A Phase I Trial of Ifosfamide and Paclitaxel with Granulocyte-Colony Stimulating Factor in the Treatment of Patients with Refractory Solid Tumors

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Supported in part by a grant from Bristol Myers Oncology Division.

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Received June 18, 1997; accepted July 28, 1997.

BACKGROUND. Ifosfamide and paclitaxel are antineoplastic agents with broad activity and with different mechanisms of action. A Phase I trial was conducted to determine the maximum tolerated dose and associated toxicities of these agents when used in combination.

METHODS. Patients with refractory, incurable solid tumors were entered on a 5-step Phase I trial of ifosfamide, given in doses of 2–3 g/m^2 intravenous (i.v.) bolus for 3 days with mesna support, and paclitaxel, given in doses of 135–190 g/m^2 i.v. by continuous infusion over 24 hours. Paclitaxel was given after the first dose of ifosfamide on Day 1.

RESULTS. Twenty-three patients were treated, and the maximum tolerated dose was the highest planned dose level of the trial: ifosfamide, 3 g/m^2/day i.v. for 3 days, and paclitaxel, 190 mg/m^2 i.v. over 24 hours. Hematologic toxicity was not dose-limiting, and although neutropenia occurred, it was brief (median, 2–4 days) and resulted in hospitalization for neutropenia and fever in only 7 of 111 courses of therapy. For patients treated at the highest dose level, only 1 of 50 courses of therapy resulted in hospitalization for neutropenia and fever. Nonhematologic toxicity also was not severe and no significant neuropathy occurred. Although patients entered into the study were heavily pretreated, responses were observed, particularly in patients with breast or ovarian carcinoma.

CONCLUSIONS. Ifosfamide and paclitaxel can be administered safely in the doses used in this study and there are indications of significant antitumor effect. Further studies are necessary to explore the antineoplastic activity of this regimen, particularly for patients with breast and ovarian carcinoma. ***Cancer* 1998;82:561–6.**

KEYWORDS: medical oncology, Phase I, paclitaxel, ifosfamide, granulocyte-colony stimulating factor.

Both ifosfamide and paclitaxel have demonstrated activity as single agents in the treatment of a broad range of solid tumors. Ifosfamide, an alkylating agent, has established efficacy against ovarian carcinoma, lung carcinoma, sarcomas, and many other tumor types.[1,2] Furthermore, it has shown activity against tumors that have become resistant to other agents, as in patients who have failed platinum regimens, in whom response rates of 12–20% have been reported.[3,4] Paclitaxel, which stabilizes microtubules and thereby prevents cells from undergoing mitosis successfully, has demonstrated efficacy in patients with ovarian, breast, and lung carcinoma, including those who have failed first-line therapy.[5–7] Because of the utility of both agents in the treatment of a variety of solid tumors, their different mechanisms of action, and their efficacies in patients who failed prior

TABLE 1
Dose Escalation Schema

Dose level	Ifosfamide (i.v. qd, Days 1, 2, 3)	Paclitaxel[a] (i.v. by CI over 24 hrs Day 1)	Mesna (i.v. prior to and 3, 6, and 9 hrs after each dose of IFF)
1	2 g/m^2	135 mg/m^2	400 mg/m^2
2	2 g/m^2	150 mg/m^2	400 mg/m^2
3	3 g/m^2	150 mg/m^2	600 mg/m^2
4	3 g/m^2	175 mg/m^2	600 mg/m^2
5	3 g/m^2	190 mg/m^2	600 mg/m^2

i.v.: intravenously; qd: every day; CI: continuous infusion; IFF: ifosfamide.

[a] Paclitaxel infusion was initiated on Day 1, after completing the first ifosfamide dose.

Granulocyte-colony stimulating factor, 5 μg/kg subcutaneously every day beginning on Day 4, was used for all dose levels and continued until neutrophil recovery.

regimens, we designed a Phase I study employing both agents in a dose-escalating fashion to define the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) when these agents were used concurrently in the treatment of patients with refractory solid tumors. Because hematologic toxicity has been dose-limiting in prior ifosfamide-containing and paclitaxel-containing dose-intensive regimens,[1–3,6,7] we included granulocyte-colony stimulating factor (G-CSF) support in an attempt to maximize the doses of both ifosfamide and paclitaxel.

METHODS

Eligibility Criteria

Patients with histologically confirmed carcinoma that was not curable with surgery, radiation therapy, or standard chemotherapy or who had failed standard therapies were eligible. Patients also were required to have adequate bone marrow function (neutrophil count of $>1250/mm^3$; platelet count of $>100,000/mm^3$), renal function (serum creatinine within the institution's range of normal, [$<$1.7 mg/dL], or creatinine clearance $\geq$ 50 mL/minute), hepatic function (aspartate aminotransferase $<$ 4$\times$ normal; bilirubin $\leq$1.5 mg/dL), age $>$17 years, an Eastern Cooperative Oncology Group performance status $\leq$ 2, and written informed consent must have been obtained. This Phase I trial was approved by the Brigham and Women's Hospital Institutional Review Board, and written, informed consent was obtained from all patients.

Treatment Plan

After fulfilling the eligibility criteria and undergoing staging procedures, patients were enrolled sequentially at the appropriate dose level. The chemotherapy dose schedule is shown in Table 1. Paclitaxel was administered on Day 1, with the 24-hour infusion beginning after the first dose of ifosfamide, followed by the second and third doses of ifosfamide. This schedule was used consistently throughout the study.

All patients received premedication for paclitaxel with diphenhydramine, dexamethasone, and an H_2 antagonist. All dose levels included G-CSF support at a dose of 5 μg/kg subcutaneously every day that began on Day 4 and continued until the absolute neutrophil count was $\geq$10,000/mm^3 on 2 consecutive blood counts. Complete blood counts were obtained every Monday, Wednesday, and Friday after discharge from the hospital. Cycles were administered every 21 days, providing neutrophil and platelet counts achieved levels previously required for study eligibility. If blood counts were inadequate to proceed, they were rechecked weekly and therapy initiated when they achieved adequate levels. If the neutrophil or platelet counts were not adequate for treatment by Day 42 after initiation of the previous cycle of therapy, the patient was removed from study.

Cohorts of three patients were treated at each dose level. If no DLT was encountered, patients were enrolled on the next level. If one patient experienced a DLT, an additional three patients were enrolled at the same level. If no further DLT was observed, the dose would be escalated for the next cohort. If two or more DLTs were observed in any cohort of three or six patients at any level, dose escalation would stop and the previous dose level would be considered to be the MTD. We planned to treat each patient with at least two cycles of therapy followed by disease reevaluation. Patients with disease progression or unacceptable toxicity were removed from study. Patients with stable disease or documented response were allowed to received additional cycles until maximal response was achieved or disease progression or excessive toxicity occurred. Neither intrapatient dose-escalation nor dose modifications were allowed. Five dose levels were defined prior to initiating the study.

Definition of DLT

DLT was defined as either: (1) neutrophil count $<$ 500/mm^3 for $\geq$10 days or platelet count $<$25,000/mm^3 for $\geq$10 days, or (2) failure to achieve a neutrophil count of $\geq$1250/mm^3 or a platelet count of $\geq$100,000/mm^3 by Day 35, or (3) serum creatinine $\geq$1.5$\times$ pretreatment value for $>$ 21 days, or (4) any Grade IV nonhematologic toxicity (according to the Common Toxicity Criteria).

Response Criteria

A complete response was defined as disappearance of all measurable disease and biochemical changes

TABLE 2
Patient Characteristics

Age (yrs)	Median, 59 y (range, 32–73 y)
Gender	Male: 4 Female: 19
Performance status (ECOG)	
0	15 patients
1	5 patients
2	3 patients
Tumor primary	
Breast	13 patients
Ovarian	4 patients
NSCLC	5 patients
Colon	1 patient
No. of previous chemotherapy regimens	
0	1 patient
1	15 patients
2	3 patients
3	4 patients
Total no. of courses administered: 111 (median number of courses, 5)	

ECOG: Eastern Cooperative Oncology Group; NSCLC: nonsmall cell lung carcinoma.

related to the tumor for >4 weeks. A partial response was defined as a reduction of > 50% in the sum of the products of the perpendicular dimensions of all measurable lesions. Progressive disease was defined as an increase of 25% in the sum of the products of the perpendicular dimensions of all measurable lesions or the interval development of any new lesions. Stable disease was defined as insufficient change in lesions to meet the criteria for either response or progression. For nonmeasurable cancers with an elevated tumor marker, a complete response required normalization of the marker; partial response required a decline in the marker by 80% from the baseline value. These tumor marker parameters were set to be conservative in estimating tumor response.

RESULTS

Twenty-three patients were treated. Their pretreatment characteristics are shown in Table 2. The majority of patients had breast, ovarian, or lung carcinoma and previously had been treated with chemotherapy. Approximately 33% had received ≥2 regimens. Seventeen patients (74%) had received prior radiation. Patients typically received multiple cycles of ifosfamide and paclitaxel, with a median of five courses (range, one to ten courses). A total of 111 complete cycles were delivered. One patient with nonsmall cell lung carcinoma enrolled at Dose Level 3 had his initial cycle interrupted due to mental status changes. He eventually was discovered to have brain metastases and was removed from study and deemed inevaluable.

As expected, myelosuppression was the major toxicity of treatment, with granulocytopenia predominating. A clear dose-dependent relationship with either the incidence or duration of Grade 3 or 4 neutropenia could not be discerned. Granulocyte nadirs occurred 8.7 ± 0.9 days after the start of each cycle. Most courses of therapy were associated with Grade 4 neutropenia, but neutrophil nadirs were brief at all dose levels, as shown in Table 3. For patients treated at Dose Level 5, there appeared to be a lack of cumulative neutrophil toxicity as evidenced by similar nadirs in subsequent courses compared with initial courses (Table 4).

Seven of 111 courses resulted in hospitalizations for fever and neutropenia. Five of these episodes occurred in two patients, one of whom was treated at Dose Level 2, the other at Dose Level 3. Only 1 of 50 courses at Dose Level 5 resulted in an episode of fever and neutropenia. However, one patient at Dose Level 5 was hospitalized for disseminated herpes zoster. Another patient at Dose Level 5 had a prolonged hospitalization for a presumed viral infection marked by recurrent fevers, bilateral interstitial infiltrates, persistent elevation of hepatic transaminases, diarrhea, and prolonged myelosuppression. All cultures remained negative except for a bronchoalveolar lavage shell vial that was positive for cytomegalovirus (CMV), although the bronchial washings revealed no viral cytopathic changes and shell vials of buffy coat and stool were negative for CMV. Another patient at Dose Level 1 had an episode of uncomplicated varicella zoster infection.

Grade 4 thrombocytopenia was uncommon and, in general, quite brief. A dose-response relationship was not discernable. Platelet nadirs occurred 9.6 ± 1.4 days after the start of each cycle and cumulative toxicity was not observed.

Red blood cell toxicity was mild and quite manageable, with only five patients experiencing Grade 3 toxicity. Although occasional patients did receive blood transfusions, parameters for transfusions were left to the discretion of treating physicians. The variability in transfusion parameters made data regarding the number of transfusions received uninterpretable.

Nonhematologic toxicities tended to be mild and of brief duration. Although several patients reported mild paresthesias associated with prolonged treatment, in only one patient (at Dose Level 5) did the peripheral neuropathy reach a grade 2. This patient reported 24 hours of ''neurologic-type pain'' throughout her body 17 days after her third cycle, the etiology of which remained unclear. The patient received a subsequent cycle without recurrence of the pain.

Myalgias, potentially attributable to either the G-CSF or paclitaxel, were not uncommon, but also generally were mild and of brief duration. One patient at

TABLE 3
Frequency and Duration of Grade 4 Neutropenia and Thrombocytopenia

Dose level	No. of courses	No. of courses with Grade 4 neutropenia	Mean duration of Grade 4 neutropenia (days) (range)	No. of courses with Grade 4 thrombocytopenia	Mean duration of Grade 4 thrombocytopenia (days) (range)
1	12	10	3 (2–5)	None	—
2	17	7	2.4 (1–4)	None	—
3	16	16	3.9 (2–5)	6	3 (2–6)
4	16	8	3.2 (1–5)	None	—
5	50	40	2.7 (1–9)	2[a]	4.5 (4–5)

[a] One episode of Grade 4 thrombocytopenia was associated with a fatal intracerebral hemorrhage.

TABLE 4
Neutropenic Nadirs in Patients Treated at Dose Level 5

Course	No. of patients	Neutrophil nadir (per mm^3) median (range)	Duration of grade 4 neutropenia (days) median (range)
1	9	54 (0–608)	2 (0–9)
2	7	263 (24–1770)	2 (0–3)
3	7	117 (20–460)	2 (1–3)
4	6	232 (45–1700)	2 (0–5)
5	5	50 (12–450)	2 (1–5)
6	4	19 (12–600)	2 (0–4)
7	4	205 (90–810)	2 (0–4)
8	2	303 (20–585)	2 (0–4)

Dose Level 5 had Grade 3 and Grade 2 neuromood toxicity (anxiety/depression) associated with her first and second cycles of treatment, respectively. However, these symptoms predated the start of her first treatment and largely resolved during subsequent cycles. It appears unlikely that the drugs were responsible for her psychiatric symptoms.

One patient with breast carcinoma and a prior history of Hodgkin's disease treated with mantle and paraaortic radiation 12 years earlier developed an asymptomatic pericardial effusion and left pleural effusion after her second cycle of therapy at Dose Level 5. Asymptomatic paroxysmal atrial fibrillation was present and a pericardiocentesis revealed a serosanguinous effusion negative for malignant cells. Follow-up echocardiograms demonstrated no further reaccumulation of fluid. She received two additional cycles without a recurrence of the effusions or arrhythmia, and a complete response was achieved.

One patient with a history of a deep vein thrombosis treated with warfarin had a marked increase in her prothrombin time on Day 3 of her ifosfamide dose. Her international normalized ratio increased from a baseline of 2.4 to 9.5. The cause of the increase, an interaction between warfarin and ifosfamide, has been described previously.[8] The patient's prothrombin time corrected rapidly after discontinuing her warfarin for 2 days, and similar episodes were avoided in subsequent cycles by decreasing her warfarin dose during the days she received ifosfamide.

There appeared to be no relation between dose level and duration of G-CSF use. The median duration of G-CSF use was 10 days for Dose Levels 1, 2, and 5. The durations for Dose Levels 3 and 4 were 10.5 and 8.5 days, respectively.

Two patients at Dose Level 5 had DLTs. The patient described earlier with presumed CMV infection experienced prolonged myelosuppression and required >35 days for her platelets to increase to $100{,}000/mm^3$ and her absolute neutrophil count to exceed $10{,}000/mm^3$ on 2 consecutive blood draws, as stipulated in the protocol. The second patient, heavily pretreated with chemotherapy and radiation, had a fatal intracranial hemorrhage in the setting of thrombocytopenia refractory to platelet transfusions.

Response Data

Twenty-one patients were evaluable for response. Complete responses were observed in five patients, partial responses in six patients, stable disease in

TABLE 5
Response by Primary Disease Site (21 Patients)

Disease	Complete responses[a]	Partial responses[a]	Stable disease[a]	Progressive disease[a]
Breast carcinoma	4	4	3	2
Ovarian carcinoma	1	2	1	—
Nonsmall cell lung carcinoma	—	—	3	—
Colon carcinoma	—	—	—	1
Total	5	6	7	3

[a] Number of patients with each category of response.

seven patients, and disease progression in three patients (Table 5). Responses were observed primarily in patients with breast and ovarian carcinoma.

DISCUSSION

Both ifosfamide and paclitaxel have demonstrated significant activity in a broad range of tumors, both as first-line agents and in the treatment of refractory tumors. Although a dose-response relation has been demonstrated with other alkylating agents, including the related agent cyclophosphamide, a dose-response relationship with ifosfamide in particular has not been established definitively. Conflicting results in poorly or uncontrolled studies and variable dosing schedules have confounded such analyses. Similarly, many dose-escalation studies have been performed with paclitaxel in anticipation of such a relation. Given that these two agents are among the most active single agents for a broad range of tumors and that numerous prior Phase I studies have been predicated on the assumption of dose-response relation for each of these drugs, we made similar assumptions. Because hematologic toxicity has been dose-limiting in previous Phase I-II studies, we provided G-CSF support in an attempt to escalate the dose of each agent.

This study was designed to define the maximal achievable doses of two currently approved and well studied agents. Because the duration of neutropenia and thrombocytopenia is known to be related closely to the complications of both toxicities, we defined the duration rather than the degree of cytopenia to be dose-limiting. This is in accordance with many protocols currently being designed in which dose intensity is a primary objective.

As expected, myelosuppression (specifically neutropenia) was the major toxicity of treatment. However, neutropenic nadirs were brief (generally lasting 2 days), and neither the incidence nor duration of neutropenia appeared to be dose-dependent. That there was no difference in the required duration of G-CSF use between dose levels either may support the lack of a dose-dependent relation or attest to the abrogation of such a relation by the G-CSF. Although G-CSF support was continued until the absolute neutrophil count was $\geq$10,000/mm^3 on 2 consecutive blood counts to ensure patient safety, this requirement may have been unnecessarily conservative.

Only 7 of 111 of evaluable courses (6%) resulted in febrile neutropenic episodes. Curiously, three patients developed herpes virus infections, two with varicella zoster virus and a third with possible CMV. Whether this regimen produces any increased risk for herpetic infections is intriguing. An apparent increase attributable to these agents has not been reported in the literature.

Although Grade 4 thrombocytopenia did occur, it was uncommon and also usually of brief duration. An obvious dose-dependent relation was not observed. Although it occurred only at dose levels of $\geq$3, no other dose-dependent relation could be discerned beyond that observation. Although one of the DLTs was an intracranial hemorrhage that occurred in the setting of refractory thrombocytopenia, the patient had been pretreated extensively with both chemotherapy and radiation and had received multiple platelet transfusions prior to enrollment in the protocol.

Data regarding the most appropriate sequencing of paclitaxel and alkylators when these agents are used in combination are limited. Some in vitro studies have suggested that maximum cytotoxicity may be achieved when paclitaxel administration precedes that of alkylators.[9] Other investigators have demonstrated not only enhanced antineoplastic activity when paclitaxel preceded cisplatin administration, but also decreased hematologic toxicity over the same regimen when cisplatin preceded paclitaxel.[10] The precise mechanisms responsible for these findings are not known. Altered pharmacokinetics or interaction with normal and tumor cell cycling may be involved. We administered paclitaxel after the first dose of ifosfamide on Day 1,

followed by subsequent ifosfamide doses on Days 2 and 3, in a ''sandwich'' approach. This was performed in a consistent fashion and as demonstrated previously, limited hematologic toxicity was observed. The limited nature of hematologic toxicity was surprising considering the expected toxicity from each drug when given as a single agent.

Other toxicities tended to be mild, brief, and manageable. Not unexpectedly, several patients experienced mild paresthesias due to paclitaxel, but none were significantly compromised by peripheral neurotoxicity. Similarly, several patients experienced myalgias due to paclitaxel, G-CSF, or both, but these were brief and easily treated with analgesics. In retrospect, although our definition of nonhematologic DLT may have been somewhat ambitious, no clinically significant nonhematologic toxicities were observed.

Given the lack of DLTs in any of the first three patients enrolled at Dose Level 5, we enrolled an additional seven patients for a total of ten patients treated at that dose level. The study was closed to enrollment, per protocol, after two patients enrolled at Dose Level 5 experienced DLTs. Nevertheless, given the nature of the two dose-limiting events and the number of cycles of chemotherapy delivered at that dose level without significant untoward effects, it appears that Dose Level 5 was a reasonably well tolerated and safe dose. We consider it to be the MTD.

Although this was a Phase I study conducted to evaluate the toxicities of combined therapy with ifosfamide and paclitaxel and therefore did not have a sufficient number of patients to evaluate dose-response relation, the response data deserve note. A definitive relation between dose level and response could not be discerned. However, patients with breast and ovarian carcinoma were more likely to be among the responders. This observation is not surprising considering the known activity of both agents in patients with these diseases. Nevertheless, given the heavily pretreated character of these patients, the high overall response rate for breast carcinoma and ovarian carcinoma are encouraging and support consideration for future evaluation of this regimen in patients with these diseases.

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