Infusional 5-FU, Folinic Acid, Paclitaxel, and Cisplatin for Metastatic

Review Article [1] | April 01, 1997
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Our phase II study results demonstrating high efficacy and low toxicity for a weekly schedule of high-dose, 24-hour infusional 5-fluorouracil(5-FU)/folinic acid (HD5-FU/FA) in intensively pretreated patients with metastatic breast cancer.

Introduction
A phase I/II study of high-dose 5-fluorouracil/folinic acid (5-FU/FA), given weekly for six weeks by 24-hour infusion, demonstrated high efficacy, with a response rate of 41% (13 of 32 patients), and low toxicity in intensively pretreated patients with metastatic breast cancer.[1] Based on these results, we added paclitaxel (Taxol) to the regimen in a second phase I/II study, also in pretreated patients with metastatic breast cancer.[2] The combination of paclitaxel with weekly high-dose infusional 5-FU/FA was well tolerated and highly effective (response rate, 59%; 32 of 54 patients) in these patients, including those with anthracycline-refractory disease. In an ongoing phase II study, we intend to estimate the value of adding cisplatin to this regimen as first-line treatment of metastatic breast cancer to create an effective treatment for patients who have received anthracyclines in the adjuvant setting.

PATIENTS AND METHODS
In June 1995, we initiated this phase II study of first-line treatment in patients with metastatic breast cancer and no prior chemotherapy for metastatic disease.

Eligibility Criteria
All patients had histologically proven breast cancer; were pretreated with chemotherapy only in the adjuvant setting; had not had any chemotherapy for metastatic disease; had bidimensionally measurable disease with or without evaluable disease (ie, bone metastases); and had adequate hematologic, renal, and hepatic function, as well as no severe, uncontrolled comorbidities. Additional eligibility criteria included an Eastern Cooperative Oncology Group performance status of 0, 1, or 2; life expectancy of at least 3 months; and age 18 or more years. Pregnancy was excluded prior to study entry. All patients gave informed consent before participating in this study, which was approved by the institutional review board. A quality-of-life analysis was performed throughout the study and during follow-up.

Patient Characteristics
At this time, 28 patients have entered this ongoing phase II study. Patients had progressive disease and/or tumor-related symptoms prior to study treatment. All patients had at least one bidimensionally measurable tumor site. The characteristics of the patients treated are outlined in Table 1.

Study Design
Patients were treated with high-dose 5-FU 2.0 g/m² (by 24-hour infusion) plus FA 500 mg/m² (by 2-hour infusion prior to 5-FU) weekly for 6 weeks (days 1, 8, 15, 22, 29, and 36). Cisplatin 50 mg/m² (by 1-hour infusion) was administered on days 1 and 22, and paclitaxel 175 mg/m² (by 3-hour infusion) was given on days 0 and 21 after standard premedication with corticosteroids and H₁- and H₂-receptor antagonists. Each cycle comprised 6 weeks, followed by 2 weeks of rest, with a total of three cycles planned. All patients were treated under outpatient conditions using intravenous port systems and portable pumps (Figure 1).

Mode of Administration/ Drug Therapy
All patients had intravenous port systems. Folinic acid 500 mg/m² was dissolved in 500 mL of a 0.9%
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saline solution and given over 2 hours as a continuous infusion, prior to a 24-hour continuous infusion of 5-FU (2 g/m²), given by portable pump. This application was performed weekly for 6 weeks. Cisplatin 50 mg/m² was given on days 1 and 22, and paclitaxel at a dose of 175 mg/m² was given on days 0 and 21. We used standard premedication with corticosteroids and H₁- and H₂-receptor antagonists, as well as polyvinyl chloride-free infusion material and filter systems for paclitaxel administration. Cisplatin and paclitaxel, dissolved in 1,000 mL of 0.9% saline solution, were given prior to the FA/5-FU. While the number of applied cycles depended on response and toxicity, three full cycles were planned for patients without tumor progression and without worsening of performance status or tumor-related symptoms during chemotherapy. Cytokines were not administered.

The 5-FU dosage was reduced by 20% in cases of mucositis or stomatitis or of diarrhea greater than World Health Organization (WHO) stage 2. If mucositis, stomatitis, or diarrhea greater than WHO stage 2 were present on the day of planned treatment, chemotherapy was delayed until full recovery from side effects and the dose of 5-FU was reduced by 20% for the remaining treatment period.

**Patient Evaluation**

Prior to treatment, all patients underwent physical examination, chest x-ray, abdominal ultrasound, thoracic and/or abdominal computed tomography scan if indicated, bone scan, blood cell counts, routine biochemical tests, and tumor-marker screening. Tumor response was evaluated after each treatment cycle, using those techniques required to assess tumor locations present at study entry. Full restaging was done following induction of an objective response, upon progressive disease assumed due to contradictory results between imaging techniques and biochemical tests, upon worsening of performance status or clinical symptoms despite tumor regression or stable disease, and at the end of treatment.

Blood cell counts and assessment of toxicities were done weekly during treatment, prior to each treatment period, and after the last chemotherapy cycle. Biochemical parameters and tumor markers were measured after each treatment cycle. Quality-of-life assessment was performed throughout the treatment period and during follow-up, using the European Organization for Research and Treatment of Cancer quality-of-life scale. Toxicity was graded according to the WHO scale.

**Response Criteria/Statistical Analysis**

Response guidelines were performed according to standard WHO criteria: Tumor response was documented in two evaluations performed at least 6 weeks apart. Complete remission and partial remission response duration were calculated from the date the response was first documented. Survival and time to progression were computed actuarially, using the Kaplan-Meier method, beginning with the date the patient was placed on study. Duration of response also was calculated according to Kaplan-Meier, from the date of response to the date of progressive disease.[3]

**RESULTS**

**Toxicity**

With a total of 65 treatment cycles and a median of two treatment cycles per patient (range, one to three cycles), all 28 patients were evaluable for toxicity. No serious acute hypersensitivity reactions were attributed to paclitaxel. Neutropenia was common but moderate in most patients (WHO grade 3 in 35% of cycles). No hospitalizations were necessary for febrile neutropenia. The duration of grade 3 and 4 neutropenia was generally brief. No cytokines were used. Aside from common total alopecia, nonhematologic toxicities consisted primarily of moderate (defined as WHO grade 2 in percent of cycles) myalgia (45%), diarrhea (53%), mucositis (39%), nausea and vomiting (52%), and hand-foot syndrome (51%). Peripheral polyneuropathy was cumulative and occurred most frequently during the third treatment cycle, with mild-to-moderate expression. World Health Organization grade 3 toxicity occurred in 7% of cycles as nausea and vomiting and in 11% of cycles as diarrhea.

**Response**

The following results have been achieved: 25% (7 of 28) of patients have attained a complete remission and 57% (16 of 28) a partial remission; 11% (3 of 28) have stable disease, and 7% (2 of 28) have progressive disease. Overall response rate was 83% (95% confidence interval, 66% to 100%) (Table 2). Median time to maximum response was 2 months (range, 1 to 5), median remission duration was 8 months (range, 4 to 22). Eight of the 28 patients are still receiving treatment, and the median survival time has not yet been reached.

**DISCUSSION**

Sledge and coworkers[4] summarized cisplatin as a significant, active single agent for the first-line
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Treatment of metastatic breast cancer. Additionally, preclinical data suggest a synergistic interaction for combining cisplatin with either paclitaxel or 5-FU.[5,6] Further, our own clinical toxicity data of combination paclitaxel plus high-dose 5-FU/FA allows the addition of a third combination partner for use in a less-pretreated patient population.[2]

The preliminary results of this ongoing phase II study of weekly high-dose, 24-hour infusional 5-FU/FA with paclitaxel/cisplatin indicate an active outpatient combination regimen for first-line treatment of women with metastatic breast cancer. In this study, we will further estimate the value of this regimen with respect to response duration, survival, toxicity, and quality of life during and after treatment. This active combination could have an impact on the management of metastatic breast cancer because of the more frequent use of anthracyclines and high-dose chemotherapy with peripheral stem cell support in the adjuvant setting.

References:

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