in our trial). Moreover, a high rate of extrahematologic toxicities occurred that questions the role of G-CSF. Despite a lower delivered dose intensity, response rates, time to failure, and survival in our study were of the same magnitude as that reported by Livingston et al.; furthermore, the results reported by Udom et al. with a two-weekly schedule also corroborate our findings.[10] Several differences in inclusion criteria between these two series must be underscored: impaired liver or kidney function, bone marrow involvement, and asymptomatic brain metastases were not excluded from our study. Failure with a taxane was not an inclusion criterion in Livingston et al.'s trial, even though all patients included had been pretreated with taxanes, with a large proportion (38 of 40) being refractory to these compounds. It is difficult to determine to what extent these differences in the study populations might explain the high number of neurologic toxicities in our series (12 of 40 patients vs. 7 of 40 patients in Livingston et al.'s trial). Our population is, however, a better reflection of what might be expected in daily clinical practice because of "broad-spectrum" inclusion criteria.

Even without CSF support, vinorelbine is among the most active salvage agents after failure with taxanes provided a sufficient delivered dose intensity is achieved. This activity gives rise to significant nonhematologic toxicity including severe peripheral neuropathy and ileus. Because quality of life is a major concern in breast carcinoma patients with metastatic disease receiving palliative salvage therapy, candidates for vinorelbine should be selected according to their predicted ability to tolerate this regimen rather than according to their taxane resistance status. In particular, patients with residual taxane-induced neuropathy should not receive weekly vinorelbine as salvage therapy.

Because weekly taxanes proved capable of reversing resistance to conventional every 3 week taxane schedules to a certain extent, it may produce noteworthy results to combine them with weekly vinorelbine

for a salvage regimen.[20,21] Preliminary results with such schedules are, however, conflicting if not disappointing.[21] However, the hypothesis that resistance to taxanes might be mediated by an excess of depolymerized tubulin provides a strong biologic rationale in favor of first-line taxane-vinorelbine combinations because it suggests that sensitivity to these compounds is likely to be enhanced in such tumors.[2–4] Although there is no clinical evidence that this mechanism might be relevant in vivo, the responses observed in our series in taxane-refractory patients with massive visceral involvement together with the striking results reported by Livingston et al. have to be underscored.[9] Several pilot studies published show promising results but at the expense of significant toxicity.[22–26] Answers to numerous questions are awaited, especially concerning the definition of an optimal schedule. It should be emphasized that the sequence in which paclitaxel and vinorelbine are administered could be a key issue in experimental models.[27]

REFERENCES

1. Ellis MJ, Hayes DF, Lippman ME. Treatment of metastatic breast cancer. In: Harris JR, Lippman ME, Morrow M, Osborne CK, editors. Diseases of the breast. Philadelphia: Lippincott Williams and Wilkins, 2000:749–98.
2. Minotti AM, Barlow SB, Cabral F. Resistance to antimitotic drugs in Chinese hamster ovary cells correlates with changes in the level of polymerized tubulin. *J Biol Chem* 1991;266:3987–94.
3. Diaz JF, Menedez M, Andreu JM. Thermodynamics of ligand-induced assembly of tubulin. *Biochemistry* 1993;32: 10067–77.
4. Ohta S, Nishio N, Kubota N, et al. Characterization of a taxol-resistant human small-cell lung cancer cell line. *Jpn J Cancer Res* 1994;85:290–7.
5. Spielmann M, Zelek L. Vinorelbine. In: Nabholtz JM, Tonkin K, Aapro MS, Buzdar AU, editors. Breast cancer management. application of evidence to patient care. London: Martin Dunitz, 2000:87–97.
6. Delord JP, Zelek L, Rixe O, et al. Celliptium acetate: an "old" active new drug in advanced breast cancer. A phase I-II combination vith vinorelbine. *Breast Cancer Res Treat* 1998; 50:265.
7. Fizazi K, Zelek L. Is "one cycle every three or four weeks" obsolete? A critical review of dose-dense chemotherapy in solid neoplasms. *Ann Oncol* 2000;11:133–49.
8. Fazeny B, Zifko U, Meryn S, et al. Vinorelbine-induced neurotoxicity in patients with advanced breast cancer pretreated with paclitaxel—a phase II study. *Cancer Chemother Pharmacol* 1996;39:150–6.
9. Livingston RB, Ellis GK, Gralow JR, et al. Dose-intensive vinorelbine with concurrent granulocyte colony-stimulating factor support in paclitaxel-refractory metastatic breast cancer. *J Clin Oncol* 1997;15:1395–400.
10. Udom DI, Vigushin DM, Linardou H, et al. Two weekly vinorelbine: administration in patients who have received at least two prior chemotherapy regimens for advanced breast cancer. *Eur J Cancer* 2000;36:177–82.
11. Piccart M, Raymond E, Aapro M, et al. Cytotoxic agents with activity in breast cancer patients previously exposed to anthracyclines: current status and future prospects. *Eur J Cancer* 1995;31A:S1–10.
12. Valero V, Jones SE, Von Hoff DD, et al. A phase II study of docetaxel in patients with paclitaxel-resistant metastatic breast cancer. *J Clin Oncol* 1998;16:3362–8.
13. Waintraub S E, Cantwell S, DeVries J. Phase II study to evaluate the efficacy of weekly paclitaxel (WP) in patients with metastatic breast cancer (MBC) who have failed prior anthracycline (A) ± taxane (T) therapy. *Proc Annu Meet Am Soc Clin Oncol* 2000;19:470.
14. Blum JL, Jones SE, Buzdar Au, et al. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. *J Clin Oncol* 1999;17:485–93
15. Spielmann M, Kalla S, Llombart-Cussac A, et al. Activity of gemcitabine in metastatic breast cancer (MBC) patients previously treated with anthracycline-containing regimens. *Eur J Cancer* 1997;33(Suppl 8):S149.
16. Adjei AA. Pemetrexed: a multitargeted antifolate agent with promising activity in solid tumors. *Ann Oncol* 2000;11:1335–41.
17. Martin M, Spielmann M, Namer M, et al. MTA (multitargeted antifolate, LY231514) in metastatic breast cancer patients (pts) with prior anthracycline exposure: an European phase II study. *Proc Annu Meet Am Soc Clin Oncol* 1999;18: 427a.
18. Degardin M, Bonneterre J, Hecquet B, et al. Vinorelbine (navelbine) as a salvage treatment for advanced breast cancer. *Ann Oncol* 1994;5:423–6.
19. Jones S, Winer E, Vogel C, et al. Randomized comparison of vinorelbine and melphalan in anthracycline-refractory advanced breast cancer. *J Clin Oncol* 1995;13:2567–74.
20. Cohen RB, Mueller SC, Haden K, de Souza P. Phase I study of weekly vinorelbine in combination with weekly paclitaxel in adult patients with advanced refractory cancer. *Cancer Invest* 2000;18:422–8.
21. Frasci G, Comella P, D'Aiuto G, et al.Weekly docetaxel plus gemcitabine or vinorelbine in refractory advanced breast cancer patients: a parallel dose-finding study. Southern Italy Cooperative Oncology Group (SICOG). *Ann Oncol* 2000;11: 367–71.
22. Fumoleau P, Fety R, Delecroix V, Perrocheau G, Azli N. Docetaxel combined with vinorelbine: phase I results and new study designs. *Oncology* 1997;11:29–31.
23. Tortoriello A, Facchini G, Caponigro F, et al. Phase I/II study of paclitaxel and vinorelbine in metastatic breast cancer. *Breast Cancer Res Treat* 1998;47:91–7.
24. Romero Acuna L, Langhi M, Perez J, et al. Vinorelbine and paclitaxel as first-line chemotherapy in metastatic breast cancer. *J Clin Oncol* 1999;17:74–81.
25. Ellis GK, Gralow JR, Pierce HI, et al. Infusional paclitaxel and weekly vinorelbine chemotherapy with concurrent filgrastim for metastatic breast cancer: high complete response rate in a phase I-II study of doxorubicin-treated patients. *J Clin Oncol* 1999;17:1407–12.
26. Budman DR, Weiselberg L, O'Mara V, et al. A phase I study of sequential vinorelbine followed by paclitaxel. *Ann Oncol* 1999;10:861–3.
27. Kano Y, Akutsu M, Suzuki K, et al. Schedule-dependent interactions between vinorelbine and paclitaxel in human carcinoma cell lines in vitro. *Breast Cancer Res Treat* 1999; 56:79–90.