A Phase I Study of Ifosfamide and Doxorubicin with Recombinant Human Granulocyte Colony-stimulating Factor in Stage IV Breast Cancer

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ABSTRACT

Our objective was to define the maximum tolerated dose of an escalating dose of ifosfamide in combination with a fixed dose of doxorubicin supported by granulocyte colony-stimulating factor (Neupogen). Eighteen women with stage IV breast cancer were enrolled in a Phase I study of an escalating dose of ifosfamide (1.2 g/m²/day for 5 days–2.75 g/m²/day for 5 days) with doxorubicin 20 mg/m²/day for 3 days. Granulocyte colony-stimulating factor was used at 5 µg/kg on day 6 until hematological recovery. Prophylactic antibiotics were also used. The maximum tolerated dose of ifosfamide in combination with doxorubicin was 2.75 g/m²/day for 5 days. The objective response rate was 83% with a complete response rate of 33% (6/18 patients); the median time to treatment failure was 11.5 months. The median survival has not been reached and will exceed 18 months. We concluded that the recommended dose of ifosfamide in combination with doxorubicin is 2.5 g/m²/day for 5 days. This combination shows promise in stage IV breast cancer.

INTRODUCTION

Combination antineoplastic chemotherapy is an effective mode of palliation for women with stage IV breast cancer whose cancers are either hormone refractory or hormonally independent. Studies using high-dose chemotherapy with ABMT1 have been conducted in women with stage IV breast cancer in an attempt to increase the CR rate and with the hope that the increased CR rate would translate into an increased median survival and long-term survival (1, 2). To date, there is unequivocal evidence that high-dose chemotherapy with ABMT increases the CR rate of women with stage IV breast cancer; however, there is controversy as to the survival advantage, if any (3).

The high-dose chemotherapy trials conducted in stage IV breast cancer support the theory of tumor dose response in humans. An alternate means of exploiting the dose-response relationship is to use repeated cycles of high-dose chemotherapy with recombinant hematopoietic growth factor support. The advantages of this type of approach are obvious because patients would not require lengthy hospitalization, there would be no need for reinfusion of autologous bone marrow or peripherally derived hematopoietic progenitor cells, and, finally, this approach is more easily transferable center to center. There are trials underway examining the feasibility of high dose-chemotherapy with rhG-CSF (Neupogen) or recombinant human granulocyte-monocyte colony-stimulating factor (Leukine), as well as trials examining PIXY321 or interleukin 3, either alone or in combination. The objective of these ongoing trials is to define the MTD of antineoplastic chemotherapeutic drugs when used in combination with the aforementioned hematopoietic growth factors.

Ifosfamide is an oxazaphosphorine analogue of cyclophosphamide, in which one of the two 2-chloroethyl groups is shifted to the nitrogen atom on the oxazaphosphorine cyclic ring (4). Single-agent ifosfamide is an active drug in women with breast cancer (5). Ifosfamide-based combinations with either etoposide, epirubicin, doxorubicin, or methotrexate with 5-FU have activity in women with stage IV breast cancer (6–9). On the basis of the clinical activity of ifosfamide in breast cancer and the relatively favorable toxicity profile when used on conventional dose, ifosfamide is an ideal drug to use in high dose with hematopoietic growth factor support. In this article, we report the results of a Phase I trial of escalating doses of ifosfamide with Neupogen in combination with a fixed dose of doxorubicin in women with stage IV breast cancer.

PATIENTS AND METHODS

From October 1, 1991 to June 30, 1994, 18 women with stage IV hormone refractory or hormonally independent (ER/PR negative) breast cancer were enrolled in a Phase I study of ifosfamide and doxorubicin. The eligibility criteria included: women older than 18 years with stage IV breast cancer who either had hormonally refractory or ER/PR-negative breast cancer and were previously untreated with chemotherapy for stage IV disease (adjuvant chemotherapy was permitted as long as the prior cumulative doxorubicin dose did not exceed 200 mg/m²). Women were required to have an Eastern Cooperative Oncology Group performance status ≤2; they were required to have a normal cardiac ejection fraction (≥50%, by gated heart scan), normal renal function (serum creatinine, ≤1.5 mg/dl), normal liver function (total bilirubin, ≤2.0 mg/dl), and normal hematological parameters (hemoglobin, ≥10.0; absolute neutrophil count, ≥1500; platelets, ≥100,000). Patients with central nervous system metastases were permitted in this study after receiving whole-brain irradiation which was shown to have controlled the symptoms of the central nervous system metastases.
Documentation of stage IV disease was carried out clinically with appropriate imaging studies.

**Treatment Schema.** Dose escalation of ifosfamide was done using modified Fibonacci schema shown below, with a minimum of three patients entered per dose level and maintained at that dose level throughout their therapy. The dose levels of ifosfamide were: level I, ifosfamide 1.2 g/m²/day i.v. infusion with mesna for 5 days, total dose, 6.0 g; level II, ifosfamide 1.8 g/m²/day i.v. infusion with mesna for 5 days, total dose, 9.0 g; level III, ifosfamide 2.25 g/m²/day i.v. infusion with mesna for 5 days, total dose, 11.25 g; level IV, ifosfamide 2.5 g/m²/day i.v. infusion with mesna for 5 days, total dose, 12.5 g; level V, Ifosfamide 2.75 g/m²/day i.v. infusion with mesna for 5 days, total dose, 13.75 g.

The ifosfamide was reconstituted and placed in 100 ml of normal saline and infused over 30–45 min daily for 5 days. Doxorubicin was dosed at 20 mg/m² i.v. bolus via a rapidly running i.v. line on days 1, 2, and 3. Cycles of ifosfamide and doxorubicin were repeated every 21 days. The MTD of the combination was defined as that dose level either given for one cycle or on repetitive cycles that led to grade 4 toxicity other than neutropenia in two of three patients or three of five patients. The toxicities were graded by common collaborative group toxicity criteria.

Neupogen was given daily at a dose of 5 μg/kg s.c. starting on day 6, 24 h after ifosfamide and doxorubicin, and continued to day 20 or until the leukocyte count exceeded 10,000 cells/μl. If the WBCs did not exceed 10,000 cells/μl by day 20, the Neupogen dose was increased to 10 μg/kg. Acetaminophen was used to alleviate any arthralgias and myalgias as a consequence of Neupogen therapy. Prophylactic antibiotics, including ciprofloxacin (500 mg p.o. every 12 h) and fluconazole (100 mg p.o. every morning), were given on days 7–14. Chemotherapy was administered in the ambulatory setting for all but 3 of these 18 patients whose health insurance carriers would not provide coverage for ambulatory chemotherapy. Intravenous fluids (normal saline) were administered prior to ifosfamide and doxorubicin. Mesna was used and dosed milligram per milligram with ifosfamide. The total dose of mesna was then divided into thirds and administered prior to the ifosfamide and at 4 and 8 h following ifosfamide, respectively. Ondansetron was dosed at 0.2 mg/kg and administered 30 min prior to ifosfamide. The ondansetron dose was repeated at 4 and 8 h. With the recent availability of oral ondansetron the last three patients were given ondansetron tablets in lieu of the 8-h dose. Patients were encouraged to vigorously take fluids by mouth on days 1–5. Patients were checked for hematuria daily by urinalysis on days 1–5 prior to each ifosfamide dose. Patients were followed closely after each cycle of ifosfamide and doxorubicin and had complete blood counts and platelet counts on days 10, 14, 19, and 21 or until hematological recovery occurred. Patients had complete physical examinations done on days 10, 14, and 21 following each cycle of treatment. At the completion of 6 cycles of ifosfamide and doxorubicin (total dose of doxorubicin, 360 mg/m², 126 days of treatment) patients were removed from study and treated at the discretion of their attending physician. This included the option of continuing therapy with the combination of ifosfamide and doxorubicin until a total of 450 mg/m² of doxorubicin was administered.

**Statistical Considerations.** The objective of this Phase I trial was to define the MTD of ifosfamide when given in combination with doxorubicin. The MTD was defined as that dose which results in severe toxicities (grade 4) other than leukopenia or neutropenia and occurs in the majority of patients at a given dose level (i.e., 2/3, 3/5, etc.). Additional patients could be added to a given dose level to define the severe toxicities in the majority.

**Response, Time to Treatment Failure, and Survival.** Responses were classified as CR, PR, stable disease, or no response in accordance with standard response criteria. Patients attaining an objective response (CR or PR) had to have a response duration of at least 30 days. Time to treatment failure was defined as death or progressive disease and was calculated from day 1 of the first cycle of ifosfamide and doxorubicin. Survival was calculated from day 1 of the first cycle of ifosfamide and doxorubicin.

**RESULTS**

Between December 1, 1991 and July 1, 1994, 18 women were enrolled in this Phase I study. The median time of follow-up was 18 (range, 4–30) months. The 18 women entered in the study had a median age of 52 (range, 36–74) years and a median performance status of Eastern Cooperative Oncology Group (range, 0–2). The dominant sites of metastatic breast cancer were bone and bone marrow (9 patients), nodal and soft tissue (4 patients), lung (3 patients), and diffuse metastatic involvement of the lungs, liver, and bone (2 patients). One of these two patients had, in addition, brain metastasis. Of the 18 patients enrolled in this study, 10 patients had received prior adjuvant chemotherapy. Of these 10 patients, 4 patients received cyclophosphamide, methotrexate, and 5-FU, while the other 6 patients received low-dose cyclophosphamide, doxorubicin, and 5-FU. The six patients receiving FAC had each received a prior total cumulative dose of 180 mg/m² of doxorubicin. The median time to metastatic breast cancer for the 10 patients who received prior adjuvant chemotherapy was 24 (range, 16–72) months.

These 18 women received 68 cycles of ifosfamide and doxorubicin. The MTD for the combination of ifosfamide and doxorubicin with Neupogen and prophylactic antibiotic support was 2.75 g/m² of ifosfamide for 5 days (total dose, 13.75 g of ifosfamide, level V). At this dose two of three patients developed grade 4 toxicities. Two patients developed grade 4 thrombocytopenia; one patient had a platelet nadir of 15,000/μl on day 13 following cycle 1 and the second patient had a nadir of 12,000/μl platelets/μl on day 11 following cycle 2; both patients required platelet transfusions. The third patient at level V developed grade 3 anemia following the third cycle of the combination. Thus, the recommended dose of ifosfamide for use in Phase II trials is (one dose level below the MTD) 2.5 g/m² for 5 days (total dose, 12.5 g/m²). Other grade 3 observed with this regimen are shown in Table 1 and included confusion, anemia, thrombocytopenia, nausea, and vomiting. The mucositis observed with this regimen was mild and did not require narcotic analgesics. Alopecia was universal and nausea and vomiting were generally mild and well controlled with ondansetron.
Table 1  Toxicity Grade

<table>
<thead>
<tr>
<th>Ifosfamide Dose Level (*)</th>
<th>Anemia</th>
<th>Thrombocytopenia</th>
<th>CNS-confusion</th>
<th>GI (n + v)</th>
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<tr>
<td></td>
<td>grade 3</td>
<td>grade 4</td>
<td>grade 3</td>
<td>grade 4</td>
</tr>
<tr>
<td>1(3)</td>
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<td>0</td>
</tr>
<tr>
<td>3(4)</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4(5)</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>5(3)</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

*= number of patients

Table 2  Hematologic Toxicities of Ifosfamide and Doxorubicin with rh-G-CSF

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>No of patients</th>
<th>Median ANC/µl nadir for all cycles</th>
<th>Median platelets/µl nadir for all cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>3 (18)</td>
<td>2150</td>
<td>110,000</td>
</tr>
<tr>
<td>II</td>
<td>3 (12)</td>
<td>1425</td>
<td>83,000</td>
</tr>
<tr>
<td>III</td>
<td>4 (13)</td>
<td>300</td>
<td>43,000</td>
</tr>
<tr>
<td>IV</td>
<td>5 (19)</td>
<td>50</td>
<td>40,000</td>
</tr>
<tr>
<td>V</td>
<td>3 (06)</td>
<td>20</td>
<td>18,000</td>
</tr>
</tbody>
</table>

= number of cycles.

The median nadir for granulocytes and platelets occurred on day 10. The median absolute neutrophil count and platelet count for all cycles at a given dose level of ifosfamide are shown in Table 2. Despite exceedingly low granulocyte counts at levels 3, 4, and 5, no patient required hospitalization for neutropenic fever. The duration of the neutropenia was brief and by day 14 granulocyte recovery had occurred; similarly, recovery of the platelet count occurred by day 19, including the two patients who developed grade 4 platelet toxicity at level V. No patient required the continuation of Neupogen beyond day 19. Every patient at dose levels I-IV was able to be treated on a 21-day schedule.

While the primary objective of this study was to define the MTD of ifosfamide, a secondary objective was to determine the activity of this combination. Objective responses were documented in 15 of 18 patients [83% (95% confidence levels, 59–96%) with 6 patients attaining a CR (33%) and 9 patients attaining a PR (50%)]. The duration of response was difficult to assess because after six cycles of ifosfamide/doxorubicin, the subsequent treatment was left to the discretion of the physician. Of the 18 patients enrolled in this study, 4 patients underwent high-dose chemotherapy with ABMT, 8 patients were continued on ifosfamide and doxorubicin until they reached 450 mg/m² of doxorubicin and then usually ifosfamide alone was continued, 4 patients received 5-FU and leucovorin, 1 patient received i.v. Navelbine, and 1 patient died of progressive breast cancer following the first cycle of ifosfamide and doxorubicin. As of July 1, 1994, six patients had relapsed and five of these six patients died. The actuarial median time to treatment failure for all 18 patients was 11.5 months (Fig. 1). The actuarial median survival has not been reached and will exceed 18 months; the projected survival is 63% at 18 months.

DISCUSSION

Ifosfamide is an active drug in the treatment of breast cancer both as a single agent and when used in combination (4–12). Prior studies using ifosfamide in combination with either mitoxantrone or doxorubicin have reported high response rates with tolerable side effects (8, 10). Millward et al. (8) treated 31 women with stage IV breast cancer with a combination of 5 g/m² ifosfamide and 40 mg/m² doxorubicin every 21 days. Twenty-two (71%) of 31 patients had an objective response, with 5 of 31 patients achieving a CR. Grades 3 and 4 leukopenia were seen in 7% of patients and the median survival was 44 weeks. Perez et al. (10) reported on 48 women with stage IV breast cancer who were treated with a combination of ifosfamide 2.0 g/m² i.v. on days 1–3 and mitoxantrone 12 mg/m² 1VP on day 1 every 21 days as first-line chemotherapy. Twenty-eight patients (60%) achieved an objective response, with 6 patients (12%) achieving a CR. Grades 3 and 4 leukopenia were observed in 39% of the 48 patients; the median time to treatment failure for the entire group was 9 months and the median survival was 19 months. There is sound clinical rationale for exploring ifosfamide in a dose escalation study supported with rhG-CSF to determine the MTD in the setting of advanced breast cancer.

We defined the MTD of ifosfamide when given as a 5-day daily i.v. infusion in combination with doxorubicin 20 mg/m² i.v. bolus on days 1–3, every 21 days. The MTD of ifosfamide was 2.75 g/m² for 5 days for a total dose of 13.75 g/m². This dose of ifosfamide is very close to bone marrow transplant doses of ifosfamide when used in combination with other drugs and...
supported by autologous bone marrow support (13, 14). The use of rhG-CSF (Neupogen) and prophylactic antibiotics permitted repeated dosing of the combination and allowed for outpatient therapy. The use of Neupogen accounted for a brief granulocyte nadir (day 10). By day 14, Neupogen raised the ANC to greater than 1000 cells/µl. The reason for choosing the dose and schedule of doxorubicin is based on a report by Jones et al. (15). This doxorubicin dose would have permitted exploiting the MTD of ifosfamide without running into significant toxicities from doxorubicin. We were pleasantly surprised by the activity of this program (83% objective response rate with 33% CR) as well as the actuarial median survival for all patients which will exceed 18 months. It should be remembered that this was a Phase I study, with cohort dose escalation, so that many patients received relatively lower doses of ifosfamide, yet these results are slightly better than those reported by Perez et al. (10).

The recommended dose of ifosfamide in combination with doxorubicin and supported with rhG-CSF is 2.5 g/m² for 5 days. This regimen shows promise in the therapy of stage IV breast cancer and is being evaluated in a Phase II study.

REFERENCES
A phase I study of ifosfamide and doxorubicin with recombinant human granulocyte colony-stimulating factor in stage IV breast cancer.

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