Abstract. Purpose: To determine the maximum tolerated doses (MTD) and dose-limiting toxicities (DLTs) of vinorelbine (VNR) with fixed doses of cyclophosphamide (CPM) and 5-fluorouracil/leucovorin (5-FU/LV) in patients with metastatic breast cancer (MBC) pretreated with anthracyclines and taxanes. Patients and Methods: Eighteen patients with MBC pretreated with anthracyclines and taxanes were enrolled. VNR was administered as a 10-min intravenous infusion (i.v.) on day 1 at escalated doses with CPM 300 mg/m² i.v. bolus and LV 500 mg/m² as a 2-hour i.v. infusion, followed by 5-FU 1500mg/m² as a 22-hour continuous infusion (c.i.) for two consecutive days. Treatment was repeated every two weeks. Results: At the dose of VNR 22.5mg/m² without rhG-CSF and 25mg/m² with rhG-CSF support, the DLT had been reached. Grade 3 or 4 neutropenia occurred in six (33%) patients and in fourteen (27%) cycles with no episode of febrile neutropenia. One (5.5%) patient developed grade 4 thrombocytopenia. Grade 3 neurotoxicity occurred in two patients and grade 2 and 3 asthenia in five (28%). Conclusion: The recommended doses for phase II studies are 20mg/m² for VNR (22.5mg/m² with rhG-CSF support) and 300mg/m² for CPM on day 1, with 500mg/m² for LV and 1500mg/m² for 5-FU on days 1 and 2.

The prognosis of patients who progress under, or relapse early after, anthracycline and taxane-based chemotherapy is poor since few drugs are still active in this setting (1, 2). Therefore, it is necessary to develop new active salvage regimens for these patients; this is important since anthracyclines and taxanes are increasingly used as front-line treatment and are actively evaluated in the adjuvant setting. Recently, we reported that the combination of cyclophosphamide and 48-hour continuous infusion (c.i.) of 5-fluorouracil (5-FU) with high-dose leucovorin proved to be a well-tolerated and effective salvage regimen in patients with metastatic breast cancer (MBC) heavily pretreated with both anthracyclines and taxanes (3). The overall response rate was 27% with 5% complete responses. In addition, the median duration of response and the median time to disease progression was 8 and 9.5 months, respectively, whereas the median overall survival was 13 months.

Vinorelbine (NVR), a new semi-synthetic vinca alkaloid, is active against MBC with objective response rates ranging from 35% to 41% when used as single agent in the first-line setting, and about 20% in the second-line setting (4, 5). Moreover, the combination of VNR and protracted infusion of 5-FU in heavily pretreated MBC patients resulted in an objective response rate of 68% with 14% complete responses; in this study, 43% of the patients had received anthracycline-based front-line treatment and most of them had refractory disease or relapse after an initial response. The toxicity of this combination was particularly low since only two out of thirty patients developed more than grade II toxicity (6).

Based on these encouraging data, we decided to conduct a phase I study in order to determine the maximum tolerated dose (MTD) and the dose-limiting toxicity (DLT) of VNR in combination with fixed doses of CPM and 5-FU/LV as salvage chemotherapy in MBC patients pretreated with both anthracyclines and taxanes.
Patients and Methods

Eligibility criteria. Patients with histologically or cytologically confirmed MBC and measurable or assessable disease were enrolled. All patients had to have either progression during, or within 3 months after, the completion of an anthracycline- and taxane-based chemotherapy. Other eligibility criteria were: age 18-75 years; performance status (WHO) 0-2; life expectancy of at least 3 months, and at least 4 weeks from prior cytotoxic chemotherapy; adequate bone marrow (absolute neutrophil count ≥ 1500/dl, hemoglobin ≥ 10g/dl and platelets ≥ 100,000/dl), hepatic (serum bilirubin ≤ 1.5 times the upper limit of normal; aspartate aminotransferase and alanine aminotransferase ≤ 5.0 times the upper limit of normal) and renal (serum creatinine ≤ 1.5mg/dl) function. Patients with brain metastases were eligible provided that they had been irradiated and had clinical and radiological improvement. Patients with severe cardiac dysfunction or unstable agina pectoris, or prior irradiation affecting more than 30% of the bone marrow, were not eligible. Patients with active infection, malnutrition or a second primary tumour, apart from adequately treated in situ carcinoma of the cervix or a non-melanoma skin cancer, were ineligible. The protocol was approved by the Scientific and Ethics Committees of our Institution and all patients gave written informed consent in order to participate in the study.

Treatment plan. Vinorelbine (Navelbine; Pierre Fabre, Paris, France) (starting dose 20mg/m²) was administered as a 10-min intravenous infusion (i.v.) on day 1 at escalating doses with increments of 2.5mg/m². Cyclophosphamide was administered on day 1 at the dose of 300mg/m² i.v. bolus. Leucovorin (LV) was administered at the dose of 500mg/m² as a 2-hour i.v. infusion, followed by 5-FU at the dose of 1500mg/m² as a 22-hour c.i. on days 1 and 2. Treatment was repeated every two weeks. No intrapatient dose escalation was allowed.

Treatment was postponed for 1 week if the laboratory inclusion criteria were not met. If laboratory values had improved after that period, treatment was administered at the next lower dose level. Doses were also reduced to the previous dose level in case of grade 4 neutropenia or thrombocytopenia and febrile neutropenia. In case of grade 3-4 non-hematological toxicity, treatment was withheld until the resolution of toxicity to ≤ grade 1; treatment was then resumed at the previous dose level. Toxicity was graded according to the WHO common toxicity criteria (7). Three patients were enrolled at each dose level. If a dose-limiting event (DLT) occurred in one of three patients, three additional patients were enrolled at that dose level. DLTs were assessed during the first cycle. The DLT was defined as the occurrence of any of the following: grade 4 neutropenia or thrombocytopenia lasting for more than 5 days; any febrile (>38.5°C) neutropenia; grade 3-4 non-hematological toxicity apart from alopecia, nausea and vomiting; and any treatment delay on day 15 due to unresolved toxicity (granulocytes < 1500/µl, platelets < 100,000/µl or non-hematological toxicity > grade 2). The dose level at which DLTs occurred in one of six patients presented DLT. Patients presenting a DLT were enrolled at each dose level. DLTs were assessed during the first cycle. The DLT was defined as the occurrence of any of the following: grade 4 neutropenia or thrombocytopenia lasting for more than 5 days; any febrile (>38.5°C) neutropenia; grade 3-4 non-hematological toxicity apart from alopecia, nausea and vomiting; and any treatment delay on day 15 due to unresolved toxicity (granulocytes < 1500/µl, platelets < 100,000/µl or non-hematological toxicity > grade 2). The dose level at which DLTs were grade 4 neutropenia lasting more than 5 days or febrile neutropenia was repeated with prophylactic administration of rhG-CSF (5 µg/kg/d subcutaneously, Granocyte; Aventis Pharma, Collegeville, USA) from day 7 to day 12. The MTD was defined as the next lower dose level at which at least two out of three or three out of six patients presented DLT. Patients presenting a DLT continued the treatment at the next lower dose level after the resolution of hematological and non-hematological toxicity.

Patient evaluation. Pre-treatment evaluation included a detailed medical history and physical examination, a complete blood cell count with differential and platelet cell count, whole blood chemistry, determination of serum levels of carcinoembryonic antigen (CEA) and CA 15-3 and computed tomographic scans (CT scans) of the chest and abdomen. Additional CT scans and magnetic resonance imaging were performed if clinically indicated. Pre-treatment evaluation had to be performed within 2 weeks prior to protocol entry.

During treatment, whole blood counts with differential and platelet counts were performed weekly. A medical history, a physical examination as well as biochemical tests, determination of serum levels of CEA and CA 15-3 and chest X-rays were performed every 4 weeks in order to evaluate symptoms of the disease and treatment toxicity. Lesions were evaluated after each cycle if they were assessable by physical examination or by chest X-rays. All patients were assessed by ultrasound and/or CT scans every 6 cycles using the standard WHO criteria (7).
achieved complete response (CR), partial response (PR) and stable disease (SD) received a maximum of 12 chemotherapy cycles. Patients experiencing progressive disease (PD) during the treatment were withdrawn from the study.

**Results**

**Patients’ demographics.** Eighteen patients were enrolled and their characteristics are shown in Table I. The median age was 65 years (range, 31-75) and performance status (WHO) was 0-1 in 14 (78%) patients and 2 in four (22%). Sixteen patients (89%) had received 2 or more chemotherapy regimens including taxanes and anthracyclines for treatment of MBC. Twelve patients (67%) had bidimensionally measurable disease and were evaluable for response whereas the remaining six were not evaluable as they had no measurable disease. All patients enrolled in the study were assessable for toxicity.

**Dose escalation.** Table II shows the dose escalation scheme with the DLT observed during the first chemotherapy cycle. At dose level 2, four out six patients developed DLTs (grade 4 neutropenia: 2 patients; treatment delay on day 15 due to grade 3 neutropenia: 2 patients) indicating that further escalation of vinorelbine was precluded (DLT 1). Therefore, the addition of a third dose level decreasing the dose of vinorelbine to 22.5mg/m² was decided on. This modification was also unsuccessful since two out of three patients developed DLTs (grade 4 thrombocytopenia: 1 patient; grade 3 neurotoxicity: 1 patient). This dose level was repeated with the addition of rhG-CSF. None of the three patients at this dose level developed DLT and the second dose level was repeated with the addition of rhG-CSF. Again, two of the three patients developed DLT (grade 4 neutropenia: 1 patient; grade 3 neurotoxicity: 1 patient) indicating that the DLT level with G-CSF had been reached (DLT2). Therefore, the MTD of vinorelbine was 20mg/m² without and 22.5mg/m² with rhG-CSF support.

**Toxicity.** Fifty-two treatment cycles were administered with a median of 6 cycles/patient (range, 1-6). Two (11%) patients

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### Table II. Dose levels and dose-limiting events (DLT) by the first cycle and response to treatment.

<table>
<thead>
<tr>
<th>Dose level</th>
<th>VNL (mg/m²)</th>
<th>CPM (mg/m²)</th>
<th>5-Fu (mg/m²)</th>
<th>LV (mg/m²)</th>
<th>rhG-CSF</th>
<th>No. of patients</th>
<th>DLT (No. of dose-limiting events)</th>
<th>Response (No. of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>300</td>
<td>1500</td>
<td>500</td>
<td>-</td>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>300</td>
<td>1500</td>
<td>500</td>
<td>-</td>
<td>6</td>
<td>Neutropenia G4 (2) Neutropenia G3 (delay) (2)</td>
<td>1 2</td>
</tr>
<tr>
<td>3</td>
<td>22.5</td>
<td>300</td>
<td>1500</td>
<td>500</td>
<td>-</td>
<td>3</td>
<td>Neutropenia G2 (delay) (1) Thrombocytopenia G4 (1)</td>
<td>- -</td>
</tr>
<tr>
<td>4</td>
<td>22.5</td>
<td>300</td>
<td>1500</td>
<td>500</td>
<td>+</td>
<td>3</td>
<td>-</td>
<td>- 1</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>300</td>
<td>1500</td>
<td>500</td>
<td>+</td>
<td>3</td>
<td>Neutropenia G4 (1) Neurotoxicity G3 (1)</td>
<td>- 1</td>
</tr>
</tbody>
</table>

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### Table III. Hematological toxicity in all patients and cycles at the different dose levels.

<table>
<thead>
<tr>
<th>Dose level</th>
<th>No. of cycles</th>
<th>Anemia Grade</th>
<th>Neutropenia Grade</th>
<th>Thrombocytopenia Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2 3 4 2 3</td>
<td>2 3 4 2</td>
<td>3 4 2 3</td>
</tr>
<tr>
<td>1</td>
<td>11</td>
<td>1 (9)</td>
<td>2 (18)</td>
<td>3 (27)</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>3 (15)</td>
<td>3 (15)</td>
<td>6 (30)</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>1 (17)</td>
<td>4 (67)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>2 (22)</td>
<td>1 (11)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>1 (17)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

In parentheses: % of cycles
received 12 cycles; three patients received only two cycles because of progressive disease (n=2) and grade 3 neurotoxicity (n=1), while another patient continued the treatment without the administration of vinorelbine. Twenty-seven (28%) cycles were delayed for 4-14 days (median 7 days) because of hematological toxicity (n=19 cycles), non-hematological toxicity (n=1 cycle) and other reasons unrelated to treatment or the disease (n=7 cycles).

The hematological toxicity in all delivered courses by dose level is presented in Table III. Neutropenia was the most common DLT at all dose levels, since a total of 14 (27%) cycles were complicated with grade 3-4 neutropenia. Nevertheless, no episode of febrile neutropenia was observed. Grade 3-4 neutropenia was more common in the second dose level with the highest dose of vinorelbine. Only one patient developed grade 4 thrombocytopenia and there was no patient with grade 3 or 4 anemia.

Non-hematological toxicity was generally mild and infrequent (Table IV). Grade 2 and 3 nausea/vomiting were observed in nine (44%) patients and 17% of cycles. The other most common toxicity was grade 2 and 3 asthenia observed in 6 (12%) and 1 (2%) cycles, respectively, corresponding to five (28%) patients. Grade 2 and 3 constipation, mucositis and neurotoxicity were uncommon.

Response to treatment. Among twelve patients assessable for response, one (8.3%) patient achieved a partial response (95% c.i. 0.23.97%). Four patients (33%) experienced disease stabilization and seven (58%) progressed (Table II). The median time to disease progression was 2.2 months (range 1.0-9.9 months) and the median overall survival 14.2 months.

Discussion
The therapeutic options for patients with breast cancer who relapse after an anthracycline- and taxane-based chemotherapy are limited. Therefore, the development of new active chemotherapy regimens in this setting is a continuing need. The results of this study indicate that the integration of vinorelbine to the combination of cyclophosphamide and 5-FU c.i. with high-dose LV is a feasible and well-tolerated regimen. The MTD of vinorelbine was 20mg/m² without and 22.5mg/m² with rhG-CSF support.

The dose-limiting events were mainly neutropenia, grade 4 thrombocytopenia and grade 3 neurotoxicity. The hematological toxicity was generally mild since only 21% of cycles were complicated with grade 3-4 neutropenia with no episode of febrile neutropenia. The addition of vinorelbine does not seem to increase the hematological toxicity of the cyclophosphamide plus 5-FU/LV combination (2). Non-hematological toxicity was also uncommon and mild. These findings are similar to the results of another phase I/II study in breast cancer patients pretreated with anthracyclines and taxanes (7). In that study, the weekly administration of infusional 5-FU in combination with folinic acid and vinorelbine showed moderate hematological toxicity with grade 3 and 4 leucopenia occurring in 35% and 5% of cycles, respectively. Other hematological and non-hematological toxicities were mild and did not exceed grade 2.

The assessment of the activity of this regimen was not a primary end-point in this study. However, one patient (8.3%) achieved partial response and four (33%) stable disease. It is also noteworthy that all patients were heavily pretreated with primary resistance to both anthracyclines and taxanes. Therefore, the efficacy data could be considered acceptable, thus encouraging further evaluation of this regimen in this particular group of patients. Previous studies with a similar regimen without vinorelbine reported response rates of 6% in patients with primary resistance and 40% in patients with secondary resistance to anthracycline/taxanes (2). On the contrary, the combination of vinorelbine with protracted infusion of 5-FU resulted in an overall response rate of 68% with 14% complete responses in heavily pre-treated patients; in this trial, most of the patients were refractory or relapsed after an initial response to anthracycline-based first-line chemotherapy regimen and 43% of them after a taxane-based second-line treatment (5). A high overall response rate has also been reported with vinorelbine in combination with a weekly schedule of folinic acid and infusional 5-FU (47%) (7);
However, in these trials there were no details concerning the primary and secondary resistance to previous therapy, a fact that is critical for the assessment of activity in patients with MBC pre-treated with anthracyclines and taxanes. Conversely, in our study patients were refractory or resistant to both anthracyclines and taxanes.

The relative utility of this regimen should be compared with single-agent chemotherapy such as vinorelbine, gemcitabine or capecitabine, which does not require hospital admission or infusion pumps. Although, there is a theoretical advantage for a combination, due to the additive or synergistic effects between the used agents, it is unclear whether combinations are truly superior to single agents in terms of activity or quality of life for this particular poor prognosis group of patients.

In conclusion, the combination of vinorelbine with high-dose 5-FU/LV and conventional doses of cyclophosphamide is a feasible and well-tolerated regimen for patients with MBC who progress under anthracyclines and taxanes. The main DLT is neutropenia and the recommended doses for further phase II studies are 20mg/m² (22.5mg/m² with rhG-CSF support) for vinorelbine on day 1, 300mg/m² for cyclophosphamide on day 1, 1500mg/m² and 500mg/m² for 5-fluorouracil and LV, respectively, on days 1-2 every two weeks. This combination merits further evaluation as salvage treatment in patients with primary resistance to taxanes and anthracyclines.

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References


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