Phase I Study of Escalating Doses of Mitoxantrone and Paclitaxel with Granulocyte-Macrophage Colony Stimulating Factor Support

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BACKGROUND. Both paclitaxel and mitoxantrone demonstrate significant antineoplastic activity in breast cancer patients. Colony stimulating factor support allows significant dose escalation of each of these drugs when administered as a single agent.

METHODS. We performed a Phase I study employing escalating doses of paclitaxel and mitoxantrone with granulocyte-macrophage colony stimulating factor (GM-CSF) support. Initially the paclitaxel dose was fixed at 175 mg/m^2 and an attempt was made to escalate mitoxantrone from the starting dose of 14 mg/m^2. Subsequently, the dose of mitoxantrone was fixed at 14 mg/m^2 and the dose of paclitaxel was increased. Treatments were given every three weeks.

RESULTS. In neither case could we safely escalate beyond a combination of paclitaxel 175 mg/m^2 and mitoxantrone 14 mg/m^2 which is, therefore, the recommended Phase II dose. The dose limiting toxicity was neutropenia. No unexpected toxicities were observed, although two patients were removed from the study because of chest pain possibly related to GM-CSF. There were no complete or partial remissions.

CONCLUSIONS. We conclude that GM-CSF does not allow significant dose escalation of this combination of agents. ***Cancer* 1996; 77:2308–12.**

KEYWORDS: paclitaxel, mitoxantrone, granulocyte-macrophage colony stimulating factor, breast cancer, Phase I.

Preliminary results using a combination of doxorubicin and paclitaxel for the treatment of metastatic breast cancer show very promising response rates.[1] Randomized trials comparing mitoxantrone with doxorubicin with both drugs used in standard doses for the treatment of breast cancer have generally proven mitoxantrone to be slightly less effective.[2–4] However, mitoxantrone has a very steep in vitro dose response curve.[5] It also causes significantly less nonhematologic toxicity than doxorubicin, including nausea and vomiting, mucositis, fatigue, alopecia, and cardiomyopathy. These features make it an attractive candidate for dose escalation, and it has been included in regimens involving high dose chemotherapy with autologous marrow and stem cell support for a wide variety of tumor types.[6,7] It has also produced responses in refractory ovarian cancer when given intraperitoneally (i.p.).[8] Its lesser cardiotoxicity is particularly important in light of concerns raised over possibly increased rates of congestive heart failure with the combination of paclitaxel and doxorubicin.[1] We explored the feasibility of a dose-intense combination of mitoxantrone and paclitaxel using growth factor support.

PATIENTS AND METHODS

The initial objective of this study was to escalate the dose of mitoxantrone with a fixed paclitaxel dose of 175 mg/m^2 using granulocyte-macrophage colony stimulating factor (GM-CSF) support. Yeast-derived GM-CSF has been reported to be well-tolerated.[9] Subsequently, the dose of mitoxantrone was fixed at 14 mg/m^2 and the dose of paclitaxel was increased. Dose levels explored were: (1) paclitaxel 175 mg/m^2 with mitoxantrone 14 mg/m^2; (2) paclitaxel 175 mg/m^2 with mitoxantrone 18 mg/m^2; and (3) paclitaxel 210 mg/m^2 with mitoxantrone 14 mg/m^2.

Eligibility

Patients treated had a histologically confirmed solid tumor which had failed to respond to standard treatment or for which no standard treatment regimen existed. Eligibility criteria included age $\geq$ 18 years, Karnofsky performance status $\geq$ 60%, and measurable or evaluable disease. Patients were excluded for symptomatic brain metastases, clinically significant peripheral neuropathy, prior autologous marrow transplant, prior radiation therapy to the whole pelvis, prior mitoxantrone or paclitaxel therapy, prior doxorubicin dose of more than 300 mg/m^2, left ventricular ejection fraction (LVEF) $<$ 50%, clinically significant arrhythmia, bundle branch block on electrocardiogram (EKG), uncontrolled angina or myocardial infarction in the past 6 months, or concurrent digoxin or calcium channel blocker therapy. Required laboratory parameters included a total white blood cell count (WBC) $\geq$ 3500/μL, absolute neutrophil count (ANC) $\geq$ 1500/μL, platelet count (PLT) $\geq$ 100,000/μL, serum creatinine $\leq$ 1.8 mg/dL, serum bilirubin $\leq$ 1.5 mg/dL, and serum transaminases $\leq$ 4 $\times$ upper limits of normal. Patients of childbearing potential were required to have a negative pregnancy test prior to starting treatment and to use adequate contraception. Informed consent in accord with federal and institutional guidelines was obtained from all of the patients.

Treatment Schedule

All chemotherapy was delivered in the outpatient clinic. Novantrone (mitoxantrone) and Leukine or sargramostim (GM-CSF) were both supplied by Immunex (Seattle, Washington). Mitoxantrone was diluted in 50 cc normal saline (NS) or 5% dextrose in water (D5W), and administered as a 15-minute infusion immediately prior to administration of paclitaxel. Paclitaxel was diluted in 500 cc D5W and administered as a 3-hour infusion. All patients were premedicated with dexamethasone 20 mg by mouth (p.o.) 14 and 7 hours prior to paclitaxel and with diphenhydramine 25 mg and cimetidine 300 mg intravenously (i.v.) just prior to mitoxantrone. GM-CSF was administered as a single daily subcutaneous (s.c.) injection at a dose of 250 μg/m^2 starting approximately 48 hours post-chemotherapy and continuing until the ANC was $\geq$1500/μL (after nadir) on 2 consecutive determinations. Patients were observed in the clinic at least 2 hours after their first dose of GM-CSF. GM-CSF was discontinued at least 48 hours prior to further chemotherapy. Patients were retreated every 21 days. The cumulative mitoxantrone dose was limited to 160 mg/m^2 (100 mg/m^2 in patients with prior doxorubicin therapy).

Toxicities were graded using the Cancer and Leukemia Group B (CALGB) expanded common toxicity criteria. Complete blood counts were obtained 3 times a week, and chemistries were evaluated weekly. A left ventricular ejection fraction was measured after every 2 treatments. Patients were re-evaluated every 2 cycles for response. Those with a response to therapy or stable disease who did not experience dose-limiting toxicity were permitted to continue on study.

Dose Escalation

Dose-limiting toxicities (DLTs) were defined as Grade 3 or greater nonhematologic toxicity, a platelet count of less than 20,000/μL, an ANC $<$ 500/μL for more than 5 days, neutropenic fever, or a delay of more than 7 days in starting Cycle 2 for reasons of toxicity. Days of neutropenia were counted starting with the first day of documented neutropenia and ending the day prior to documented recovery. At least 3 patients were treated at each dose level. If one of the first 3 patients at a dose level experienced DLT, up to 3 additional patients were added at that dose level. No intrapatient dose escalation was permitted. The recommended Phase II dose was the highest level tested at which no more than 2 of 6 patients experienced any DLT with Cycle 1, and no more than 1 of 6 patients experienced nonhematologic DLT with Cycle 1.

RESULTS

Seventeen patients were entered into this study between October 1994 and June 1995. Their characteristics are summarized in Table 1. A total of 47 cycles of chemotherapy were administered with a median of 2 per patient (range: 1–10). Fourteen patients were fully evaluable for toxicity. One male missed the majority of his scheduled blood counts. He was replaced at his dose level, and is considered evaluable only for nonhematologic toxicity. Two patients were removed from the study for possible GM-CSF toxicity. They were also replaced at their dose level.

GM-CSF Toxicity

Two patients experienced chest discomfort possibly related to GM-CSF. The first was a female age 49 years with a perihilar adenocarcinoma of the lung. Approximately 1 hour after her third dose of GM-CSF, while at rest at

TABLE 1
Patient Characteristics

No. entered	17
Male/female	10/7
Median age in years (range)	62 (31–70)
Performance status 0/1/2	10/5/2
Light pretreated[a] or untreated	9
Heavily pretreated[b]	8
Prior doxorubicin	4
Cancer diagnosis	
Lung	3
Esophageal	3
Unknown primary	3
Head and neck	2
Bladder	2
Prostate	1
Mesothelioma	1
Testicular	1
Colon	1

[a] Defined as no more than one prior chemotherapy regimen, no prior nitrosoureas, mitomycin C, or melphalan, and no prior radiotherapy to the spine.
[b] Any level of therapy beyond that defined for lightly pretreated.

home, she experienced dyspnea, chest pain, and nausea with a tight feeling in her throat. This lasted approximately 40 minutes, and resolved after she took lorazepam. The second, a female age 70 years with adenocarcinoma of the lung was taking atenolol for hypertension. She had a distant history of chest pain and a cardiac catheterization showing disease in the right coronary artery. Approximately 30 minutes after her first dose of GM-CSF she experienced chest tightness with dyspnea, vomiting, and hypotension. The patient was given nasal oxygen therapy and symptoms resolved within 15 minutes. In both cases the treating physicians opted not to rechallenge the patients with GM-CSF. GM-CSF was otherwise well-tolerated, and routine premedication with acetaminophen was not necessary.

Hematologic Toxicity

Hematologic toxicity is summarized in Table 2. Neutropenia and neutropenic fevers were dose-limiting. Of patients with dose-limiting toxicity, 2 were heavily pretreated and 4 were lightly pretreated. Some patients had progressively lower ANC and PLT nadirs after multiple cycles. The median time of nadir after Cycle 1 for both PLT and ANC was Day 10; the median day of recovery to ANC $> 1500/\mu L$ was Day 14. As has been previously reported with GM-CSF, eosinophilia was observed (median peak absolute count 418: range 0–2604).

Nonhematologic Toxicity

Six patients (2 at dose Level 1) experienced Grade 2 myalgias attributed to paclitaxel, and 7 patients (3 at dose Level 1) experienced Grade 2 or 3 fatigue at some point during their treatment. One patient on dose Level 3 complained of rectal burning and also developed Grade 3 esophagitis after Cycle 3 despite having been dose-reduced to Level 1. No clinical congestive heart failure was observed. Nine patients had serial ejection fractions performed. None had a decrease to <45% or a decrease of >15% from the baseline value.

RESPONSES

No complete or partial responses were observed. One woman with a parotid gland tumor had shrinkage of pulmonary metastases but developed a new spinal cord compression. A man with testicular cancer had a decrease in α-fetoprotein from 30,270 ng/mL to 3110 ng/mL, but no decrease in the size of his lung nodules.

DISCUSSION

Published studies suggest that CSF support allows a 2 and 1 half- to 3-fold dose-escalation of single agent mitoxantrone. Schiller et al. found that 37 mg/m^2 was tolerable with GM-CSF support, and neutropenia was dose-limiting at 48 mg/m^2.[10] Demetri et al. reported that 16 mg/m^2 without CSF produced dose-limiting neutropenia (median: 6.5 days of ANC < 1000), whereas with G-CSF, dose-limiting toxicity had not yet been reached at 32 mg/m^2. Mucositis was not observed.[11]

A regimen consisting of 150 mg/m^2 of paclitaxel (given over 3 hours) and 14 mg/m^2 of mitoxantrone without CSF support is currently being employed in a large Phase III trial. Moreover, a dose of 60 mg/m^2 of doxorubicin (which should produce about the same degree of myelotoxicity as 12 mg/m^2 of mitoxantrone)[12] combined with paclitaxel 175 mg/m^2 was tolerable with no CSF support in breast cancer patients who had not received prior chemotherapy.[13]

We had therefore anticipated being able to achieve at least a modest dose escalation of mitoxantrone in combination with a standard dose of paclitaxel. However, our results are similar to those of Rosenthal et al. who explored a 3-hour paclitaxel infusion combined with mitoxantrone and G-CSF support in breast cancer patients who had failed at least 2 other treatments, and found a maximum tolerated dose of paclitaxel 175 mg/m^2 and mitoxantrone 14 mg/m^2.[14] We considered several reasons why we might have been unable to achieve more significant dose-intensity. Our dose and schedule of GM-CSF are similar to that used in published studies, and are unlikely to have been inadequate. Higher doses of GM-CSF are more toxic.[9,10] We chose to stop growth factor administration after an ANC greater than $1,500/\mu L$ was observed on 2 successive measurements, whereas many studies continue CSF support until the ANC is greater than $10,000/\mu L$. However, the dose-limiting events occurred during

TABLE 2
Cycle 1 Hematologic Toxicity

Dose level (mg/m^2) (Paclitaxel/mitoxantrone)	No. of patients (Level pretreatment)	No. with DLT	ANC nadir median (range)	PLT nadir median (range)
175/14	6 (3L, 3H)	0	232 (0–516)	127 (20–239)
175/18	4 (2L, 2H)	3[a]	174 (12–405)	87 (70–135)
210/14	4 (3L, 1H)	3[b]	183 (28–650)	109 (46–329)

[a] Dose limiting events were 1 patient with neutropenic fever and 2 patients with an absolute neutrophil count of <500 for 7 days duration.
[b] Dose limiting events were 2 patients with neutropenic fever and 1 patient with an absolute neutrophil count of <500 for 7 days duration.
L: lightly pretreated or untreated; H: heavily pretreated; DLT: dose-limiting toxicities; ANC: absolute neutrophil count; PLT: platelet count.

Cycle 1 while CSF was still being administered, so it is unlikely that more prolonged administration would have allowed for further dose escalation. It is unknown whether the use of G-CSF as opposed to GM-CSF would have made a difference. However, as noted above, our results do not differ from those of Rosenthal et al., who used G-CSF.

The sequence of administration of mitoxantrone given prior to paclitaxel was chosen because a Phase I study of prolonged infusions of paclitaxel and doxorubicin showed both increased toxicity and increased doxorubicin plasma levels when paclitaxel was given prior to doxorubicin.[13] However, similar results have not been observed with shorter durations of drug infusion,[15,16] and there is no reason to suppose that the sequence of administration should affect the ability to achieve dose-escalation with CSF support.

It may be that CSF support will not permit a significant dose escalation of certain drug combinations even when the dose-limiting toxicity of both agents is neutropenia. CSFs can reduce both the depth and duration of neutropenia.[17] With very myelosuppressive regimens, their primary effect may be a shortening of duration of severe neutropenia. Perhaps if the timing of the nadirs of the individual drugs is different, some of this effect is abrogated. The neutrophil nadir after single agent paclitaxel is reported to occur 8 to 10 days after drug administration,[18] and that of mitoxantrone between 10 and 14 days after treatment.[19]

A final explanation is that our patients could have had more prior therapy than those studied in other reports. However, our patients were not particularly heavily pretreated. Those with prior pelvic radiotherapy and marrow transplant were excluded, and over half were either previously untreated or had only one prior regimen. However, there could be other differences between our patients and those studied in other trials. We were primarily interested in achieving dose-intensity, and did not attempt to define a maximum tolerated dose without G-CSF in our population. It might have been lower than we supposed.

Not enough patients received multiple cycles of chemotherapy for us to draw conclusions about the cardiotoxicity of this combination, but none was observed in this trial. Results of ongoing studies with paclitaxel and doxorubicin and paclitaxel and mitoxantrone should better define the risks of cardiotoxicity with each regimen.

The combination of paclitaxel with mitoxantrone appears to be well-tolerated. The highest doses achieveable with GM-CSF support are mitoxantrone 14 mg/m^2 and paclitaxel 175 mg/m^2. The role of this combination in the treatment of breast cancer or other malignancies remains to be determined.

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