A phase II study of cisplatin and vinorelbine in patients with metastatic breast cancer

G. Mustacchi*, M. Muggia, S. Milani, R. Ceccherini, M. L. Leita & C. Dellach

Centro Oncologico, Azienda per i Servizi Sanitari I, Università di Trieste, Trieste, Italy

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Background: To evaluate the efficacy and safety of the combination of cisplatin and vinorelbine in metastatic breast cancer.

Patients and methods: Cisplatin (80 mg/m² day 1) and vinorelbine (25 mg/m² days 1 and 8) were administrated every 3 weeks to 52 patients (mean age 57 years; range 35–75 years) with metastatic breast cancer. Thirty-two patients were previously untreated for metastatic disease. Treatment was repeated for a maximum of six cycles.

Results: Objective responses were obtained in 27 patients (52.9%; complete response 9.8%). The response rate was similar in pretreated and untreated patients (50% and 54.7%, respectively; P = 0.7). ECOG performance status was good (grade 0 or 1) in 55.7% of patients at baseline assessment and in 90.3% at the end of treatment (P = 0.0001). Median time to progression was 8.5 months (8.5 months in first-line and 8.7 months in second-line patients). Median survival was 16.6 months (21.2 months in first-line and 16.1 months in second-line patients). Grade 3/4 toxicity included neutropenia (44% in first-line, 60% in second-line patients), nausea (17.3%), anemia (17%), asthenia (3.8%) and thrombocytopenia (1.9%). There were no cases of febrile neutropenia or treatment-related deaths. Alopecia did not develop in any of the patients.

Conclusions: Cisplatin plus vinorelbine is active and tolerable in metastatic breast cancer, in untreated and pretreated patients.

Key words: chemotherapy, cisplatin, metastatic breast cancer, vinorelbine

Introduction

Many breast cancer patients are treated in the adjuvant setting with anthracycline-based regimens, often in combination with a taxane. In many countries, this combination is the standard first-line treatment for metastatic disease. Furthermore, some patients cannot be treated with anthracyclines because of impaired cardiac function. It is thus important to identify active, well-tolerated, not anthracycline cross-resistant, first- and second-line regimens.

Cisplatin has been shown to be active in carcinoma of the breast when given alone [1, 2] and in combination with new drugs like docetaxel [3–5] and gemcitabine [6]. Vinorelbine has been widely used in metastatic breast cancer, alone [7–14] or in combination with docetaxel [15–17], paclitaxel [18], doxorubicin [19] and epirubicin [20], in first- and second-line treatment.

We first reported the activity of the combination of cisplatin and vinorelbine in first- and second-line treatment for metastatic breast cancer in 1994 [21] and, more recently, anthracyclines were shown not to be not cross-resistant with the regimen [22], suggesting the need for further studies at a dose of 80 mg/m² of cisplatin and 25 mg/m² of vinorelbine.

Subsequent investigations with the same or similar combinations have been few in number, and the series studied have been small [23–27], particularly in untreated patients [28, 29]. We present the long-term results of our study, which is more extensive in terms of population size and follow-up.

Patients and methods

Patient selection

Eligible patients had histologically confirmed metastatic breast cancer that was measurable or assessable, regardless of prior chemotherapy, with adequate bone marrow, hepatic and renal function, age ≤75 years, and life expectancy ≥3 months. Patients were not suitable for anthracycline chemotherapy because of pretreatment in an adjuvant or metastatic setting, inadequate cardiac function or refusal of alopecia.
Patients were considered unsuitable for anthracycline treatment if the cumulative received dose was >450 mg/m² for doxorubicin and >900 mg/m² for epirubicin. Treatment was repeated for up to six times every 3 weeks in the absence of progression, toxicity or refusal.

The criteria used to consider patients suitable for cisplatin treatment were creatinine <1.5 mg/dl, creatinine clearance ≥60 ml/min and LVEF ≥50%, in order to tolerate the high intravenous fluid intake.

Written informed consent was required.

**Treatment plan**

Patients received cisplatin (80 mg/m² on day 1) and vinorelbine (25 mg/m²) by intravenous bolus injection over a few minutes on days 1 and 8. Treatment was repeated for up to six times every 3 weeks in the absence of progression, toxicity or refusal.

Prophylactic granulocyte colony-stimulating factor (G-CSF) (5 µg/kg s.c. days 13–15) was used after a first delay for neutropenia. For prophylaxis of acute and delayed emesis, dexamethasone (25 mg i.v.) and an anti-serotonergic (1 vial i.v.) on day 1, followed by metholectramide (10 mg × 3 p.o.) and methylprednisolone (4 mg p.o. days 2–4) were administered.

Pamidronate and palliative radiotherapy were not allowed until progression.

**Criteria for response and toxicity evaluation**

Physical examination, chest X-ray or computed tomography (CT) scan, and CT scan of abdomen, bone scan and bone radiographs (if bone scan was abnormal), were required within 3 weeks of registration. Assessment was repeated after cycle 3, at the end of treatment, and every 3 months thereafter until disease progression. After progression, patients were followed only to determine survival.

Eastern Cooperative Oncology Group (ECOG) criteria were used to define response and performance status (PS) [30]. PS was evaluated subjectively. Response criteria in bone disease only were the following: CR, complete recalcification of all lytic lesions on X-ray; PR, recalcification of ≥50% of all lytic lesions on X-ray (in both cases lasting >3 months).

Toxicity was evaluated according to National Cancer Institute (NCI) criteria [31]. Resistance to anthracyclines was defined as relapse on adjuvant chemotherapy or within 12 months, or disease progression on anthracycline treatment. For 2 table comparisons, an exact test was used. All patients were analyzed for safety.

**Statistical analyses**

The primary end-points were the efficacy and the safety of the regimen, measured as objective response rate, time to progression, survival and toxicity.

Statistical calculations were performed using NCSS 2000 statistical software (NCSS, Kaysville, UT, USA).

Continuous data were summarized using descriptive statistics. Confidence intervals (CI) were constructed at the 95% level. Survival curves for time to progression and overall survival were estimated using the Kaplan–Meier method [32], with failed observations censored to 0. For some analyses, patients were grouped on the basis of response to the previous anthracycline-based regimen. For 2 × 2 table comparisons, a two-sided Fisher’s exact test was used. All patients were analyzed for safety.

**Results**

**Patient characteristics**

Fifty-two patients were enrolled between January 1994 and April 1999. Fourteen were premenopausal and 38 postmenopausal. Twenty-one were oestrogen/progesterone receptor positive. Twenty had been treated previously with one or two regimens of chemotherapy for metastatic disease, and 32 had never received any chemotherapy for metastatic disease. Twenty-six patients had been pretreated with anthracyclines, and 17 were resistant.

Five patients had been pretreated with adjuvant Tamoxifen, 10 patients with Tamoxifen for metastatic disease, two with Tamoxifen, aminoglutethimide and megestrol acetate for metastatic disease, and another four patients with adjuvant Tamoxifen and aminoglutethimide for metastatic disease. The median disease-free survival from primary treatment was 35.5 months and the mean time to study entry was 60.6 months.

The patients’ characteristics are listed in Table 1. The median age was 57.5 years (range 35–73 years); seven patients (13%) had liver metastases, 10 (19%) lung metastases, 15 (29%) soft tissue metastases, five (10%) bone metastases and 14 (27%) multiple metastatic sites. Twenty-three patients (35%) had received prior adjuvant chemotherapy.

Adjuvant chemotherapy regimens and further treatments in patients pretreated for metastatic disease are listed in Table 2. One of pretreated patients had undergone further chemo- and hormonotherapy. Among patients treated as first line, 11 had received no further therapy, 10 had been treated with taxanes, five with 5-fluorouracil as continuous infusion, and five with aminoglutethimide and megestrol.

**Response and survival data**

The response data are listed in Table 3. Among 51 patients assessable for response, there were 27 objective responses (52.9%; 95% CI 38.4% to 67%), including five complete responses (9.8%; 95% CI 3.2% to 21.4%) and 22 partial responses (43.1%; 95% CI 29.3% to 57.7%).

In previously untreated patients there were 17 objective responses (54.7%; 95% CI 34.7% to 71%), including two complete responses (6.4%; 95% CI 0.7% to 21%) and 15 partial responses (48.3%; 95% CI 29% to 65%).

In pretreated patients there were 10 objective responses (50%; 95% CI 27% to 73%), including three complete responses (15%; 95% CI 3% to 38%) and seven partial responses (35%; 95% CI 15% to 59%).

The difference in objective response rate between anthracycline-resistant (44.4%) and not-resistant patients (64.7%) was not significant (P = 0.4).

The metastatic sites of response are listed in Table 4. Six of 22 objective responses (27.2%) were in lung metastases (with four complete responses) and nine (40.9%) were in multiple sites, including bone.
The median time to progression was 8.5 months (95% CI 7.2–13.2 months in untreated patients, 5.9–11.2 months in pretreated patients). Median survival was 21.2 months (95% CI 16.9–28.9 months) for untreated patients and 16.1 months (95% CI 11.5–25.8 months) for pretreated patients.

Median survival of the 17 anthracycline-resistant patients was 15.7 months (95% CI 8.7–30.5 months) and 16.5 months (95% CI 3.3–29.9 months) for the nine non-resistant patients (Wilcoxon t-test, \(P = 0.6\)).

Survival curves for untreated and pretreated patients are presented in Figure 1. Sixty-two percent of untreated patients survived 1 year, 46.8% 2 years, 21.8% 3 years and 6.2% 4 years. Fifty-five percent of pretreated patients survived 1 year, 25% 2 years and 5% 3 years.

**Subjective response**

Patients’ PS at the end of the treatment, compared with the PS at baseline, are listed in Table 5. At the baseline assessment, 14 patients were had PS 0 (26.9%), 15 had PS 1 (28.8%), 20 had PS 2 (38.4%) and three had PS 3 (5.7%). At the end of treatment, 29 patients had PS 0 (55.7%), 18 had PS 1 (34.6%),
four had PS 2 (7.6%) and one had PS 3 (1.9%). Considering ECOG PS 0 and 1 to be a 'good' PS, the difference was significant \( (P = 0.0001) \).

**Treatment duration and reasons for discontinuing therapy**

A total of 233 cycles was given and 52 patients were assessable for toxicity. The actual delivered dose of cisplatin was 78.3 mg/m\(^2\) (day 1) and that of vinorelbine was 47.8 mg/m\(^2\) (days 1 and 8), over a total of 807 weeks (instead of the planned 699 weeks because of 108 1-week delays).

Twenty-four patients (46.1%) received six cycles and six patients received five cycles (11.5%). These patients received 85% of the planned dose intensity (in treatment-given analysis). There were 11 withdrawals because of progression of disease (21.1%), seven because of stable disease after three cycles and patient refusal, and four because of toxicity (three grade 4 emesis and one acute cardiac failure in pretreated patients). The overall mean number of cycles per patient was 4.8 (range one to six cycles) and the dose intensity per six cycles for all patients was 74.65% of the planned dose (in intention-to-treat analysis).

**Toxicity**

The main toxicities are listed in Table 6. Grade 3 or 4 neutropenia was observed in 14 of 32 untreated patients (43.7%) and in 12 of 20 pretreated patients (60%). A total of 108 of 233 cycles was delayed for 1 week because of neutropenia, and 25 of 32 patients were treated with G-CSF. There was no delay on day 8. No febrile neutropenia was observed.

Grade 3 or 4 anemia was observed in four of 32 untreated patients (28%) and in five of 20 pretreated patients (25%). Grade 3 thrombocytopenia was observed in one patient. Grade 3 or 4 vomiting was observed in five of 32 untreated patients (15.6%) and in four of 20 pretreated patients (20%). Grade 3 asthenia was observed in two of 52 patients.

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**Table 3. Objective response rate**

<table>
<thead>
<tr>
<th></th>
<th>Overall [no. (%)]</th>
<th>Untreated [no. (%)]</th>
<th>Pretreated [no. (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>5 (10)</td>
<td>2 (6.4)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>PR</td>
<td>22 (43)</td>
<td>15 (48)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>NC</td>
<td>13 (25)</td>
<td>6 (18.7)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>PD</td>
<td>11 (21)</td>
<td>8 (25)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Not assessable</td>
<td>1 (1.9)</td>
<td>1 (3.1)</td>
<td>0</td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; NC, stable disease; PD, progressive disease.

**Table 4. Objective response rate according to metastatic sites of response**

<table>
<thead>
<tr>
<th>Site of metastases</th>
<th>Overall</th>
<th>Untreated</th>
<th>Pretreated</th>
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<tbody>
<tr>
<td></td>
<td>CR (%)</td>
<td>PR (%)</td>
<td>CR (%)</td>
</tr>
<tr>
<td>Lung</td>
<td>4 (40)</td>
<td>2 (20)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Liver</td>
<td>0</td>
<td>3 (43)</td>
<td>0</td>
</tr>
<tr>
<td>Soft tissues</td>
<td>0</td>
<td>6 (40)</td>
<td>0</td>
</tr>
<tr>
<td>Bone</td>
<td>0</td>
<td>3 (60)</td>
<td>0</td>
</tr>
<tr>
<td>Multiple</td>
<td>1 (7)</td>
<td>8 (57)</td>
<td>1 (7)</td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response.
Seven patients (13.4%) had grade 1/2 neurotoxicity, and two grade 1/2 nephrotoxicity (3.8%). One patient who had been heavily pretreated with anthracyclines (basal LVEF of 52%) developed congestive cardiac failure after the third cycle and was hospitalized. There were no treatment-related deaths. No patient developed alopecia.

**Discussion**

This open phase II clinical trial evaluated the efficacy and safety of a combination of cisplatin and vinorelbine in patients treated for metastatic disease in a first- and second-line setting. The duration of recruitment of the 52 patients was long (1994–1999), mainly because of the restrictive inclusion criteria (LVEF >45% and creatinine clearance >60 ml/min), and also because of the availability of taxanes after 1996, labeled for second-line treatment in Italy.

The results of this study show that the combination of cisplatin and vinorelbine is active in previously untreated and in pretreated patients, and confirmed our previous data showing only a partial cross-resistance in anthracycline-resistant patients. The efficacy of the regimen is confirmed by the excellent median time to progression in both groups (8.5 months) and by median overall survival, which was particularly good in pretreated patients (16 months) compared with other reports [15, 25, 26]. The combination appears to be particularly active in lung and bone metastases. The combination was also very effective for survival. Fifty-five percent of the patients who had been treated previously survived for 1 year and 25% for 2 years. Of those who had not been treated before, 63% survived for >12 months and 47% for >2 years.

We observed an overall improvement of at least one ECOG PS score in 55.7% of patients and in ~62% (eight of 13) of patients with stable disease as their best ever response. An improvement in PS, even in the absence of any measurable response, could be regarded as an outstanding feature of the combination, and as a clinical benefit.

<table>
<thead>
<tr>
<th>Table 5. PS at baseline and at the end of treatment</th>
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<tr>
<td>ECOG PS</td>
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<tr>
<td>-----------</td>
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<tr>
<td>0</td>
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<tr>
<td>1</td>
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<tr>
<td>2</td>
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<td>3</td>
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</table>

Table 6. Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Untreated patients (%)</th>
<th>Pretreated patients (%)</th>
<th>Overall (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>14/32 (43.7)</td>
<td>12/20 (60)</td>
<td>26/52 (50)</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>4/32 (28)</td>
<td>5/20 (25)</td>
<td>9/52 (17.3)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>1/20 (5)</td>
<td>1/52 (1.9)</td>
</tr>
<tr>
<td>Neutrotoxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1/2</td>
<td>3/32 (9.3)</td>
<td>4/20 (20)</td>
<td>7/52 (13.4)</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1/2</td>
<td>0</td>
<td>2/20 (10)</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Asthenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>1/32 (3.1)</td>
<td>1/20 (5)</td>
<td>2/52 (3.8)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>5/32 (15.6)</td>
<td>4/20 (20)</td>
<td>9/52 (17.3)</td>
</tr>
<tr>
<td>Alopecia</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Any grade</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CHF</td>
<td>0</td>
<td>1/20 (5)</td>
<td>1/52 (1.9)</td>
</tr>
<tr>
<td>Treatment-related deaths</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Heavy anthracycline pretreatment.*
Hematological toxicity was marked in patients who had been treated before, and was limited in the others. There was no difference with regard to leukopenia, since it was limited in severity and thus controlled by moderate use of growth factors. Hematological toxicity in our study is higher than in our first report with fewer patients [21], but is consistent with other reports (37–77% [25–29]). Neurotoxicity and nephrotoxicity were infrequent and mild, as reported by others [25–29].

There were no remarkable clinical complications. As a result of supportive care, toxicity was not seen in most of the patients and only had a minor effect on costs, since the combination itself is not expensive. As regards emesis, the effects of the regimen were well controlled by the anti-serotoninergic anti-emetics and, as expected, this side effect occurred more frequently in patients who had been treated before. A further important factor is that none of the patients complained of alopecia, which is regarded by women as a very distressing condition.

We consider that the cisplatin–vinorelbine combination is very effective clinically for metastatic breast cancer. It appears to be easy to manage on an outpatient basis and subjectively is not very aggressive, provided CSF are used in order to prevent neutropenia and renal function is carefully monitored.

It is a very good regimen for second- or third-line treatment, but our study suggests that it is active even as first-line treatment for patients who cannot be treated with anthracyclines. For patients who have already had cardiac failure and have not received chemotherapy with taxanes either as an adjuvant or as first-line treatment, use of a taxane is considered a better option. It would be interesting to determine whether the combination vinorelbine–cisplatinum would be effective in taxane-pretreated patients. Unfortunately, this information cannot be deduced from the present study as only two patients received paclitaxel as first-line treatment.

References