# Vinorelbine Combined with Paclitaxel Infused over 96 Hours (VI-TA-96) for Patients with Metastatic Breast Carcinoma

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**BACKGROUND.** Vinorelbine (VI) and paclitaxel (TA) are among the most active single agents in the treatment of patients with breast carcinoma, and both have microtubules as their cytotoxic target. This Phase I–II study combined these 2 agents and used a 96-hour intravenous (i.v.) infusion of paclitaxel to maximize their cytotoxic activities.

**METHODS.** Patients with metastatic breast carcinoma who were previously treated with chemotherapy were administered increasing doses of a 96-hour paclitaxel i.v. infusion from Days 1 to 5, with a first fixed dose of vinorelbine (12.5 mg/m$^2$ on Days 1 and 5) every 3 weeks. The dose of paclitaxel was then decreased starting from the previously established tolerated dose, and a second fixed dose of vinorelbine (15 mg/m$^2$ on Days 1 and 5) was given. This identified 2 acceptable doses of paclitaxel (110 mg/m$^2$ with VI 12.5 mg/m$^2$ and 90 mg/m$^2$ with VI 15 mg/m$^2$). The latter was used in the subsequent Phase II study.

**RESULTS.** For the 50 patients treated with any dose, the complete response (CR) and the CR plus partial response (PR) rates were, respectively, 14% and 48% (95% confidence interval [CI], 34–67%). When only the 27 patients treated with the Phase II dose were considered, the figures were, respectively, 11% and 52% (95% CI, 42–62%). The median time to progression was 26 weeks, and the median survival 51 weeks. The dose-limiting toxicity was febrile neutropenia.

**CONCLUSIONS.** At the dose schedule identified for the Phase II study, the VI-TA-96 combination has considerable antitumor activity; pharmacoeconomic interest (it requires about half the doses of the agents administered singly); no major toxicity, except G4 neutropenia; and no need for premedication. This combination may be recommended as one of the most effective therapeutic options for patients with metastatic breast carcinoma who were pretreated mainly with anthracycline-containing chemotherapy. ***Cancer*** **2000;88:2731–8.**
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**KEYWORDS: advanced breast carcinoma, chemotherapy, vinorelbine, paclitaxel, 96-hour infusion.**

Paclitaxel and vinorelbine affect microtubules in opposite ways, and so the cytotoxic effects of their combination might be antagonistic or synergistic. The drugs have been found to have sinergistic cytotoxic effects both in tissue culture and in murine models.[1–6]

The optimal paclitaxel administration schedule has not been established yet. Pharmacokinetic–pharmacodynamic relations have been proposed between paclitaxel availability and two of its major side effects: neurologic and white blood cell (WBC) toxicity. The short and logistically convenient 3-hour infusion schedule allows higher doses to be administered and higher plasma concentrations to be

achieved, but neuropathy may become the limiting side effect; conversely, the commonly used 24-hour infusion schedule is associated with significantly more frequent neutropenia.[7] In general, the degree of neutropenia seems to be related to how long the plasma concentration of paclitaxel is above a given threshold.[8,9] Increased doses of paclitaxel are not associated with a greater probability of tumor response in metastatic breast carcinoma.[10]

The 24-hour infusion schedule sometimes has been reported as being significantly more active than the 3-hour infusion in metastatic breast carcinoma,[11] and long infusion schedules are theoretically more appropriate for a phase specific drug such as paclitaxel.[12] Because the prolonged exposure of different tumor cells to paclitaxel in vitro leads to a greater degree of cytotoxicity than increasing the dose for a shorter period,[13,14] greater interest is being shown in the clinical use of even longer paclitaxel infusions of 72 and 120 hours.[15,16] Particularly the 96-hour infusion schedule has been favorably tested in a few clinical studies.[17,18]

The idea for the current study came from the compassionate and personalized treatment of two patients with breast carcinoma who had been heavily pretreated with chemotherapy and were in a terminal stage because of massive liver involvement. The administratioon of vinorelbine on Days 1 and 5, combined with paclitaxel infused over 96 hours from Day 1 to 5, led to an unexpected and rapid objective shrinkage of the liver, albeit with severe life-threatening febrile neutropenia and stomatitis. In addition to providing the rationale for conducting this study, these observations suggested that it would be better to start with a low vinorelbine dose that would allow the administration of a not excessively low dose of paclitaxel.

The objective of the study was to test two potentially innovative ideas for the treatment of metastatic breast carcinoma: i.e., the combination of paclitaxel and vinorelbine and the use of the 96-hour paclitaxel infusion schedule. We report here the results of the Phase I study aimed at finding a regimen with acceptable doses and schedules and a subsequent Phase II study aimed at assessing its activity in patients with metastatic breast carcinoma pretreated with chemotherapy.

## PATIENTS AND METHODS

### Patients and Staging

Between May 1996 and August 1998, 50 patients were enrolled in this single-institution study. The main entry criteria for the Phase I and II studies were the same and included a histologic or cytologic diagnosis of breast carcinoma; progressive metastatic disease with measurable or evaluable tumor parameters; prior chemotherapy as neoadjuvant and/or adjuvant and/or metastatic disease treatment; WBC count $>$ 3500; platelet count $>$ 100,000; creatinine $<$ 1.5 mg/dL; total bilirubin $<$ 2.0 mg/dL; Eastern Cooperative Oncology Group performance status $\leq$ 3. Written informed consent was obtained from all of the patients according to institutional guidelines.

The patients initially were evaluated by history and physical examination, complete blood count, routine biochemistry, chest X-ray, liver ultrasound or computed tomography (CT) scan, bone X-ray and/or bone scan, and CT scans of the chest, abdomen, pelvis, and brain when clinically indicated to assess or measure tumor parameters.

The patients were monitored clinically on Day 1 of each cycle, at which time the hematology and biochemistry tests were repeated. Complete blood counts were repeated twice during each intercycle period.

### Response Criteria

Response to treatment was evaluated on the basis of World Health Organization (WHO) criteria[19] after three cycles and repeated after six cycles. All the patients were treated for six cycles provided that no progression was documented. Any early discontinuation for any reason other than progressive disease was considered as a treatment failure; all the patients were included in the denominator of the response evaluation on the basis of the intention to treat principle.

### Chemotherapy

Vinorelbine was administered intravenously as a short infusion, and paclitaxel as a 96-hour continuous infusion. All the patients received the paclitaxel infusion via a subcutaneously implanted central venous access device. The drug to be administered in each 4-day period was diluted with 500 mL of 0.9% sodium chloride; each 5-mL drug vial contained 30 mg of paclitaxel in 50% polyoxyethylated castor oil (Cremophor EL) and dehydrated alcohol. In-line 0.2-mm filters (IVEX-2; Abbott Laboratories, Abbott Park, IL) and polyethylene-lined nitroglycerin tubing were used to prevent polyvinyl chloride leaching by the drug solution. As in the case of other trials administering 96-hour continuous paclitaxel infusions, no premedication was given.[17,18]

The chemotherapy was administered using an ordinary intravenous (i.v.) apparatus in an in-patient setting when the patients lived outside Parma and/or could not come to the hospital every day. Otherwise, it was administered using the same infusion pump (Provider-5000; Abbott Laboratories) on an ambulatory

basis, with the patients remaining in the outpatient clinic for 2 hours after the initiation of the infusion (i.e., on Day 1) where they were observed for possible hypersensitivity reactions.

### Phase I Study

The Phase I study was divided into two parts. In the 1st part, a fixed dose of vinorelbine 12.5 mg/m$^2$ on Days 1 and 5 (i.e., at the beginning and end of the paclitaxel infusion) was empirically selected and combined with 6 different paclitaxel doses of 50, 65, 80, 95, 110, and 120 mg/m$^2$ (dose levels I, II, III, IV, V, and VI), every 3 weeks. Each dose was administered to 3 patients (i.e., a total of 18 patients). If Grade 4 febrile neutropenia and/or Grade 2–3 stomatitis occurred in 2 of the 3 patients in each triplet, the corresponding dose level was considered intolerable.

In the 2nd part, a 2nd fixed dose of vinorelbine 15 mg/m$^2$ on Days 1 and 5 was combined with 3 different dose levels of paclitaxel (110, 100, and 90 mg/m$^2$), which were gradually deescalated starting from the dose (110 mg/m$^2$) found to be tolerable with the lower dose of vinorelbine: this dose (level A) was administered to 1 patient, the 2nd (level B) to 4 patients, and the 3rd (level C) to 3 initial patients. This last regimen of vinorelbine 15 mg/m$^2$ on Days 1 and 5, combined with paclitaxel 90 mg/m$^2$ 96-hour i.v. infusion, every 3 weeks, was selected for the subsequent Phase II study.

### Phase II Study and Assessment of Response

The patients enrolled in the Phase I study received the first three cycles at the planned doses of vinorelbine and paclitaxel to assess toxicity. In the case of Grade 4 febrile neutropenia and/or Grade 2–3 stomatitis during any of the cycles, the treatment was continued with the administration of the immediately lower paclitaxel dose. Response was evaluated after the first three cycles and, in the case of no progression, the treatment was continued for a further three cycles, and a second evaluation was made. At the end of chemotherapy program, the patients were monitored for response every 6 weeks until progression. On the basis of this study design, all the patients entered in the Phase I and subsequent Phase II study were included in the response evaluation because of the identical entry criteria and identical planned duration of treatment.

### Toxicity

Side effects were evaluated according to WHO criteria[19] on Day 1 of each cycle, and then whenever clinically necessary. Hematologic toxicity was systematically monitored by means of two further blood counts during the interval between successive cycles. The worst degree of toxicity was attributed to each patient whether it occurred during the first three cycles of the Phase I study, or during any of the six cycles in the Phase II study.

**TABLE 1**
**Planning of Phase I–II Study**

| | VI[a] | TA[a] | No. of patients |
|---|---|---|---|
| First part (level) | | | |
| I | 12.5 | 50 | 3 |
| II | 12.5 | 65 | 3 |
| III | 12.5 | 80 | 3 |
| IV | 12.5 | 95 | 3 |
| V[b] | 12.5 | 110 | 3 |
| VI | 12.5 | 120 | 3 |
| Second part (level) | | | |
| A | 15 | 110 | 1 |
| B | 15 | 100 | 4 |
| C[b] | 15 | 90 | 27[b] |
| Total | | | 50 |

VI, vinorelbine; TA, paclitaxel.
[a] VI doses in mg/m$^2$ on Days 1 and 5; TA doses in mg/m$^2$, continuous i.v. infusion Days 1–5.
[b] Feasible paclitaxel dose levels at the two different doses of vinorelbine; level C was selected for the Phase II study.

### Statistical Analysis

Differences in patient characteristics, types of responses, and toxicities among the patient subgroups were evaluated using the $\chi^2$ test and Fisher exact test. Time to failure, time to progression, and the duration of survival were analyzed using the Kaplan and Meier product-limit method.[20] All of the time parameters were calculated from Day 1 of the 1st cycle. All of the statistical analyses were made using SPSS software.

## RESULTS

The plan of the whole Phase I–II study is shown in Table 1. The major expected toxicities were febrile neutropenia and/or Grade 2–3 stomatitis. During the 1st part of the study, 2 of the 3 patients receiving dose level VI experienced Grade 4 febrile neutropenia (both lasting 2 days), and 2 and 1 patients experienced Grade 2 (lasting 6 days) and Grade 1 stomatitis, respectively. The suggested feasible paclitaxel dose for a possible further Phase II study using vinorelbine 12.5 mg/m$^2$ on Days 1 and 5 therefore was 110 mg/m$^2$ in a 96-hour i.v. infusion from Day 1 to Day 5.

In the second part of the study, dose level A was planned in one patient but actually not tested because she developed a disseminated intravascular coagulation syndrome, with severe thrombocytopenia, hemorrhagic manifestations, and concomitant pulmonary embolism, which began early during the administra-

**TABLE 2**
**Patient Characteristics**

| Characteristic | No. of patients | % |
|---|---|---|
| Total | 50 | 100 |
| Median age (yrs) (range) | 60 (34–73) | |
| Performance status | | |
| ≤ 1 | 36 | 72 |
| 2 | 9 | 18 |
| 3 | 5 | 10 |
| Menopausal status | | |
| Premenopause | 9 | 18 |
| Menopause ≤ 60 yrs | 20 | 40 |
| Menopause > 60 yrs | 21 | 42 |
| Disease free interval | | |
| Absent | 4 | 8 |
| ≤ 2 yrs | 21 | 42 |
| > 2 yrs | 25 | 50 |
| Dominant disease sites | | |
| Soft tissue | 5 | 10 |
| Bone | 11 | 22 |
| Viscera | 34 | 68 |
| No. of disease sites | | |
| 1 | 9 | 18 |
| 2 | 18 | 36 |
| 3 | 12 | 24 |
| ≥ 4 | 11 | 22 |
| Estrogen and/or progesterone receptor | | |
| Positive | 24 | 48 |
| Negative | 19 | 38 |
| Unknown | 7 | 14 |

**TABLE 3**
**Prior Treatment with Chemotherapy**

| Prior chemotherapy | No. of patients | % |
|---|---|---|
| No. of chemotherapy lines | | |
| One | 11 | 22 |
| Two | 16 | 32 |
| Three | 13 | 26 |
| Four or more | 10 | 20 |
| Types of chemotherapy | | |
| Primary and adjuvant only | 8 | 16 |
| Adjuvant only | 3 | 6 |
| Advanced disease plus primary and/or adjuvant | 22 | 44 |
| Advanced disease only | 17 | 34 |
| Presence of anthracycline | | |
| No | 6 | 12 |
| Yes | 44 | 88 |

**TABLE 4**
**Response to the VI-TA-96 Combination Schedule, at Any Dose Level**

| Types of response | No. of patients | % |
|---|---|---|
| Total | 50 | 100 |
| Not evaluable (considered "no response") | 2 | 4 |
| Progression | 7 | 14 |
| No change | 17 | 34 |
| Partial response | 17 | 34 |
| Complete response | 7 | 14 |
| Complete plus partial response | 24 | 48 |
| 95% confidence interval | | 34–67 |

tion of chemotherapy. She slowly recovered from this life-threatening medical episode but was no longer treated with chemotherapy. At level B, 3 of the 4 patients experienced Grade 4 febrile neutropenia (lasting 2, 2, and 3 days), and 1 patient experienced Grade 2 stomatitis (lasting 6 days); at level C, none of the first 3 patients developed Grade 4 neutropenia, and only 1 experienced Grade 2 stomatitis. The suggested feasible paclitaxel dose for a possible further Phase II study using vinorelbine 15 mg/m$^2$ on Days 1 and 5 therefore was 90 mg/m$^2$ in a 96-hour i.v. infusion from Day 1 to Day 5. This dose schedule was used to treat the 27 patients who entered the extended Phase II study.

The characteristics of all of the patients entering the study are shown in Table 2. Their median age was 60 years, and the majority had a good performance status. Half of the patients had a disease free interval of less than 2 years; approximately two-thirds had viscera as the dominant disease site, and approximately half had 3 or more disease sites.

The prior chemotherapy treatments are shown in Table 3. All of the patients had been pretreated: the median number of previous therapies was 2 (range, 1–5). Only 22% of the patients had been pretreated with only adjuvant chemotherapy (with or without neoadjuvant chemotherapy); the others had received chemotherapy for advanced disease (with or without adjuvant/neoadjuvant chemotherapy). The previously administered chemotherapy included anthracycline in approximately 90% of the patients. Thirty-eight percent of the patients had been treated with adjuvant endocrine therapy and 58% with endocrine therapy for advanced disease.

The response to the combination schedule of the patients as a whole is shown in Table 4. Two patients were not evaluable for response because they received only one cycle of chemotherapy (the life-threatening medical episode described above and one early death due to progressive disease); they were included as nonresponders in the denominator of the response rate evaluation on an intention to treat basis. Seven of the 50 patients (14%) achieved a complete response (CR) and 24 a partial response (PR); the objective (CR + PR) response rate was 48% (95% CI, 34–67%).

The objective responses according to prior anthracycline exposure are shown in Table 5. Patients considered clinically resistant to anthracycline included those showing no change as a best response to primary chemotherapy or to chemotherapy for ad-

**TABLE 5**
**Objective Response According to Prior Anthracycline Exposure**

| Patient characteristics | No. of patients | CR (%) | CR + PR (%) |
|---|---|---|---|
| Total | 44 | | |
| Clinically resistant to anthracycline | 13 | 8 | 38 |
| Clinically sensitive to anthracycline | 24 | 17 | 50 |
| Information not available | 7 | 14 | 57 |

CR, complete response; PR, partial response.

**TABLE 6**
**Response to VI-TA-96 at the Dose Regimen Selected for the Phase II Study**

| Type of response | No. of patients | % |
|---|---|---|
| Total | 27 | 100 |
| Progression | 3 | 11 |
| No change | 10 | 37 |
| Partial response | 11 | 41 |
| Complete response | 3 | 11 |
| Complete plus partial response | 14 | 52 |
| 95% confidence interval | | 42–62 |

vance disease; those showing objective response followed by disease progression during chemotherapy treatment; those relapsing ≤ 12 months after the completion of the last cycle of adjuvant chemotherapy. Patients considered clinically sensitive included those showing objective response followed by discontinuation of chemotherapy before disease progression. The overall results confirm that, like most taxane-containing regimens, the VI-TA-96 regimen is also highly active in patients pretreated with anthracyline even if they are clinically resistant to the same.

The responses to the VI-TA-96 combination schedule in the 27 patients treated with the doses used in the Phase II study are shown in Table 6: three patients achieved a CR and 11 a PR. The CR rate was 11%, and the CR plus PR rate was 52% (95% CI, 42–62%).

The median time to progression was 26 weeks (range, 1–78) in the patients as a whole, and 27 weeks (range, 8–78) in those treated with the doses used in the Phase II study; median survival was 51 weeks (range, 1–131 weeks) and 51 weeks (range, 12–78 weeks), respectively.

The toxicities observed in the 27 patients participating in the Phase II study are shown in Table 7. Alopecia is not included because a number of the patients had different degrees of alopecia at baseline due to previous chemotherapy. However, although this combination schedule constantly induced alopecia, Grade 2 (i.e., requiring a wig) was not universal.

**TABLE 7**
**Toxicities of the Dose Schedule Used for the Phase II Study**

| Toxicities | G1 (%) | G2 (%) | G3 (%) | G4[a] (%) |
|---|---|---|---|---|
| Hematologic | | | | |
| White blood cell | 4 | 22 | 30 | 37[a] |
| Platelet | 26 | 11 | — | — |
| Hemoglobin | 37 | 11 | 11 | 4 |
| Nonhematologic | | | | |
| Stomatitis | 15 | 11 | 15 | 4 |
| Nausea-vomiting | 22 | 19 | — | — |
| Diarrhea | 7 | 4 | — | — |
| Neuromuscular | 7 | 19 | 4 | — |
| Liver | 4 | — | — | — |
| Skin | 4 | 4 | — | — |
| Hypersensitivity | 4 | — | 4 | — |

[a] Febrile neutropenia occurred in 22% of the patients.

The major toxicities were Grade 2 or 3 stomatitis in 26% of the patients and mainly Grade 4 neutropenia, which was experienced by 37% and was febrile in 22%, but of short duration (median values 2 days). Other types of toxicity were infrequent and mild. Note particularly the rather low frequency and the generally low severity of the neurologic toxicity. As in other studies administering 96-hour paclitaxel infusions,[17,18] the patients were not premedicated to prevent drug hypersensitivity reactions: among the 27 Phase II patients, there were 2 episodes of hypersensitivity (1 Grade 1 and 1 Grade 3); 2 additional Grade 1 reactions were observed in the Phase I patients.

## DISCUSSION

The administration of adjuvant chemotherapy has substantially changed over the last few years and is likely to change further in the near future. Adjuvant chemotherapy originally was used for so-called "high risk" premenopausal patients with lymph node positive disease but subsequently was extended to postmenopausal patients with lymph node positive estrogen receptor negative disease, and then to lymph node -negative estrogen receptor negative pre- and postmenopausal patients.[21–23] Recently, a few randomized clinical trials (and an overview of all randomized trials) have suggested that the combination of chemotherapy and tamoxifen is superior to hormone therapy alone in postmenopausal patients with estrogen receptor positive breast carcinomas irrespective of lymph node status.[24,25]

The combination of cyclophosphamide, methotrexate, and fluorouracil (CMF) was long adopted as conventional adjuvant chemotherapy. Then, a few single studies[26] and the overview of adjuvant chemotherapy[27] demonstrated a further significant reduction in

the risk of recurrence and death if anthracycline combinations were administered. On the basis of these observations, adjuvant chemotherapy with one or more of the drugs of the CMF combination plus an anthracycline is now (or is becoming) indicated in most patient categories, and so the large majority of patients at first recurrence already will have been treated with an anthracycline-containing adjuvant or neoadjuvant chemotherapy.

Chemotherapy for metastatic disease has mainly palliative objectives, but it sometimes can lead to repeated and prolonged regressions of the different disease sites and thus improve the quality and duration of life.[28] On the basis of the above considerations, there is growing interest in the availability of new drugs active in this disease setting other than CMF and the anthracyclines.

As single agents, the semisynthetic vinca alkaloid vinorelbine[29–31] and the taxanes (paclitaxel and docetaxel)[32–37] have shown an activity that is generally superior to that of all of the other agents used to treat metastatic breast carcinoma in pretreated patients. It therefore would be interesting to investigate whether their high single-agent activity in pretreated patients, and the finding that they have the same microtubule cell target, may lead to an ideal nonanthracycline-based combination with a single mechanism of cytotoxic activity. It already has been suggested that this common target may make the combination of vinorelbine and paclitaxel a potentially total microtubule poison.[38]

A large number of regimens and doses of the paclitaxel and vinorelbine combination have been tested in many Phase I–II studies of advanced breast carcinoma ,[38–49] and one Phase II study has used it as first-line chemotherapy.[38] The response rates observed in the various studies all demonstrate that the combination is "active," but also that neutropenia is the dose-limiting toxicity that makes it necessary to reduce the dose or dose intensity of the two drugs to levels that are considerably lower than those normally used when they are administered as single agents.

As a single agent, vinorelbine is mainly used at a dose of 30 mg/m$^2$/week,[29,31] and paclitaxel, at short infusion schedules, often has been studied at a dose of 175 mg/m$^2$ every 3 weeks, or at higher doses of approximately 250 mg/m$^2$.[50] However, the studies of the combination of these 2 agents generally have used lower paclitaxel doses of 135 mg/m$^2$ every 3 weeks.[38,41,44,45] Vinorelbine sometimes has been used at single doses that are apparently similar to those used when given alone—30 mg/m$^2$ [38,45,46] or 25 mg/m$^2$ [40,41,48]—but only for 1–2 administrations every 3 weeks, and therefore at a lower dose intensity. Furthermore, these studies sometimes adopted highly conservative criteria to reduce the dose of subsequent cycles in the case of the onset of hematologic toxicity,[38] or reported difficulties in respecting the planned regimen.[41]

In addition to the type of combination, our study is characterized by its use of continuous 96-hour paclitaxel infusions. Our interest in this type of infusion was prompted by the finding that 1) the prolonged infusion of a phase specific drug can increase its cytotoxic effect;[12,51] 2) 24-hour infusions have been shown to be more efficacious than 3-hour infusions;[11] 3) individual studies have shown that 96-hour infusions lead to a response in a number of patients who have experienced disease progression when treated with shorter taxane infusions;[18] 4) the use of 96-hour paclitaxel infusions per se increases its bone marrow toxicity (neutropenia), which makes it necessary to reduce the maximum dose that can be administered (105–140 mg/m$^2$).[17]

The VI-TA-96 combination used in this study has a high degree of antitumor activity: given the finding that the patients had been heavily pretreated, the objective response (OR) and CR rates of 48% and 14%, respectively, in the population as a whole are higher than those expected with any other combination. This is confirmed by the OR and CR rates of 52% and 11% observed during the Phase II part of the study. Response rates of this order are similar to those obtained with the most active conventional first-line treatments, such as CMF or anthracycline. To the best of our knowledge, only one other trial has used the combination of vinorelbine and 96-hour paclitaxel infusions;[47] however, the adopted regimen was different from ours insofar as vinorelbine was administered on Days 8 and 15, and the average dose intensity of vinorelbine and paclitaxel was 13.5 mg/m$^2$/week and 35.0 mg/m$^2$/week, respectively (as against our Phase II dose intensities of 10 mg/m$^2$/week and 30 mg/m$^2$/week, respectively). This probably explains why GSF had to be administered from the beginning. The CR and OR rates in the 32 pretreated patients were 22% and 50%, respectively, which seem to confirm the considerable power of this combination.[47]

The regimen adopted for our Phase II study was well tolerated, with the exception of the episodes of severe and sometimes febrile neutropenia (which remains a quite frequent toxic effect, although of short duration). Neurologic toxicity was not a relevant clinical problem. This finding has to be particularly stressed, compared with the alarm reported by other authors using vinorelbine and paclitaxel combination at different doses and schedules.[52]

Given that our study was designed to investigate two variables (the type of combination and the pacli-

taxel infusion regimen), we cannot say whether, or to what extent, the use of prolonged paclitaxel infusion contributed to producing more favorable results than those already known to be attributable to the combination itself. Nevertheless, the finding that the OR and CR rates obtained in a population of mainly heavily pretreated patients are similar to those reported in a population of nonpretreated patients by using the same combination but only short paclitaxel infusions,[38] makes it possible to hypothesize that the prolonged infusions used by us had an additional effect.

The 96-hour paclitaxel regimen is also noteworthy from a pharmacoeconomic point of view: for example, in comparison with the weekly regimen,[53] the drug cost is approximately three times less. However, remember that this substantial reduction in drug costs is at least partially compensated for by the greater expenses due to the implantation of central catheters, the use of pumps, and the possible need for periods of hospitalization.

In conclusion, the combination of vinorelbine and 96-hour paclitaxel infusions has a high degree of antitumor activity in pretreated patients with metastatic breast carcinoma, uses decidedly low doses of both drugs, leads to a generally low level of toxicity (except for quite frequent neutropenia), and does not require premedication. We think that this regimen should be tested as first-line chemotherapy in further studies concerning metastatic disease and may eventually have use in early disease despite the need for an infusion pump. In any case, this combination schedule already can be adopted in clinical practice as one of the most efficacious and useful therapeutic options for patients with metastatic disease pretreated with anthracycline-containing chemotherapies.

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