# Sequential Therapy with Capecitabine Followed by Vinorelbine/Cisplatin in Patients with Anthracycline/Taxane-refractory Metastatic Breast Cancer

Peng-Chan Lin, Wei-Shu Wang, Muh-Hwa Yang, Chueh-Chuan Yen, Ta-Chung Chao, Liang-Tsai Hsiao, Po-Min Chen*

*Division of Hematology and Oncology, Department of Medicine, Taipei Veterans General Hospital, and National Yang-Ming University School of Medicine, Taipei, Taiwan, R.O.C.*

**Background:** Currently, there is no standard treatment for patients with anthracycline and taxane-refractory metastatic breast cancer (MBC). Capecitabine or vinorelbine plus cisplatin is an effective palliative regimen for taxane-refractory MBC. In this study, we analyzed the efficacy and toxicity of sequential therapy with capecitabine followed by biweekly vinorelbine plus cisplatin in 37 patients with anthracycline and taxane-refractory MBC in Taipei Veterans General Hospital.

**Methods:** Capecitabine (2,500 mg/m$^2$ twice daily for 2 weeks, followed by 1 week of rest) was repeated every 3 weeks until the disease progressed. Patients then received biweekly vinorelbine (25 mg/m$^2$) plus cisplatin (40 mg/m$^2$) (arm A, $n = 17$) or best supportive care (BSC) (arm B, $n = 20$) in accordance with patient preference and clinical judgment. The clinical variables and response to capecitabine were well balanced in both arms.

**Results:** The overall response rate to capecitabine was 32%, with a complete response rate of 5% and a partial response rate of 27%. Stable disease was achieved in an additional 46%. The disease control rate with capecitabine was 78%. Median progression-free survival and overall survival with capecitabine were 5.9 and 9.5 months, respectively. There was a trend toward better overall survival in arm A patients compared with arm B (BSC) patients, though statistical significance was not reached (10.4 *vs.* 7.4 months; $p = 0.08$); however, a significantly better overall survival rate was observed in the subgroup with capecitabine-controlled disease (10.8 *vs.* 6.9 months; $p = 0.015$). The safety profile of vinorelbine/cisplatin was acceptable: only 6% developed grade 4 neutropenia.

**Conclusion:** We suggest that sequential therapy is not necessarily effective compared with capecitabine alone, but is probably effective in patients initially controllable with capecitabine. [*J Chin Med Assoc* 2006;69(7):304–309]

**Key Words:** capecitabine, metastatic breast cancer, sequential therapy, vinorelbine

## Introduction

Breast cancer is one of the leading causes of cancer-related death in women in Western countries.[1] Its incidence has increased rapidly in recent years in Taiwan.[2] For most women diagnosed with metastatic breast cancer (MBC), median survival is 18–36 months.[3] Because palliation is an important component of treatment of systemic disease, the goals of therapy are focused on relieving cancer-related symptoms, minimizing treatment-related toxicity, and improving quality of life. Anthracycline and taxane are generally considered to be the most active cytotoxic agents for the management of MBC.[4,5] However, when patients relapse following anthracycline- and taxane-based chemotherapy, there are few therapeutic options. Efficacious and well-tolerated agents are urgently needed for use in this situation.

*Correspondance to: Dr Po-Min Chen, Division of Hematology and Oncology, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, R.O.C.
E-mail: pmchen@vghtpe.gov.tw • Received: February 6, 2006 • Accepted: February 21, 2006

Capecitabine (XELODA; Hoffman–LaRoche, Nutley, NJ, USA), a fluoropyrimidine carbamate, was designed as an orally active drug that would deliver fluorouracil (5-FU) selectively to the tumor. It is an effective palliative agent because of its acceptable toxicity,[6,7] and has been reported to benefit anthracycline- and taxane-refractory MBC patients.[8,9] However, a treatment strategy for patients after capecitabine failure has not been identified. Since it is undetermined whether adding to the chemotherapy regimen in capecitabine-failure cases will prolong survival and have palliative effects, further investigation is mandatory. Vinorelbine (VNR) is a newly developed semi-synthetic vinca alkaloid, which chemically differs from the vinblastine-type compounds.[10] Preclinical data have demonstrated a difference in tubulin binding sites of VNR and taxane, suggesting a lack of cross-resistance.[11,12] Vinorelbine has been reported to be an effective agent in taxane-refractory MBC patients.[12,13] The synergistic antitumor activity of VNR with cisplatin has been demonstrated in animal models,[14] and combination VNR with cisplatin has been reported for anthracycline/taxane-refractory MBC patients.[15,16] We, therefore, conducted a study to investigate the efficacy and tolerability of sequential therapy with capecitabine followed by a biweekly VNR/cisplatin regimen in anthracycline/taxane-refractory MBC patients.

## Methods

### *Patient eligibility and characteristics*

This was an open-label, phase II prospective trial to evaluate the efficacy and safety of sequential therapy of capecitabine followed by biweekly vinorelbine/cisplatin in anthracycline- and taxane-refractory MBC patients. Patients signed consent forms before entering the study approved by the Taipei Veterans General Hospital Institutional Review Board. Eligibility criteria included histologically proven breast cancer with at least 1 measurable metastatic lesion of $2 \times 2$ cm. All patients received prior anthracycline and taxane treatment and had documented disease progression during or within 6 months of the last doses of chemotherapy. No more than 2 months elapsed between demonstration of treatment failure and study inclusion. Patients also fulfilled the following pretreatment criteria: life expectancy ≥6 months; Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; normal bone marrow function (white blood count ≥3,000/mm$^3$, platelet count ≥100,000/mm$^3$), liver function (serum total bilirubin <1.5 mg/dL), renal function (creatinine <1.5 mg/dL), and heart function (stable cardiac rhythm, no active angina, and no clinical evidence of congestive heart failure). Patients with other malignancies or brain metastases were excluded, as were patients with inadequate renal or hepatic function. Baseline biologic and radiologic assessments were performed within 14 days of starting treatment. From February 2001 to August 2003, a total of 37 patients with anthracycline- and taxane-refractory MBC at Taipei Veterans General Hospital were enrolled. Capecitabine was given to all of them in the first part of the study; after capecitabine failure, patients were divided into arm A (biweekly VNR [25 mg/m$^2$] plus cisplatin [40 mg/m$^2$], $n = 17$) and arm B (best supportive care [BSC], $n = 20$) in accordance with patient wishes and clinical judgment. The two arms were well balanced with respect to age, sex, performance status, hormone receptor status, prior chemotherapy regimens, response rate, and progression-free survival with capecitabine therapy. The patient characteristics are listed in Table 1. None of the patients received herceptin (trastuzumab) in combination with chemotherapy drugs.

### *Treatment schema*

In the first part of the trial, patients received oral capecitabine (repeated 3-week cycles of 2,500 mg/m$^2$ twice a day for 2 weeks, followed by 1 week of rest, until disease progression). After failure of capecitabine treatment, the second part of the study divided the patients into 2 groups: biweekly VNR (25 mg/m$^2$) plus cisplatin (40 mg/m$^2$) (arm A), or BSC (arm B) in accordance with patient wishes and clinical judgment. The VNR/cisplatin regimen was administered until the disease progressed or the patient reached a maximal dose (defined as 12 cycles). BSC was defined as measures designed to provide palliation of symptoms and improve quality of life as much as possible without use of any cytotoxic agents after capecitabine failure. The treatment schema of the study is illustrated in Figure 1.

### *Dose modifications*

Drug dosage was adjusted during the study on the basis of related adverse events as defined by the National Cancer Institute–Common Toxicity Criteria (NCI–CTC), version 1.0. Study treatment was readministered only when the absolute neutrophil count (ANC) reached ≥1,500/mm$^3$ and platelet count was ≥7.5 × 10$^4$/mm$^3$, and a maximum of 2-week delay was allowed for recovery. If recovery failed within these 2 weeks, treatment was stopped. In cases of grade 4 hematologic toxicity, doses of the administered drugs were reduced to 75% of the planned dose in subsequent courses even after full recovery. Cisplatin dose was reduced by 50%

**Table 1.** Characteristics of 37 MBC patients

| Variables | Arm A | Arm B | Total | *p* |
|---|---|---|---|---|
| Patients, *n* | 17 | 20 | 37 | |
| Median age, yr | 52 | 50.5 | 52 | 0.25* |
| Range | 47–84 | 34–76 | 34–84 | |
| Menopausal status, *n* (%) | | | | 0.20† |
| Premenopausal | 6 (35) | 8 (40) | 14 (38) | |
| Postmenopausal | 11 (65) | 12 (60) | 23 (63) | |
| Performance status, *n* (%) | | | | 0.52† |
| 0 | 10 (59) | 12 (60) | 22 (60) | |
| 1/2 | 6 (35)/1 (6) | 7 (35)/1 (5) | 13 (35)/2 (5) | |
| ER/PR status, *n* (%) | | | | 0.29‡ |
| P/N | 13/4 (76/24) | 14/6 (70/30) | 27/10 (73/27) | |
| Her-Neu status, *n* (%) | | | | 0.79‡ |
| P | 4 (24) | 4 (20) | 8 (22) | |
| U/N | 10/3 (59/18) | 13/3 (65/15) | 23/6 (62/16) | |
| Metastastic site(s), *n* (%) | | | | |
| Lung/N | 10/7 (59/41) | 10/10 (50/50) | 20/17 (54/46) | 0.59† |
| Liver/N | 5/12 (30/70) | 6/14 (30/70) | 11/26 (30/70) | 0.96† |
| Bone/N | 12/5 (70/30) | 8/12 (40/60) | 20/17 (54/46) | 0.06† |
| Response/survival to capecitabine therapy, *n* (%) | | | | 0.08‡ |
| Disease control rate/progressive disease | 13/4 (77/23) | 16/4 (80/20) | 29/8 (78/22) | |
| Complete response | 1 (6) | 1 (5) | 2 (5) | |
| Partial response | 5 (29) | 5 (25) | 10 (27) | |
| Stable disease | 7 (41) | 10 (50) | 17 (46) | |
| Progressive disease | | | | |
| Progression-free survival (mo) | 6.2 | 5.7 | 5.9 | |

**Independent-samples t test; †$\chi^2$ test; ‡Fisher's exact test. ER = estrogen receptor; PR = progesterone receptor; P = positive; N = negative; U = unknown.*

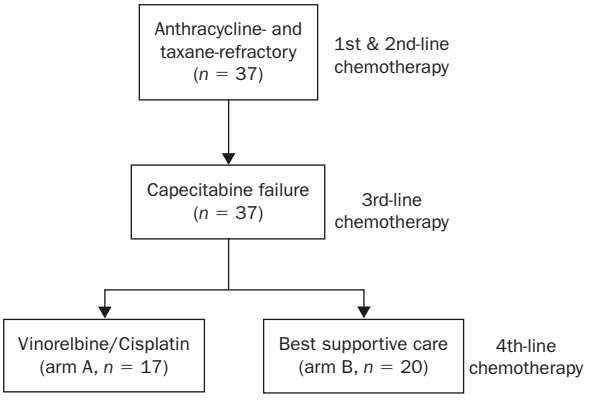


**Figure 1.** Chemotherapy algorithm of MBC used at the Taipei Veterans General Hospital. *n* = case number.

in cases of creatinine clearance (CCr) 40–60 mL/minute, and was withheld when CCr <40 mL/minute. If patients developed grade 2 neurologic toxicities, treatment was delayed until recovery to grade 1 or less for a maximum of 2 weeks. If patients suffered from grade 3 neurologic toxicities, treatment was discontinued. The treatment was discontinued permanently if the bilirubin level was higher than 2 times the upper normal limit, or if grade 4 cutaneous toxicity had developed.

### *Evaluation of treatment response and toxicity*

Before initiation of chemotherapy, patients were evaluated by a complete history and physical examination, performance status recording, complete blood cell count, and serum biochemistry. Computed tomography scan was performed for evaluation of the measurable metastatic lesion. Other examinations were performed only in the presence of a clinical indication. Laboratory tests were repeated before the start of each cycle. The tumor response was evaluated every 3 courses of treatment or when disease progression or intolerance to treatment was noted.

The primary endpoints of the study were to investigate the treatment response and toxicity. The tumor

response was evaluated by the same radiologist on the basis of the Response Evaluation Criteria In Solid Tumors (RECIST) guidelines.[17] In the responsive cases, a confirmatory evaluation was done in 4 weeks. Toxicities were evaluated according to NCI–CTC, version 1.0. The second endpoint was to evaluate the survival differences between patients receiving VNR/cisplatin following capecitabine failure (arm A) and those receiving BSC (arm B).

### *Statistical analysis*

Survival was analyzed using the Kaplan–Meier method, and the significance of difference was examined using a log-rank test. Associations between categorical variables were examined by independent-samples $t$ test, $\chi^2$ test, or Fisher's exact test (if expected cell number <5). All analyses were performed using the SPSS 12.0 software package for Windows. Statistical significance was defined as $p < 0.05$.

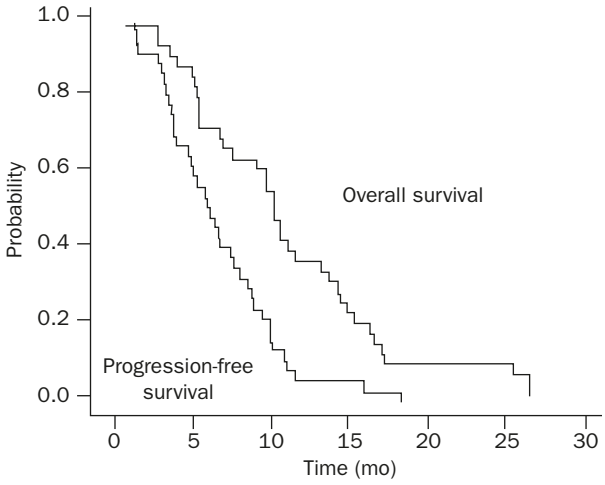


**Figure 2.** Kaplan–Meier estimated progression-free survival and overall survival curves of 37 MBC patients receiving capecitabine treatment.

## Results

### *Treatment response and survival analysis*

In the first part of the trial, the overall response rate to capecitabine was 32%, with a complete response rate of 5% (2/37 patients) and a partial response rate of 27% (10/37 patients). Stable disease was achieved in an additional 46% (17/37 patients). The disease control rate with capecitabine was 78%. Median progression-free survival and overall survival with capecitabine were 5.9 and 9.5 months, respectively (Figure 2).

In the second part of the trial, the median number of cycles of biweekly VNR/cisplatin administration was 5 (range, 2–12), and a total of 101 cycles were administered. The response/progression-free survival of capecitabine therapy was balanced in both arms (Table 1). The overall response rate of arm A treated with biweekly VNR/cisplatin was 17% (3/17 patients) and stable disease was 29% (5/17), with a median progression-free survival of 2.9 months (95% CI, 2.6–3.2 months). There was a trend toward better overall survival of arm A patients compared with arm B (BSC) patients, though statistical significance was not reached (10.4 *vs.* 7.4 months; $p = 0.08$); however, a significantly better overall survival rate was observed in the subgroup with capecitabine-controlled disease (10.8 *vs.* 6.9 months; $p = 0.015$) (Figure 3).

### *Toxicity*

The important adverse effects of capecitabine treatment (≥NCI–CTC grade 3) included hand–foot syndrome (19%), diarrhea (14%), emesis (16%), and stomatitis (14%). With the VNR/cisplatin regimen, treatment-related toxicity was mild and well tolerated. The most common adverse effects were hematologic toxicities: ≥grade 3 neutropenia, which occurred in 24% of patients without symptomatic infection, and anemia or thrombocytopenia, which occurred in a few cases. The 6% of patients with grade 4 neutropenia received 25% dose reduction modification. The incidence of non-hematologic toxicities was relatively low (grade 3 neurotoxicity in 1 and grade 3 stomatitis in 1). Treatment was well tolerated by all patients and there was no withdrawal due to treatment-related morbidity/mortality. The toxicity profile of VNR/cisplatin treatment is given in Table 2.

## Discussion

Adequate management of heavily pretreated MBC is a major issue for treatment of breast cancer. Effective and manageable regimens to achieve maximum palliation, especially in patients who have been pretreated with anthracyclines and taxanes, are still being sought. Previous studies demonstrated the efficacy of capecitabine[8,9] and VNR/cisplatin in anthracycline- and taxane-refractory MBC;[15,16] however, the proper order of sequential therapy for heavily pretreated MBC is still undetermined. Our study demonstrates that sequential therapy with capecitabine followed by VNR/cisplatin is a more effective and better tolerated regimen for anthracycline/taxane-refractory MBC than capecitabine alone: the median overall survival was

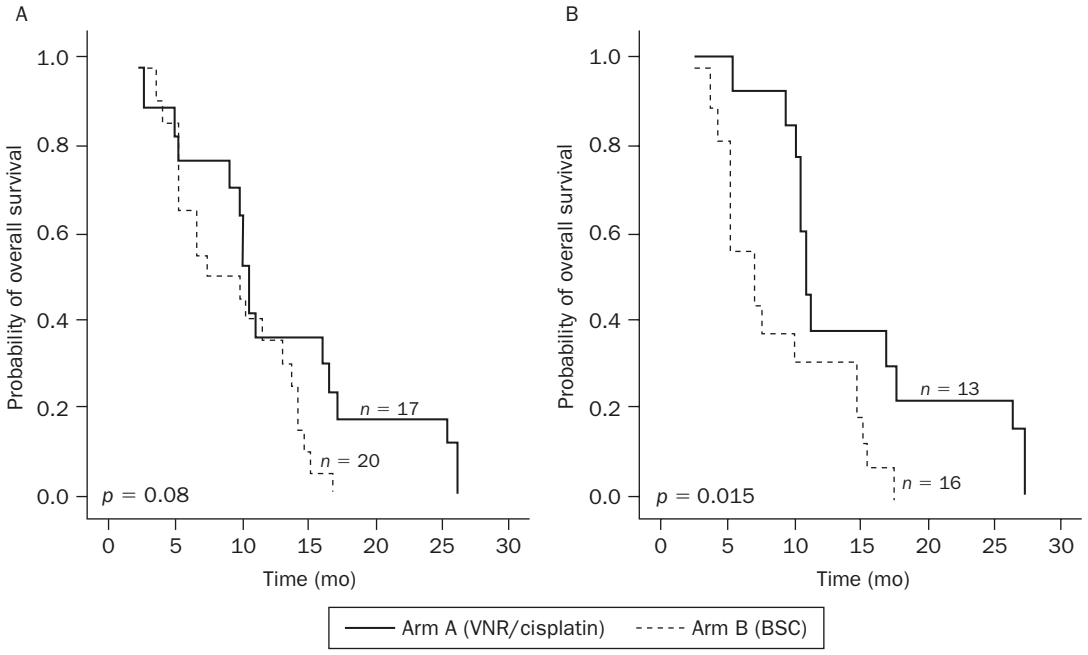


**Figure 3.** Kaplan–Meier estimated overall survival curves of (A) 37 MBC patients receiving sequential capecitabine/VNR-cisplatin or capecitabine alone and best supportive care (BSC); (B) subgroup with capecitabine-controlled disease. The *p* value is estimated by a log-rank test.

**Table 2.** Treatment-related toxicity of VNR/cisplatin

| Adverse event | NCI–CTC, *n* (%) | | | |
|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Hematologic | | | | |
| Neutropenia | 4 (24) | 7 (41) | 3 (18) | 1 (6) |
| Anemia | 1 (6) | 2 (12) | 1 (6) | 0 (0) |
| Thrombocytopenia | 1 (6) | 2 (12) | 1 (6) | 0 (0) |
| Nonhematologic | | | | |
| Neuropathy | 5 (29) | 2 (12) | 1 (6) | 0 (0) |
| Nausea | 5 (29) | 2 (12) | 0 (0) | 0 (0) |
| Vomiting | 3 (18) | 2 (12) | 0 (0) | 0 (0) |
| Anorexia | 3 (18) | 1 (6) | 0 (0) | 0 (0) |
| Ileus | 2 (12) | 2 (12) | 0 (0) | 0 (0) |
| Diarrhea | 1 (6) | 1 (6) | 0 (0) | 0 (0) |
| Stomatitis | 3 (18) | 1 (6) | 1 (6) | 0 (0) |
| AST | 2 (12) | 1 (6) | 0 (0) | 0 (0) |
| ALT | 2 (12) | 1 (6) | 0 (0) | 0 (0) |

*NCI–CTC = National Cancer Institute–Common Toxicity Criteria; n = number of patients whose worst degree of toxicity was at this grade; AST = aspartate aminotransferase; ALT = alanine aminotransferase.*

10.4 months in the sequential therapy group (arm A) compared with 7.4 months in the capecitabine alone group (arm B). There was a trend toward prolonging overall survival in the sequential therapy group: approximately 3-month survival advantage was observed, though statistical significance was not reached because of the limited case number ($p = 0.08$). Therefore, subgroup analysis was performed to demonstrate that adding VNR/cisplatin after capecitabine failure does provide a survival benefit in the subgroup with disease controlled by prior capecitabine therapy: the median survival of arm A significantly improved compared with that of arm B (10.8 *vs.* 6.9 months, $p = 0.015$). Verma et al[18] reported the 3-month survival benefit of sequential therapy in MBC patients, which was compatible with our result. Our result suggests that sequential capecitabine/VNR-cisplatin prolongs survival in heavily pretreated MBC patients, especially in the subgroup with capecitabine-controlled disease.

One major concern in application of the VNR/cisplatin regimen is treatment-related myelosuppression. Ray-Coquard et al[16] reported that about 47% of MBC patients receiving weekly VNR plus cisplatin had ≥grade 3 neutropenia. Modification of treatment schema to decrease the hematologic toxicity of VNR/cisplatin is mandatory. Udom et al[19] reported that a biweekly dose of vinorelbine is an effective regimen with markedly decreased toxicity in heavily pretreated patients with advanced breast carcinoma. We, therefore, selected biweekly VNR/cisplatin rather than weekly VNR for our patients, and the toxicity profile of VNR/cisplatin seemed to be manageable: only 24% had ≥grade 3 and 6% had grade 4 neutropenia without other complications. This result confirms the safety

and tolerability of biweekly VNR plus cisplatin in heavily pretreated MBC patients.

In conclusion, sequential therapy with capecitabine/VNR-cisplatin is not necessarily effective compared with capecitabine alone, but is probably effective in patients initially controllable with capecitabine. Since the number of patients tested was limited, the effectiveness should be toned down. A larger randomized study is required to confirm our findings.

## References


1. Weir HK, Thun MJ, Hankey BF, Ries LA, Howe HL, Wingo PA, Jemal A, et al. Annual report to the nation on the status of cancer, 1975–2000, featuring the uses of surveillance data for cancer prevention and control. *J Natl Cancer Inst* 2003;95:1276–99.
2. Shen YC, Chang CJ, Hsu C, Cheng CC, Chiu CF, Cheng AL. Significant difference in the trends of female breast cancer incidence between Taiwanese and Caucasian Americans: implications from age-period-cohort analysis. *Cancer Epidemiol Biomarkers Prev* 2005;14:1986–90.
3. Olin JJ, Muss HB. New strategies for managing metastatic breast cancer. *Oncology (Williston Park)* 2000;14:629–48.
4. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 1998;352:930–42.
5. Singal PK, Iliskovic N. Doxorubicin-induced cardiomyopathy. *N Engl J Med* 1998;339:900–15.
6. Liu G, Franssen E, Fitch MI, Warner E. Patient preferences for oral versus intravenous palliative chemotherapy. *J Clin Oncol* 1997;15:110–5.
7. Borner MM, Schoffski P, de Wit R, Caponigro F, Comella G, Sulkes A, Greim G, et al. Patient preference and pharmacokinetics of oral modulated UFT versus intravenous fluorouracil and leucovorin: a randomised crossover trial in advanced colorectal cancer. *Eur J Cancer* 2000;38:349–58.
8. Blum JL, Jones SE, Buzdar AU, LoRusso PM, Kuter I, Vogel C, Osterwalder B, et al. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. *J Clin Oncol* 1999;17:485–93.
9. Blum JL, Dieras V, LoRusso PM, Horton J, Rutman O, Buzdar A, Osterwalder B. Multicenter, phase II study of capecitabine in taxane-pretreated metastatic breast carcinoma patients. *Cancer* 2001;92:1759–68.
10. Langlois N, Gueritte F, Langlois Y, Potier P. Application of a modification of the Polonovski reaction to the synthesis of vinblastine-type alkaloids. *J Am Chem Soc* 1976;98:7017–24.
11. Fazeny B, Zifko U, Meryn S, Huber H, Grisold W, Dittrich C. Vinorelbine-induced neurotoxicity in patients with advanced breast cancer pretreated with paclitaxel—a phase II study. *Cancer Chemother Pharmacol* 1996;39:150–6.
12. Livingston RB, Ellis GK, Gralow JR, Williams MA, White R, McGuirt C, Adamkiewicz BB, 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.
13. Zelek L, Barthier S, Riofrio M, Fizazi K, Rixe O, Delord JP, Le Cesne A, et al. Weekly vinorelbine is an effective palliative regimen after failure with anthracyclines and taxanes in metastatic breast carcinoma. *Cancer* 2001;92:2267–72.
14. Cros S, Wright M, Morimoto M, Lataste H, Couzinier JP, Krikorian A. Experimental antitumor activity of Navelbine. *Semin Oncol* 1989;16:15–20.
15. Vassilomanolakis M, Koumakis G, Demiri M, Missitzis J, Barbounis V, Efremidis AP. Vinorelbine and cisplatin for metastatic breast cancer: a salvage regimen in patients progressing after docetaxel and anthracycline treatment. *Cancer Invest* 2003;21:497–504.
16. Ray-Coquard I, Biron P, Bachelot T, Guastalla JP, Catimel G, Merrouche Y, Droz JP, et al. Vinorelbine and cisplatin (CIVIC regimen) for the treatment of metastatic breast carcinoma after failure of anthracycline- and/or paclitaxel-containing regimens. *Cancer* 1998;2:134–40.
17. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000;92:205–16.
18. Verma S, Trudeau M, Dranitsaris G, Clemons M, Joy AA, Mackey JR. What is the best chemotherapy treatment option for anthracycline and taxane pretreated metastatic breast cancer? *J Clin Oncol* 2005;23:6260.
19. Udom DI, Vigushin DM, Linardou H, Graham H, Palmieri C, Coombes RC. 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.