Gemcitabine and vinorelbine as second-line treatment in patients with metastatic breast cancer progressing after first-line taxane-based chemotherapy: A phase II study conducted by the Hellenic Cooperative Oncology Group

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Summary

Background: Gemcitabine and vinorelbine have shown activity in breast cancer. A phase II trial was initiated in order to evaluate the response rate (RR) and time to progression (TTP) of the combination of the two drugs in patients with metastatic breast cancer progressing after first-line taxane-based chemotherapy.

Patients and methods: Thirty-one patients were treated with the combination of gemcitabine 1000 mg/m² days 1 + 8 and vinorelbine 30 mg/m² days 1 + 8. The cycles were repeated every three weeks.

Results: Of 27 evaluable patients 1 (4%, 95% confidence interval (95% CI): 0.1%—19%) achieved complete remission (CR), five (18%; 95% CI: 6%-38%) partial remission (PR), eleven (40%; 95% CI: 22%-61%) stable disease and ten patients progressed. The median duration of response was six months (range 4-10+) and the median duration of disease stabilization was five months (range 2-22+). With a median follow-up of 16 months (range 0.4-22+) the median TTP was 3.5 months (range 0.4-22+) and the median survival was 9.5 months (range 0.4-22+). Grade 3—4 toxicities were granulocytopenia 15 patients (48%), rash 3 patients (10%), neuropathy 1 patient (3%) and thrombocytopenia 1 patient (3%). In conclusion the combination of gemcitabine/vinorelbine in the doses administered in this group of patients had a response rate of 22% and needs to be further evaluated in metastatic breast cancer.

Key words: advanced breast cancer, chemotherapy, gemcitabine, vinorelbine

Introduction

Despite the progress in the treatment of breast cancer, patients with metastatic disease have a poor prognosis. First-line combination chemotherapy results in response rates of 40%–80%, complete responses being in the range of 10%–20%. The median duration of response is less than a year, but a small proportion of patients survives more than five years.

The response rate of second-line combination chemotherapy is between 20% and 40% with a median response duration from 2–8 months. Given that in this setting, the use of combination chemotherapy is purely palliative, effective regimens must be developed which must combine therapeutic efficacy with low systemic toxicity and good tolerability. Gemcitabine is a fluorine-substituted cytarabine analog with activity against a wide range of solid tumors. In a phase II study, 44 patients with locally advanced or metastatic breast cancer were treated with gemcitabine 800 mg/m² once a week for three weeks followed by one week rest, every four weeks with a response rate of 25%. Hematological and non-hematological toxicities were mild [1]. Abratt et al. in a phase II trial in patients with non-small-cell lung cancer demonstrated that doses above 800 mg/m² and as high as 1850 mg/m²/wk can be given safely [2]. Vinorelbine is a novel vinca alkaloid with decreased neurotoxicity compared with the other vinca alkaloids. A phase I study determined the recommended dose of vinorelbine to be 20–35 mg/m²/wk [3]. The dose of 30 mg/m²/wk was used in phase II trials in advanced breast cancer [4]. An overall response rate of 41% was observed in a phase II study of vinorelbine used as first-line chemotherapy in patients with advanced breast cancer [5]. Motivated by the above data we conducted a phase II study to evaluate the response rate, the duration of response and toxicity of the combination of gemcitabine and vinorelbine in patients with advanced breast cancer progressing after first-line taxane-based chemotherapy.

Patients and methods

Patients with histologically proven advanced breast cancer who have progressed after first line taxane based chemotherapy for metastatic disease were eligible for the study. They were required to be ≥ 18 years
Table 1. Patients and disease characteristics.

<table>
<thead>
<tr>
<th>Number of metastatic sites</th>
<th>Site of metastasis</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Locoregional</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>Locoregional + distant</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>Liver</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>Lung-pleura</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>Bones</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>Nodes</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>Other breast</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>Other</td>
<td>6</td>
</tr>
<tr>
<td>9</td>
<td>Visceral metastasis</td>
<td>23</td>
</tr>
<tr>
<td>10</td>
<td>Skin</td>
<td>9</td>
</tr>
</tbody>
</table>

of age, have a performance status ≤ 3 of the ECOG scale and a life expectancy of >3 months. Measurable or evaluable disease was required. All patients should have had leukocyte and platelet counts greater than 4000/µl and 100,000/µl respectively. Creatinine <1.5 mg/dl, AST and ALT <3 normal value and PT/aPTT <1.5 x normal.

Toxicities grade 3-4 were granulocytopenia (1%); thrombocytopenia in 1 (3%), paralytic ileus in 1 patient (3%) and rash in 3 (10%). The median duration of granulocytopenia was 4 days (range 2–7). Five patients received antibiotics for febrile neutropenia. G-CSF was administered in 24 patients (5 patients who experienced neutropenia grade ≥2), red blood cell transfusions in 3 (anemia grade 2) and platelet transfusion in 1 patient. Peripheral neuropathy grades 1–2 was observed in 7 (25%) patients.

Results

Toxicity

The 31 patients received a total of 125 cycles, 56 (45%) of which at full dose. The planned dose intensity (DI) of gemcitabine was 666.6 mg/m²/wk and the median delivered was 482 mg/m²/wk. The planned DI of vinorelbine was 20 mg/m²/wk and the median delivered was 14 mg/m²/wk. Relative dose intensity was 0.72 for gemcitabine (range 0.15–1) and 0.70 for vinorelbine (range 0.15–1). Fourteen patients (48%) completed all cycles of treatment. Reasons for treatment discontinuation were disease progression in 13 patients, toxicity grade 4 in 4 patients and early tumor death in 1 patient.

Toxicities grade 3–4 were granulocytopenia in 15 patients (48%), thrombocytopenia in 1 (3%), paralytic ileus in 1 patient (3%) and rash in 3 (10%). The median duration of granulocytopenia was 4 days (range 2–7). Five patients received antibiotics for febrile neutropenia. G-CSF was administered in 24 patients (5 patients who experienced neutropenia grade ≥2), red blood cell transfusions in 3 (anemia grade 2) and platelet transfusion in 1 patient. Peripheral neuropathy grades 1–2 was observed in 7 (25%) patients.

Response to treatment and survival

One patient (4%; 95% CI: 0.1%–19%) achieved CR and 5 (18%; 95% CI: 6%–38%) PR for an overall response rate of 22% (95% CI: 9%–42%). Eleven patients (40%; 95% CI: 22%–61%) had stabilization of their disease. Responses were seen in skin (2 of 11), lymph nodes (1 of 12), lung (2 of 11), liver (5 of 17), breast (1 of 3) and bone metastases (1 of 16). Patients who responded to treatment had achieved CR (1 of 6), PR (1 of 6) stabilization of their disease (2 of 6) or progressed (2 of 6) under treatment with previous taxane-based regimens. No significant difference was found between the dose intensity of gemcitabine and vinorelbine received by responding and non-responding patients. The mean delivered dose intensity of gemcitabine was 520 mg/m²/wk for responding and 500 mg/m²/wk for non-responding patients. The mean delivered dose intensity of vinorelbine was 16 mg/m²/wk for responding and 15 mg/m²/wk for non-responding patients. The median duration of response was six months (range 4–10) and the median...
duration of disease stabilization was five months (range 3–22+).

After a median follow-up of 17 months (range 0.4–22+) the median time to progression was 3.5 months (range 0.4–22+) and median survival was 9.5 months (range 0.4–22+).

Discussion

Vinorelbine in combination with 5-FU [6, 7] and doxorubicin [8] used as first-line chemotherapy in metastatic breast cancer has shown response rates of 62%–65% and 74%, respectively. In these studies grade 3–4 toxicities were mainly neutropenia, neutropenic infections and mucositis.

As the majority of patients with breast cancer currently receive anthracycline/taxane-based chemotherapy or combinations of the two either in the adjuvant or metastatic setting, palliative regimens should include other cytotoxic drugs. The combination of vinorelbine with cisplatin has shown a RR of 43% when used as second- or third-line treatment in patients with metastatic breast cancer [9]. Livingston et al. [10] investigated a dose-intensive weekly regimen with vinorelbine plus G-CSF in patients refractory to taxanes and showed that there was no cross-resistance between the two compounds. The response rate achieved by vinorelbine + G-CSF in that study was 25% with a mean delivered dose intensity of vinorelbine 27.7 mg/m²/wk. Haider et al. [11] used the combination of gemcitabine 1000 mg/m² on days 1 + 15 + 21 and vinorelbine 40 mg/m² on days 1 + 21 and G-CSF in cycles repeated every five weeks in previously treated or untreated patients resulting in response rates of 55% and 40%, respectively.

In this study the combination of gemcitabine with vinorelbine in patients progressing or relapsing after first-line taxane based chemotherapy was 22%.

It should be noted that 21 of 31 patients have received a combination of an anthracycline with a taxane as first-line treatment. The RR of 22% achieved with this combination used as second-line treatment is promising and deserves further evaluation with the prophylactic use of G-CSF in order to maintain dose intensity and avoid neutropenia.

References


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