Paclitaxel and vinorelbine in anthracycline-pretreated breast cancer: A phase II study

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Summary

Background: Paclitaxel and vinorelbine are active in advanced breast cancer pretreated with anthracyclines. We therefore conducted a phase II study to define the toxicity and activity of paclitaxel and vinorelbine administered in combination.

Patients and methods: Our patient population consisted of 37 patients with metastatic breast cancer, 35 of whom had received prior chemotherapy including anthracyclines. The treatment regimen included vinorelbine (25 mg/m² i.v.) followed by paclitaxel (135 mg/m² i.v. as a 3-hour infusion) on day 1; vinorelbine was repeated on day 8 in the first 14 patients and on day 3 in the remaining 23 patients.

Results: Because of grade 4 neutropenia, the second dose of vinorelbine was reduced or omitted in 88% of the courses on the days 1 and 8 schedule and in 48% of the courses on the days 1 and 3 schedule. As a consequence the administered dose intensity of vinorelbine was significantly higher on the days 1 and 3 schedule (13 mg/m²/wk versus 8.3 mg/m²/wk, P = 0.005). The overall response rate was 38% (95% CI: 22–55); four responses have been observed in the ten patients with absolute anthracycline resistance. The median duration of response was 6.5 months.

Conclusions: The combination of paclitaxel and vinorelbine is a feasible and active salvage regimen in advanced breast cancer patients pretreated with anthracyclines.

Key words: breast cancer, paclitaxel, vinorelbine

Introduction

In metastatic breast cancer anthracycline-based regimens yield response rates ranging from 40% to 80% with a complete response rate lower than 20%; the median duration of response is usually less than one year and very few patients experience long-term remissions [1]. The availability of drugs with new mechanisms of action and non-cross resistance to anthracyclines might offer an opportunity to improve these results. In this setting interesting results have been reported with paclitaxel and vinorelbine. Paclitaxel, infused over 24 hours, has produced response rates of 56% to 62% in patients with minimal prior chemotherapy [2, 3] and a response rate of 22% in heavily pretreated patients [4]; with shorter infusions (3 hours) the response rate ranges from 20% to 30% [5–7]. Vinorelbine, as a single agent, has induced response rates greater than 20% after prior anthracycline [8, 9] and in the range of 40% in chemotherapy-naive patients [10, 11].

On these premises, we have evaluated the feasibility, toxicity and activity of a combination of paclitaxel and vinorelbine in anthracycline-pretreated patients with advanced breast cancer.

Patients and methods

Eligibility criteria

The study was conducted in metastatic breast cancer patients who had received at least one prior course of chemotherapy for advanced disease or who had had a disease-free interval shorter than 12 months after adjuvant chemotherapy. Other eligibility criteria included age ≤ 70 years, performance status (PS; ECOG scale) ≤ 2, expected survival > 6 months, no contraindication to chemotherapy, and normal left ventricular ejection fraction (L-VEF > 50%).

Pretreatment evaluations included a complete history and physical examination, chest X-ray, liver echotomography and any other ultrasound or computed tomographic scan useful in defining the extent of the disease. An informed consent was obtained from all patients before study entry and the protocol was approved by the ethics committee of the St. Chiara Hospital.

Treatment plan

After premedication with prednisone, diphenylhydrazine and cimetidine, the patients were treated with paclitaxel 135 mg/m², given in 3 hours, and vinorelbine, 25 mg/m², slow intravenous bolus, immediately before the paclitaxel; a second dose of vinorelbine (25 mg/m²) was given on day 8 in the first 14 patients and on day 3 thereafter. The dose of vinorelbine on day 8 or day 3 was modified according to the absolute neutrophil count observed on that day; the dose reduction scheme was the following: ANC > 1,500/µl: no dose reduction, ANC between 1,000 and 1,500/µl: 75% of the planned...
dose, ANC between 500 and 1,000 µl: 50% of the dose, ANC < 500/µl: vinorelbine omitted.

The courses were administered every 3 weeks on an outpatient basis. Chemotherapy was delayed one week if ANC was less than 1,500/µl and/or platelets were less than 100,000/µl. If grade 4 neutropenia lasted for 7 days or longer or in instances of grade > 2 non-hematologic toxicity the dosages of both drugs were reduced by 25% in subsequent courses. In case of grade 4 neutropenia all of the patients were treated with ciprofloxacin 500 mg b.i.d. orally plus fluconazole 50 mg daily. Filgrastim (5 µg/kg/die) was administered if grade 4 neutropenia lasted longer than 72 hours or in instances of febrile neutropenia (body temperature more than 38.2 ºC and ANC less than 500 µl). Chemotherapy was administered for a maximum of eight courses or two courses beyond the best response.

On study evaluations

Complete blood cell counts were performed on days 3 or 8, and thereafter repeated weekly except in instances of grade 4 neutropenia, when the counts were monitored daily; the L-VEF was evaluated every three courses.

Study parameters

Responses and toxicities were recorded according to the World Health Organization (WHO) criteria. Time to progression was calculated from the beginning of therapy to progression; overall survival was measured from the beginning of treatment to death or to the date on which the patient was last observed. Level of resistance to anthracyclines was classified according to the definitions listed in Table 1.

Dose intensity, expressed in mg/m² per week, was calculated separately for each drug of the regimen by dividing the total amount of drug given in milligrams by the body surface area and by the time elapsed between the first day of treatment and the last day of the last chemotherapy course [12].

Table 1. Level of anthracycline resistance.

<table>
<thead>
<tr>
<th>Level of resistance</th>
<th>Definition</th>
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<tr>
<td>Absolute</td>
<td>Relapse within 6 mos from adjuvant anthracycline</td>
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<tr>
<td></td>
<td>Progression or no response to first-line anthracycline for metastatic disease</td>
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<tr>
<td>Relative</td>
<td>Relapse &gt; 6 mos from adjuvant anthracycline</td>
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<td></td>
<td>TFI &lt; 6 mos after an objective response to first-line anthracycline for metastasis</td>
</tr>
<tr>
<td>Potentially sensitive</td>
<td>TFI &gt; 6 mos after an objective response to first-line anthracycline for metastasis</td>
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Abbreviation: TFI - treatment-free interval.

Results

Thus far 37 patients have entered the study; all are assessable for toxicity and 36 of them for response. One patient was lost to follow-up evaluation after the first course. All baseline cardiac parameters were normal and the median L-VEF was 58% (range 50%-70%). Patient characteristics are listed in Table 2.

Hematologic toxicity

A total of 133 courses have been administered to 37 patients. After the first 14 patients it was clear that the dose of vinorelbine had to be reduced or omitted in the majority of the courses; we decided therefore to move the second dose of vinorelbine forward to day 3 in the subsequent patients. The hematologic toxicities were analyzed separately in the two series of patients.

Vinorelbine 1.8

The median day of nadir was day 8 (range 5-14); a grade 4 neutropenia occurred in 13 of 14 patients after the first course and in 33/52 (64%) courses; the median duration of grade 4 neutropenia was 4 days (range 2-8). On day 8 when the second dose of vinorelbine was scheduled, grades 3 and 4 neutropenia occurred in 23% and 40% of the courses, respectively, and in 11 of 14 patients. Filgrastim was given to 7 patients in 18 of 52 courses (35%). Six patients developed a febrile neutropenia (2 patients after the first course) that required hospitalization of one of them.

Vinorelbine 1.3

The median day of nadir was day 10 (range 7-14); a grade 4 neutropenia occurred in all of the patients after the first course and in 50/81 (61%) courses; the median duration of grade 4 neutropenia was 3 days (range 2-6). On day 3, when the second dose of vinorelbine was scheduled, a grade 3 neutropenia was recorded in 20% of the courses. Filgrastim was given to 12 patients in 38 of 81 courses (47%) because of grade 4 neutro-

<table>
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<th>Table 2. Patient characteristics.</th>
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<tr>
<td>Characteristics</td>
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<td>-----------------------------------</td>
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<tr>
<td>No. of patients</td>
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<td>Age, years</td>
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<td>(Range)</td>
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<tr>
<td>Performance status</td>
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<td>1</td>
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<td>Prior hormonal therapy</td>
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<td>No. of prior chemotherapy</td>
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<td>1</td>
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<tr>
<td>3</td>
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<tr>
<td>Prior anthracycline</td>
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<tr>
<td>Best response prior anthracycline for metastasis</td>
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<td>CR + PR</td>
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<tr>
<td>SD + PD</td>
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<tr>
<td>Unassessable: adjuvant anthracycline</td>
</tr>
<tr>
<td>DFS &lt; 6 mos</td>
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<tr>
<td>DFS &gt; 6 mos</td>
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<tr>
<td>Dominant metastatic site</td>
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<tr>
<td>Visceral</td>
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<tr>
<td>Soft tissues</td>
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<td>Bone</td>
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Abbreviations: CR - complete response; PR - partial response; SD - stable disease; PD - progressive disease.
The objectives of the present study were to assess the treatments of our patient population and the overlap-pretreated with chemotherapy. Because of the pre-feasibility and activity of the combination of paclitaxel and vinorelbine, the schedule 1,3 courses. On days of retreatment, the chemotherapy was administered in the planned dose in 52%, reduced to 75% in 33% and omitted in 12% of the courses. For vinorelbine the median dose intensity was 8.3 mg/m²/wk and 13 mg/m²/wk (P < 0.005) and the percentage of planned dose intensity was 51% and 82% with the 1,8 and 1,3 schedules, respectively. The median dose intensities of paclitaxel were not significantly different in the two schedules. On days of retreatment, the chemotherapy was delayed in 17% of the schedule 1,8 courses and 16% of the schedule 1,3 courses.

Response to therapy

Two patients achieved complete responses, 12 patients partial remission, 14 patients showed disease stabilization and eight progressed. Five responses (one complete and four partial) occurred in 11 patients who had responded to prior anthracycline; five partial responses were observed in 14 patients with relative anthracycline resistance; four responses (one complete and three partial) were observed in 10 patients with absolute anthracycline resistance. The best response was observed after a median of 4 courses (range 2–8). The overall response rate is 38% (95% CI: 22–55) and the median duration of response is 6.5 months (range: 4–9+).

Discussion

The objectives of the present study were to assess the feasibility and activity of the combination of paclitaxel and vinorelbine in patients with advanced breast cancer pretreated with chemotherapy. Because of the pretreatments of our patient population and the overlap-pretreatment of 2 of them. Other hematologic toxicities were rare and mild; only one patient developed a grade 2 thrombocytopenia.

Non-hematologic toxicity

A moderate (G1 and G2) nausea and vomiting was observed in 18% of the courses; a grade 3 oral mucositis was reported in 3% of all the courses and occurred on the days 1 and 3 schedule only; alopecia was universal; grades 1 or 2 peripheral neuropathy was observed in 43% of the patients, only 1 patient experienced a grade 3 neuropathy which required treatment discontinuation. Myalgia was reported in 6% of the courses (G1: 4%, G2: 1% and G3: 1%). The median ejection fraction was not significantly changed during treatment.

Dose intensity analysis

The dose of vinorelbine on day 8 was administered in the planned dose in 12% of courses, reduced to 75% in 11%, to 50% in 4% and omitted in 75% of the courses. On day 3, vinorelbine was given at 100% of the planned dose in 52%, reduced to 75% in 33% and omitted in 12% of the courses. For vinorelbine the median dose intensity was 8.3 mg/m²/wk and 13 mg/m²/wk (P < 0.005) and the percentage of planned dose intensity was 51% and 82% with the 1,8 and 1,3 schedules, respectively. The median dose intensities of paclitaxel were not significantly different in the two schedules. On days of retreatment, the chemotherapy was delayed in 17% of the schedule 1,8 courses and 16% of the schedule 1,3 courses.

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