Phase II Study of Vinorelbine Administered by 96-Hour Infusion in Patients with Advanced Breast Carcinoma

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BACKGROUND. Vinorelbine given by weekly bolus injection is active and less toxic than bolus vinblastine in the treatment of patients with metastatic breast carcinoma. Vinblastine given by 5-day continuous infusion showed a steep dose-response curve. Pharmacokinetic studies of vinorelbine showed that it is possible to achieve a comparable antitumor effect with a smaller amount of the drug if it is given by continuous infusion. The purpose of this study was to determine the efficacy of vinorelbine given by 96-hour continuous infusion to patients with refractory metastatic breast carcinoma patients.

METHODS. Between May 1996 and August 1997, 47 patients with metastatic breast carcinoma were registered into the study. All patients previously had received doxorubicin and 70% had undergone prior paclitaxel treatment. Approximately 56% of the patients had $\geq$2 metastatic sites. All patients received vinorelbine according to the following dose schedule: 8 mg bolus followed by 11 mg/m^2 by continuous infusion over 24 hours every 4 days every 3 weeks.

RESULTS. Forty-four patients were evaluable for response. A total of 193 cycles were administered. The overall response rate was 16% (2 patients achieved a complete response and 5 patients achieved a partial response). The median duration of response was 4.3 months and the median overall survival was 8.6 months. Patients with visceral metastases and/or multiple sites of involvement had shorter durations of response than patients with only soft tissue disease or single-site metastasis (3.1 months vs. 4.9 months) and shorter overall survival (8.1 months vs. 12 months). Dose reductions were necessary due to cumulative stomatitis and/or fatigue in 12 cycles and neutropenia and/or infection in 13 cycles.

CONCLUSIONS. Due to toxicity, a revised maximum tolerated dose for continuous infusion vinorelbine is proposed by the authors: 8 mg intravenously over 10 minutes followed by 10 mg/m^2 by continuous infusion over 24 hours every 4 days. The current dose schedule did not offer an advantage either in response rates or survival over the weekly vinorelbine bolus injection in doxorubicin-resistant and paclitaxel-resistant patients. ***Cancer*** **1999;86:1251–7.**
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The efficacy and toxicity of cytotoxic agents can be modified significantly by changing the dose or schedule of administration. The organ specific toxicity can be altered or modified by changing the dose schedule of doxorubicin,[1] paclitaxel,[2–8] and fluorouracil.[9–13] In addition, response rates may vary with different dose schedules of the

same agent (vinblastine,[14–16] paclitaxel,[5,8,17–20] fluorouracil[21–24]). Metastatic breast carcinoma patients treated with vinblastine by continuous 5-day infusion showed an objective response rate of 37% compared with a response rate of 20% in patients who received vinblastine as an intravenous bolus every 3 weeks.[15]

Vinorelbine[25] is a hydroxy derivative of vinblastine that is synthesized by modifying the catharanthine ring rather than the vindoline ring of the molecule. This new vinca alkaloid has demonstrated activity against breast carcinoma and other tumors. Its maximum tolerated dose (MTD) is 30–36 mg/m^2 given intravenously weekly. The dose-limiting toxicity is granulocytopenia, with the nadir occurring on Days 7–10 followed by a quick recovery in 3–5 days. The incidence of nonhematologic toxicities, including peripheral neuropathy and constipation, is minimal. Because of this combination of characteristics, there is interest in determining whether administering vinorelbine by continuous infusion will enhance its efficacy and therapeutic index.

Toussaint et al.[26] demonstrated the feasibility of administering vinorelbine by continuous infusion. Their data also suggested a dose-response relation and a dose intensity/activity correlation. In a Phase I study,[27] we determined that the MTD of vinorelbine was 8 mg in a bolus injection on Day 1 followed by 11 mg/m^2 given by continuous infusion over 24 hours daily for 4 days (96 hours). Based on the reported experience with this dose schedule and the MTD we identified, we initiated a Phase II study to determine the response of heavily pretreated patients with metastatic breast carcinoma to vinorelbine given by 96-hour continuous infusion. We also determined the duration of response and the overall survival rate for patients who received such treatment.

MATERIALS AND METHODS

Between May 1996 and August 1997, 47 patients with histologically proven metastatic breast carcinoma refractory to doxorubicin-containing chemotherapy were treated with 96-hour, continuous intravenous infusions of vinorelbine. Patients were considered eligible for entry into the study if they had microscopically confirmed carcinoma of the breast with measurable metastatic disease shown by physical examination or radiologic studies. Patients could not have received >3 prior chemotherapy regimens for their metastatic breast carcinoma. Prior exposure to vinca alkaloids was an exclusion criterion. All patients had adequate bone marrow reserve, as reflected by a granulocyte count > 1500/μL and a platelet count > 100,000/mL. In addition, they had bilirubin concentration < 1.5 mg/m^2, transaminase activity ≤ 4 times the upper limit of normal, and serum creatinine concentration ≤ 1.4 mg/m^2. All patients were age > 18 years, with a life expectancy ≥ 12 weeks, and a Zubrod performance status ≤ 2. A signed, informed consent form approved by the institution's investigational review board was obtained from all patients on the study.

All patients had a complete pretreatment evaluation, including history and physical examination, complete blood counts, serum chemistry (SMA-12) tests, and measurements of carcinoembryonic antigen (CEA) level, prothrombin time, and partial thromboplastin time. Chest X-ray, ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI), when applicable, also were performed to measure extent of disease and to assess responses. A bone scan and plain X-ray studies of suspicious areas of increased activity also were required. Soft tissue lesions were documented with photographs when applicable. Before each subsequent cycle, the patient had a physical examination, complete blood count, and SMA-12 test. The CEA level was determined if it had been abnormal when previously tested. Tumor measurements were taken until the maximum response occurred, after which, measurements were taken every 3–4 months. In addition, a radiologic evaluation, including chest X-ray, ultrasonograms, CT scans, MRI scans, and/or bone scans as well as plain films of the bone, was repeated every 2–3 cycles, as applicable.

Vinorelbine was given via a central venous catheter as follows: after a fixed loading dose of 8 mg given intravenously over 10 minutes, a continuous infusion of vinorelbine (11 mg/m^2) was given over 24 hours; this was done for 4 consecutive days (44 mg/m^2 over 96 hours). All treatments were given on an outpatient basis using portable infusion pumps to ensure an even and constant flow of the medication. Treatment cycles were repeated at 3-week intervals, provided the absolute granulocyte count had recovered to ≥1500 cells/μL.

Responses were assessed after the second cycle and periodically thereafter until a maximum response or disease progression occurred. A complete response (CR) was defined as the complete disappearance of all clinically recognizable tumor for a minimum of 4 weeks, including normalization of the bone roentgenogram findings and absence of all tumor-related symptoms. A partial response (PR) was defined as a reduction ≥50% in the product of the largest perpendicular dimensions of measurable lesions that was maintained for a minimum of 4 weeks and without the appearance of new lesions, plus recalcification of osseous lytic metastasis, where applicable. A minor re-

TABLE 1
Patient Characteristics

Characteristic	No. of patients[a]	%
Patients entered	47	
Patients evaluable	44	94
Median age (yrs) (range)	47 (25–72)	
Gender:female	44	100
Pathology: invasive ductal carcinoma	44	100
Prior chemotherapy regimen		
1[b]	9	20
2	19	43
3	15	34
>4	1	2
Chemotherapy exposure		
Doxorubicin	44	100
Paclitaxel	31	70

[a] Except as noted.
[b] All received doxorubicin and paclitaxel.

TABLE 2
Sites of Metastatic Disease

Site	No. of patients (n = 44)	%
Organ involved		
Soft tissue (skin, lymph nodes)[a]	21 (6, 15)	48
Liver	20	45
Bone	15	34
Lung	13	30
Pleura/pleural effusion	4	9
No. of organs involved		
1	19	43
>1 (2, ≥3)	25 (9, 16)	56

[a] Eight patients had soft tissue as the only site of involvement with metastatic disease.

sponse or stable disease (SD) was defined as no appreciable variation in the measurable tumor for at least 2 months and without the appearance of any new lesions. Progressive disease (PD) was defined as any objective increase in any area of a measurable tumor from its smallest size during therapy or the appearance of any new lesion. The duration of the response was measured from the onset of treatment. All responses were reviewed and validated by an internal response review committee.

Statistical Analysis

We used the three-stage, Phase II design of Simon to assess the significance of response. We targeted an activity level of 30% and α and β error probabilities of 0.05 and 0.20, respectively. Therefore, drug for response rates $<1/10$ or $<5/29$ were rejected. For the drug responses that were $\geq 5/29$, we continued accrual to a total of 40 patients.

RESULTS

Three of the 47 patients entered on this study were not evaluable for response. One patient died after the second cycle, before her response was confirmed. Another patient withdrew from the study, and a third patient was unevaluable because she had blastic bone disease. Patient characteristics are shown in Table 1. The distribution of metastatic disease sites is shown in Table 2. In total, 193 cycles were administered to the 44 evaluable patients (median, 4 cycles; range, 1–12 cycles). We had to reduce the doses in 22 patients (25 cycles). The dose was reduced by 1 level in 19 of these patients and by 2 levels in 3 patients. Doses were reduced at a median time of the third cycle (range, second to eighth cycle). Dose reductions were necessitated by the development of stomatitis and/or fatigue in 12 cycles and neutropenia and/or infection in 13 cycles.

Two of the 44 evaluable patients (5%) achieved a CR, and 5 patients (11%) achieved a PR. SD was observed in 15 patients (34%), and 22 patients (50%) had PD. We also evaluated the responses in the 8 patients with soft tissue metastasis only and compared them with the responses in the 36 patients with visceral metastasis. Two patients (25%) with soft tissue metastasis achieved a CR, 1 patient (12.5%) achieved a PR, 2 patients (25%) had SD, and 3 patients (37.5%) had PD. The distribution of the responses in the 36 patients who had visceral metastases was as follows: 4 patients (11%) had a PR, 13 patients (36%) had SD, 19 patients (53%) had PD, and 0 patients had a CR. We also evaluated how tumor burden affected responses by comparing the results from patients with only 1 site of metastatic disease with the results from patients with >1 site of metastatic disease. Nineteen patients had only 1 site of metastatic disease, of whom 2 patients (11%) had a CR, 4 patients (21%) had a PR, 5 patients (26%) had SD, and 8 patients (42%) had PD. Of the 25 patients who had >1 site of involvement (range, 2–4 sites), 1 patient (4%) had a PR, 10 patients (40%) had SD, 14 patients (56%) had PD, and 0 patients achieved a CR (Table 3). Responses by extent of exposure to prior systemic (hormonal and chemotherapy) therapy also are shown in Table 3.

The median duration of response was 4.3 months (range, 1–8 months), but the overall survival was 8.6 months (range, 1.5–22.2 months). The median duration of response was 4.9 months (range, 1.1–8.0 months) in patients who had only 1 metastatic site

TABLE 3
Responses and Survival

Response	Type of response, no. (%)				Median duration of response (mos) (range)	Median overall survival (mos) (range)
	CR	PR	SD	PD		
Overall response (n = 44)	2 (5)	5 (11)	15 (34)	22 (50)	4.3 (1–8)	8.6 (1.5–22.2)
Response by metastatic site						
Soft tissue (n = 8)	2 (25)	1 (12.5)	2 (25)	3 (37.5)	4.9 (1.1–8)	12 (4.8–18.6)
Visceral (n = 36)	0	4 (11)	13 (36)	19 (53)	3.1 (1–7.5)	8.1 (1.5–22.2)
Response by no. of sites involved						
1 (n = 19)	2 (11)	4 (21)	5 (26)	8 (42)	4.9 (1.1–8)	12 (4.8–18.6)
≥2 (n = 25)	0	1 (4)	10 (40)	14 (56)	3.1 (1–8)	8.2 (1.5–22.2)
Response by no. prior regimens						
1	0	2 (5)	3 (7)	1 (2)	—	—
2	2 (5)	1 (2)	3 (7)	5 (11)	—	—
3	0	1 (2)	1 (2)	9 (20)	—	—
≥4	0	1 (2)	8 (18)	7 (16)	—	—

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

and 3.1 months (range, 1.0–7.5 months) in patients who had >1 metastatic site. The median overall survival was 12 months (range, 4.8–18.6 months) in patients with 1 metastatic site and 8.2 months (range, 1.5–22.2 months) in patients with >1 metastatic site (Table 3).

Conversely, in patients with soft tissue metastases only, the median duration of response was 4.9 months (range, 1.1–8.0 months), and the median overall survival was 12 months (range, 4.8–18.6 months). In patients who had visceral disease, however, the median duration of response was 3.1 months (range, 1–8 months), and the median overall survival was 8.1 months (range, 1.5–22.2 months).

Toxicity

The most frequent hematologic toxicity was neutropenic fever, which was encountered in 42 cycles (22%). Hospitalization for intravenous antibiotics was required in 15 cycles; in 11 cycles, however, neutropenic fever was treated on an outpatient basis with oral antibiotics and granulocyte-colony stimulating factor (G-CSF). All the others (16 cycles) had low grade fever (≤38.2°C) that required no antibiotics. The nonhematologic toxic effects are shown in Table 4. The most significant was stomatitis (National Cancer Institute [NCI] Grade 3–4), which occurred in 18 cycles (9%) and affected 16 patients (36%). Fatigue (NCI Grade 3–4) occurred in 22 cycles (11%) and affected 16 patients (36%). Constipation (NCI Grade 1–2) occurred in 36 cycles (19%); only 1 patient (2%) had NCI Grade 3 constipation. No Grade 3 or 4 diarrhea, nausea, or emesis was encountered.

TABLE 4
Nonhematologic Toxic Effects

Toxic effect	Grade 1–2[a]		Grade 3–4[a]	
	No. of cycles (%)	No. of patients (%)	No. of cycles (%)	No. of patients (%)
Fatigue	114 (59)	23 (52)	22 (11)	16 (36)
Stomatitis	86 (45)	19 (43)	18 (9)	16 (36)
Constipation	36 (19)	17 (39)	1 (0.5)	1 (2)
Diarrhea	25 (13)	15 (34)	0	0
Nausea/emesis	64 (33)	27 (61)	0	0

[a] Grade according to the classification of the National Cancer Institute.

DISCUSSION

Animal studies and clinical pharmacology data suggest that prolonged exposure to critical drug concentrations is required to obtain the optimal effect of vinblastine.[28–30] Jackson et al.[31] also reported that the cytotoxicity of vinca alkaloids appears to be critically dependent on both the duration of exposure and the drug concentration. This has been demonstrated clinically.[15] The improved activity observed for vinblastine when given by continuous infusion is because the agent may overcome drug resistance in some cases that are refractory to the bolus treatment. In addition, the toxicity associated with the prolonged duration of exposures has been found to be well tolerated. Tous-

saint et al.[26] observed further that vinorelbine administered by 96-hour infusion after a bolus injection in patients who had been pretreated heavily for metastatic breast carcinoma produced significant antitumor activity.

A pharmacokinetic study by Rahmani et al.[32] showed that the T_1/T_2, CL, and volume of distribution are comparable when vinorelbine is given by bolus or continuous infusion. The plasma concentrations (8–12 nanograms/m) obtained by the continuous administration scheme are well above the inhibitory concentrations reported for human cell lines in vivo.[33] In addition, Toussaint et al.[26] demonstrated the feasibility of the continuous intravenous administration schedule of vinorelbine in patients with advanced breast carcinoma with a better therapeutic index than the weekly vinorelbine schedule. In addition, they suggested a dose-response relationship as well as a dose intensity/activity correlation. Our study was designed to assess the response rate and tolerability of vinorelbine by continuous infusion at the MTD as well as any survival advantage in heavily pretreated patients with metastatic breast carcinoma.[27] All of the patients had prior doxorubicin-based therapy, 70% of whom had prior paclitaxel therapy.

We demonstrated that vinorelbine given as a bolus dose followed by a 96-hour continuous infusion to heavily pretreated patients with metastatic breast carcinoma achieved an overall response rate of 16% (time to progression, 27 weeks; range, 17.5–32.0 weeks), with stabilization of disease in 34% of the patients. Patients with only soft tissue metastases had an overall response rate of 37%, whereas the response rate was only 11% in patients with only visceral disease. SD occurred in 25% and 36% of the patients, respectively. In addition, the overall response rate in patients with a low tumor burden, defined as involvement of only 1 site or organ, was 32% compared with 4% in patients with >1 metastatic site. SD occurred in 26% and 40% of patients, respectively. In contrast, vinblastine by continuous infusion over 5 days resulted in an overall response rate of 37%; however, the proportion of patients with only soft tissue metastases in that study was higher (39%). Vinorelbine given by weekly injection at its MTD, defined as 30 mg/m^2 weekly, to non-anthracycline-resistant patients resulted in an overall response rate of 32–46%, a median response duration of 34 weeks,[34–37] and a response rate of 16% as second-line or third-line treatment (after prior anthracycline exposure).[38] In patients with paclitaxel-refractory metastatic breast carcinoma,[39] weekly vinorelbine and daily G-CSF resulted in an overall response rate of 25%, a median time to progression of 13 weeks, and a median survival time of 33 weeks.

Toussaint et al.,[26] in their Phase I–II trial of continuous infusion vinorelbine in patients with advanced breast carcinoma, had an overall response rate of 36%. The median duration of response in that study was 24 weeks, and the median survival duration was 24 months.

The dose-limiting toxicity of vinblastine by continuous infusion[15] was myelosuppression, most significantly resulting in neutropenic sepsis in 8% of the cycles given. Neutropenic fever without documented infection occurred in 14% of the patients, resulting in hospitalization for intravenous antibiotics. Conversely, constipation was common despite prophylactic mild laxative therapy, occurring at the rate of 10% of the cycles and ileus in 2% of the cycles given. Weekly vinorelbine resulted in cumulative hematologic toxicity, resulting in skipping of doses and therefore compromising the dose intensity of the schedule; however, with the use of daily G-CSF,[34] Livingston et al.[39] found that the occurrence of febrile neutropenia that required hospitalization was unusual, but Grade 3–4 thrombocytopenia occurred in 23% of the patients. In addition, 65% of the patients required transfusions. No severe (Grade $\geq$ 3) mucositis was observed. Neutropenic fever was observed in 18% of the cycles, with documented infection in 7% of the cycles. Stomatitis, conversely, was documented in 9% of the cycles, and constipation was documented in 1 patient and 1 cycle. No diarrhea, nausea, or emesis of Grade $\geq$ 3 occurred.

Fifty percent of the patients treated in this study required a reduction in their doses because of the development of NCI Grade 3 or 4 stomatitis, fatigue, infection, or neutropenia. Most of the reductions occurred with the third cycle, suggesting that our dose schedule resulted in cumulative toxicity. We believe that the dose at which we initiated treatment in our study is not well tolerated. Therefore, we suggest using a revised MTD for confirmatory Phase II studies or for Phase III studies. This revised MTD of vinorelbine is 8 mg by bolus intravenous injection followed by continuous intravenous infusion of 10 mg/m^2 over 24 hours $\times$ 4 days.

Vinorelbine by continuous infusion every 3 weeks did not appear to offer any advantage over the weekly bolus schedule or the vinblastine continuous infusion schedule. All of our patients were anthracycline resistant, and 70% were paclitaxel-resistant. In comparable patient populations, the response rates were 16%[38] and 25%.[39] This regimen also demonstrated cumulative hematologic and gastrointestinal (mucositis) toxicities; however, fewer cases of constipation or ileus occurred than with the vinblastine continuous infusion schedule. Therefore, we do not advocate this dose

schedule of vinorelbine over the established weekly schedule in patients with tumors resistant to doxorubicin and paclitaxel.

REFERENCES

1. Legha SS, Benjamin RS, Mackay B, Ewer M, Wallace S, Valdivieso M, et al. Reduction of doxorubicin cardiotoxicity by prolonged continuous intravenous infusion. *Ann Intern Med* 1982;96:133–9.
2. Grem JL, Tutsch KD, Simon KJ, Alberti DB, Willson JK, Tormey DC, et al. Phase I study of Taxol administered as a short I.V. infusion daily for 5 days. *Cancer Treat Rep* 1987; 71:1179–84.
3. Wiernik PH, Schwartz EL, Einzig A, Strauman JJ, Lipton RB, Dutcher JP. Phase I trial of Taxol given as a 24-hour infusion every 21 days: responses observed in metastatic melanoma. *J Clin Oncol* 1987;5:1232–9.
4. Kris MG, O'Connell JP, Gralla RJ, Wertheim MS, Parente RM, Schiff PB, et al. Phase I trial of Taxol given as a 3-hour infusion every 21 days. *Cancer Treat Rep* 1986;70:605–7.
5. Holmes FA, Walters RS, Theriault RL, Forman AD, Newton LK, Raber MN, et al. Phase II trial of Taxol, an active drug in the treatment of metastatic breast cancer. *J Natl Cancer Inst* 1991;83:1797–805.
6. Rowinsky EK, Cazenave LA, Donehower RC. Taxol: a novel investigational antimicrotubule agent. *J Natl Cancer Inst* 1990;82:1247.
7. Holmes FA, Valero V, Walters R, Buzdar AU, Booser DJ, Winn R, et al. Phase III trial of paclitaxel administered over 3 hours or 96 hours for metastatic breast cancer. *Proc Am Soc Clin Oncol* 1996;15:106.
8. Seidman AD, Hochhauser D, Gollub M, Edelman B, Yao T-J, Hudis CA, et al. Ninety-six-hour paclitaxel infusion after progression during short taxane exposure: a Phase II pharmacokinetic and pharmacodynamic study in metastatic breast cancer. *J Clin Oncol* 1996;14:1877–84.
9. Ansfield F, Klotz J, Nealon T, Ramirez G, Minton J, Hill G, et al. A Phase III study comparing the clinical utility of four regimens of 5-fluorouracil. *Cancer* 1977;39:34–40.
10. Seifert P, Baker L, Reed ML, Vaitkevicius VK. Comparison of continuously infused 5-fluorouracil with bolus injection in treatment of patients with colorectal adenocarcinoma. *Cancer* 1975;36:123–8.
11. Sullivan RD, Young CW, Miller E, Glatstein N, Clarkson B, Burchenal JH. The clinical effects of the continuous administration of flourinated pyriminidines. *Cancer Chemother Rep* 1960;8:77–83.
12. Ardalan B, Singh G. A randomized Phase I–II study of short-term infusion of high-dose 5-fluorouracil with or without *N*-(phosphonacetyl)-L-aspartic acid in patients with advanced pancreatic and colorectal cancers. *J Clin Oncol* 1988; 6:1053–8.
13. Lokich J, Bothe A, Fine N, Perri J. Phase I study of protracted venous infusion of 5-fluorouracil. *Cancer* 1981;48:2565–8.
14. Yap HY, Blumenschein GR, Keating MJ, Hortobagyi GN, Tashima CK, Loo TL. Vinblastine given as a continuous 5-day infusion in the treatment of refractory advanced breast cancer. *Cancer Treat Rep* 1980;64:279–83.
15. Fraschini G, Yap HY, Hortobagyi GN, Buzdar A, Blumenschein G. Five-day continuous-infusion vinblastine in the treatment of breast cancer. *Cancer* 1985;56:225–9.
16. Giaccone G, Bagatella M, Donadio M, Calciati A. Phase II study of divided-dose vinblastine in advanced cancer patients. *Tumori* 1989;75:248–51.
17. Reichman BS, Seidman AD, Crown JP, Heelan R, Hakes TB, Lebwohl DE, et al. Paclitaxel and recombinant human granulocyte colony-stimulating factor as initial chemotherapy for metastatic breast cancer. *J Clin Oncol* 1993; 11:1943–51.
18. Nabholtz JM, Gelmon K, Bontenbal M, Spielmann M, Clavel M, Seeber S, et al. Randomized trial of two doses of Taxol in metastatic breast cancer: an interim analysis. *Proc Am Soc Clin Oncol* 1993;12:60.
19. Swenerton K, Eisenhauer E, ten Bokkel Huinink W, Myles J, Mangioni C, van der Burg M, et al. Taxol in relapsed ovarian cancer: high vs low dose and short vs long infusion: a European-Canadian study coordinated by the NCI Canada Clinical Trials Group. *Proc Am Soc Clin Oncol* 1993;12:256.
20. 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 II trial of 96-hour infusion. *J Clin Oncol* 1994;12:1621–9.
21. Diasio RB, Harris BE. Clinical pharmacology of 5-fluorouracil. *Clin Pharmacokinet* 1989;16:215.
22. 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.
23. Chang AYC, Most C, Pandyk KJ. Continuous intravenous infusion of 5-fluorouracil in the treatment of refractory breast cancer. *Am J Clin Oncol* 1989;12:453.
24. Jabboury K, Holmes FA, Hortobagyi G. 5-fluorouracil rechallenge by protracted infusion in refractory breast cancer. *Cancer* 1989;64:793.
25. Johnson SA, Harper P, Hortobagyi GN, Pouillart P. Vinorelbine: an overview. *Cancer Treat Rev* 1996;22:127–42.
26. 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.
27. Ibrahim NK, Hortobagyi GN, Valero V, Theriault R, Willey J. Phase I study of Navelbine (vinorelbine) administered by 96-hour infusion in metastatic breast cancer patients [poster 511]. Presented at the 19th Annual San Antonio Breast Cancer Symposium, San Antonio, Texas, December 11–14, 1996.
28. Lu K, Yap HY, Loo TL. Clinical pharmacokinetics of vinblastine by continuous intravenous infusion. *Cancer Res* 1983; 43:1405–8.
29. Valeriote FA, Bruce WR, Meeker BE. A model for the action of vinblastine in vivo. *Biophys J* 1966;6:145–52.
30. Johnson IS, Armstrong JG, Gorman M, Burnett JP Jr. The vinca alkaloids: a new class of oncolytic agents. *Cancer Res* 1963;23:1390–427.
31. Jackson DV. The periwinkle alkaloids. In: Lokich JJ, editor. Cancer chemotherapy by infusion. Chicago: Precept, 1990: 10.155–75.
32. Rahmani R, Martin M, Barbet J. Radioimmunoassay and preliminary pharmacokinetic studies in rats of 5′-noranhydrovinblastine (Navelbine). *Cancer Res* 1984;44:5609–13.
33. Rahmani R, Bruno R, Iliadis A, Favre R, Just S, Barbet J, et al. Clinical pharmacokinetics of the antitumor drug Navelbine (5′-noranhydrovinblastine). *Cancer Res* 1987;47: 5796–9.

34. 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.
35. Fumoleau P, Delgado FM, Dolzier 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.
36. Romero A, Rabinovich 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.
37. Canobbio 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.
38. Jones S, Winer E, Vogel C, Laufman L, Hutchins L, O'Rourke M, et al. A randomized comparison of vinorelbine and melphalan in anthracycline-refractory advanced breast cancer. *J Clin Oncol* 1995;13:2567–74.
39. Livingston RB, Ellis GK, Gralow JR, Williams MA, White R, McGuirt C, 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.