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Original Paper

Phase I Trial of Etoposide, Doxorubicin and Cisplatin (EAP) in Combination with GM-CSF

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The aim of this study was to ameliorate the toxicity of the etoposide, doxorubicin and cisplatin (EAP) regimen and to investigate the feasibility of dose escalation, using the molgramostim form of granulocyte macrophage-colony stimulating factor (GM-CSF) 10 μg/kg/day s.c. into the regimen. The design of the trial allowed for amended scheduling of the agents in the event of suboptimal results. Initially the regimen comprised etoposide 120 mg/m^2, days 1–3, doxorubicin 40 mg/m^2, day 1, and cisplatin 40 mg/m^2, days 2 and 8. GM-CSF was begun on day 4 and continued until recovery of granulocyte counts. Courses were repeated every 21 days. 3 patients were treated at these doses. 5 patients received escalated doses (etoposide 180 mg/m^2; doxorubicin 60 mg/m^2; cisplatin 60 mg/m^2) on this schedule; 4 out of 5 had intolerable myelosuppression (grade IV neutropenia or thrombocytopenia lasting ≥7 days). These results prompted the administration of the day 8 cisplatin dose on day 3, with GM-CSF beginning on day 4. At the lowest doses of each agent (etoposide 120–doxorubicin 40–cisplatin 40), 3 of 6 patients had intolerable myelosuppression, and 3 patients had febrile neutropenia. Dose escalation of all of the drugs to etoposide 180 mg/m^2, doxorubicin 60 mg/m^2, cisplatin 60 mg/m^2 resulted in documented infections in 4 out of 4 patients. GM-CSF toxicity included rash, dyspnoea, arrhythmias and pericardial effusions. The conclusion was that the use of GM-CSF does not permit escalation of drug doses on either schedule of EAP administration, and that these results do not support the combined use of GM-CSF and EAP.

Key words: phase I trial, GM-CSF, etoposide, doxorubicin, cisplatin
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INTRODUCTION

ONLY 25% of newly diagnosed patients with gastric cancer are candidates for potentially curative surgery, and only 25% of these survive more than 5 years [1]. The majority present with regionally advanced or metastatic disease and require chemotherapy at initial diagnosis or at relapse. Single-agent chemotherapy has proven ineffective, and response rates are less than 15% [2]. Combination regimens with higher response rates have been reported [3], but complete responses are rare and the impact on survival is unclear. Preusser and colleagues reported an overall response rate of 64% with 21% complete responses in 67 patients with advanced gastric cancer using a regimen of etoposide, doxorubicin and cisplatin (EAP) [4]. Eight complete responses were pathologically confirmed with a subsequent median response duration of 16 months. Other phase II trials have demonstrated lower response rates to EAP in gastric cancer, and have shown unacceptable myelotoxicity [5–7]. The availability of colony-stimulating factors offers the possibility of decreasing the severity of myelosuppression, and enhancing chemotherapy dose-intensity.

Granulocyte macrophage-colony stimulating factor (GM-CSF) is one of several haematopoietic growth factors that are required for the survival, proliferation and differentiation of myeloid cells [8, 9]. It has been shown to reduce the duration of neutropenia associated with autologous bone marrow transplantation and combination chemotherapy [10–12]. The acceleration in neutrophil recovery has allowed for increased chemotherapy dose intensity and the suggestion of improved complete response rates and/or survival in some tumour types [13–15].

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The major goal of this phase I trial was to investigate if GM-CSF administration could reduce the myelosuppression associated with the EAP regimen, and to determine if chemotherapy dose escalation would be feasible with the combined regimen.

PATIENTS AND METHODS

Patient population

Patients with advanced malignancy were entered in this multi-institutional trial performed at Roswell Park Cancer Center and Fox Chase Cancer Center from August 1990 to December 1991. Patients eligible for this study had a histologically confirmed diagnosis of cancer refractory to all known effective therapy or were not curable by other means. They had tumours for which etoposide, doxorubicin and cisplatin would be considered appropriate treatment. Patients were 16 years or older with an ECOG performance status of 0–2. They had adequate bone marrow (white count $\geq 1500/mm^3$; platelet count $\geq 100000/mm^3$; haemoglobin >10 gl/dl), liver (bilirubin ≤ 1.5 mg/dl), renal (creatinine ≤ 1.5 mg/dl or creatinine clearance ≥ 60 m/min) and cardiac (normal cardiac ejection fraction using specific institutions criteria) function. Patients with a history of brain metastases, overt bone marrow involvement with malignancy or more than two prior chemotherapy regimens were excluded. Patients who had received radiation to more than 20% of their bone marrow were also not included. Patients could not have received chemotherapy or radiotherapy within 3 weeks of entry to the study, major surgery within 2 weeks or any prior mitomycin C, nitrosurea, thioTEPA or melphalan. Previous treatment with more than one of the study anticancer drugs (etoposide, doxorubicin, or cisplatin) was also an exclusion criterion. Patients were not enrolled who had received prior doxorubicin doses such that two full courses of EAP treatment could not be given without exceeding a cumulative doxorubicin dose of 450 mg/m^2.

Treatment plan

The treatment schedules are summarised in Table 1. Etoposide was administered as a 30-min i.v. infusion, doxorubicin i.v. over 5 min and cisplatin as a 1-h infusion in 500 ml of normal saline, USP. Saline hydration to obtain a urine output of 100 ml/h and pretreatment anti-emetics were also administered. Etoposide, doxorubicin and cisplatin are commercially available. An *E. coli*-derived, non-glycosylated form of recombinant GM-CSF (molgramostim) was supplied by the Division of Cancer Treatment, National Cancer Institute (NCI) as a lyophilised powder in vials formulated with mannitol, human serum albumin, polyethylene glycol and phosphate buffer. Reconstitution with 1 ml of sterile water yielded 700 μg/ml GM-CSF. Ten μg/kg/day was given as a single daily s.c. injection beginning on day 4 of chemotherapy and continuing until the absolute neutrophil count was $>1500/mm^3$ on two successive determinations. GM-CSF therapy was not interrupted for day 8 cisplatin treatment (dose levels 1 and 2).

Patients were treated at 3-week intervals provided that recovery of neutrophil count ≥ 1500 mm^3 and platelet count $\geq 100000/mm^3$ had occurred. Individual patients did not have drug doses escalated in subsequent chemotherapy cycles. 3 patients were assigned to each treatment cohort. If 1 of 3 patients experienced grade III or worse toxicity (excluding alopecia or nausea/vomiting), 3 additional patients were added at that level. Dose escalation occurred until the maximum tolerated dose (MTD) was determined. The MTD was defined as that dose of drug at which one-third of patients had grade IV granulocytopenia or thrombocytopenia lasting 7 days or more, or grade III or worse non-haematologic toxicity (excluding alopecia or nausea/vomiting). Escalation was eventually halted because of an unacceptable incidence of neutropenic sepsis.

Study parameters

Baseline studies included a complete history and physical examination; determination of ECOG performance status; complete blood counts; a biochemical profile (urea, electrolytes, creatinine, calcium, bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase); chest radiograph; audiogram; urinalysis; echocardiogram and cardiac-gated pool scan electrocardiogram to determine ejection fraction and appropriate radiographic studies to document the extent of disease. Complete blood counts were repeated three times weekly for the first course and weekly thereafter. Response determination was determined radiographically after every other course.

Toxicity

The results were reported using the Common Toxicity Criteria (Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, Maryland, U.S.A., 1988). Response criteria were standard [16].

RESULTS

Patient characteristics

The characteristics of the 18 patients enrolled in this multi-institutional phase I trial between August 1990 and December 1991 are summarised in Table 2. The median age was 55 years, and all patients had a good performance status. 11 patients had received prior radiation or chemotherapy.

Table 1. Chemotherapy doses and schedules

Level	Dose of etoposide (mg/m^2) on days 1–3	Dose of doxorubicin (mg/m^2) on day 1	Dose of cisplatin (mg/m^2)		No. of patients	No. of courses
			Dose	Days		
1	120	40	40	2,8	3	9
2	180	60	60	2,8	5	12
3	120	40	40	2,3	6	17
4	180	60	60	2,3	4	6

All patients received GM-CSF 10 μg/kg/day subcutaneously days 4–14.

Table 2. Patients' characteristics

Patients entered/evaluable	18/18
Sex (M/F)	9/9
Median age (years) (range)	55 (37–71)
Performance status (ECOG)	
0	8
1	10
Primary site	
Non-small-cell lung	4
Unknown primary	4
Gastric	3
Oesophagus	2
Other	5
Prior treatment	
Radiation therapy	6
Chemotherapy	5
Both	7

Treatment administration

Forty-four courses of EAP with GM-CSF were administered to the 18 patients (median number of courses per patient was 2; range 1–4). Enrollment to the four dose levels is described in Table 1.

Toxicity

Myelosuppression was the major dose-limiting toxicity encountered on this study (Table 3). The first 3 patients received the drug doses used by Preusser and associates [4] but on a schedule altered to allow initiation of GM-CSF on day 4. Preusser's original regimen consisted of doxorubicin, 20 mg/m^2, days 1 and 7; cisplatin 40 mg/m^2, days 2 and 8 with etoposide 120 mg/m^2 given on days 4, 5 and 6. Level 1 patients on our protocol received the total dose of doxorubicin on day 1, cisplatin days 2 and 8 with etoposide delivered at 120 mg/m^2/day for the first 3 days. This modified schedule was used because of information suggesting better haematological restoration when GM-CSF started as soon as possible after initial chemotherapy [17, 18]. This level was well tolerated: only 1 patient had grade IV neutropenia lasting 4 days, and thrombocytopenia was tolerable. Chemotherapy dose escalation to level 2 then occurred for the next 5 patients. At this level, 83% (10/12) of courses were associated with grade IV neutropenia, which lasted a mean of 4.6 days and 67% (8/12) with grade IV thrombocytopenia. One previously untreated 38-year-old woman with gastric cancer experienced grade IV thrombocytopenia for over 40 days. All patients experienced at least one episode of grade IV neutropenia during the first course; only 2 of these 6 patients had received prior therapy. The grade IV neutropenia and thrombocytopenia lasted longer than 7 days in 2 patients and in 3 patients, respectively.

Because of the possibility that concurrent administration of chemotherapy and GM-CSF might compromise GM-CSF benefit [17, 19], level 3 was designed to allow for all chemotherapy to be delivered on days 1, 2 and 3 before the initiation of the GM-CSF. Although 88% (15/17) of courses were associated with grade IV neutropenia, the mean duration of toxicity (4.3 days) was substantially similar to that observed in prior cycles. While 3 patients were admitted to hospital for fevers associated with urinary tract infections, they did meet criteria for retreatment at full chemotherapy doses for a total of 17 courses. Only two cycles were characterised by neutropenia lasting longer than 7 days.

These observations prompted a chemotherapy dose escalation for the next 4 patients. At level 4, grade IV neutropenia lasting from 1 to 5 days (mean 3.3 days) occurred in 67% (4/6) of courses. Grade IV thrombocytopenia occurred in 83% of courses. All patients required admission to hospital for neutropenic fever (two documented urinary tract infections and one pneumonia). It was concluded on this basis that these doses were intolerable.

DISCUSSION

In this phase I trial, the haematopoeitic growth factor, GM-CSF, was integrated into various schedules and doses of the EAP regimen in an attempt to decrease toxicity and allow for chemotherapy dose escalation. This regimen was initially developed [4] for use in patients with gastric cancer based on the known activity of the drugs as single agents [2]. The first studies demonstrated encouraging response rates ranging from 64 to 72% [4, 5]. The major toxicity was myelosuppression, which did not result in any drug-related deaths.

However, later trials did not confirm the initial results and demonstrated lower response rates (20–40%), associated with significantly more toxicity [7, 20, 21]. In a randomised trial of

Table 3. Toxicity

	Dose level			
	1	2	3	4
Mean neutrophil nadir ($\times 10^3/\mu l$)	1.2	0.2	0.10	0.37
Time to nadir (days)	12	14	12	10
Number of courses with ANC $<500/\mu l$ (%)	2/7 (28%)	10/12 (83%)	15/17 (88%)	4/6 (67%)
Mean duration, days of grade IV neutropenia	4	4.6	4.3	3.3
Mean platelet nadir ($\times 10^3$/ml)	102	32	50	21
Number of courses with platelets $<25 \times 10^3/\mu l$ (%)	1/7 (14%)	8/12 (67%)	9/17 (53%)	5/6 (83%)
Number of courses with platelets $<25 \times 10^3/\mu l$ lasting ≥ 7 days (%)	0	3/12 (25%)	1/17 (6%)	1/6 (17%)
Episodes of neutropenic fever requiring hospitalisation	0	0	3	4

ANC, absolute neutrophil count.

EAP versus FAMTX (high dose methotrexate, high dose fluorouracil, doxorubicin and leucovorin), 60 patients with gastric cancer were entered [20]. The response rates were similar (FAMTX 33%; EAP 20%), but the EAP regimen resulted in 13% (4/30) treatment-related deaths owing to sepsis, while there were none in the FAMTX arm. In another phase II trial, EAP was severely myelosuppressive with 11% (4/36) treatment-related deaths [21]. A goal of the current study was to diminish the morbidity and mortality associated with this regimen by the addition of growth factors.

While the use of CSFs in support of chemotherapy has been shown to decrease the time required for resolution of neutropenia with both standard [19, 21, 22] and highly intensified regimens [10, 17, 23, 24], these growth factors have not materially lessened the severity of neutropenia or thrombocytopenia [10, 24–27]. The results that we obtained with administration of GM-CSF in support of EAP are consistent with these observations; patients developed relatively high rates of infectious complications during haematological nadirs even when GM-CSF hastened neutrophil recovery to an ANC of 1500/μl quickly enough to allow on-time retreatment with the cytotoxic agents. In this setting, there was no apparent influence of CSF scheduling relative to chemotherapy. With dose levels 1 and 2, GM-CSF was begun on day 4 and continued through a second treatment of cisplatin on day 8. Because GM-CSF stimulates proliferation of myeloid progenitor cells [28–30], administering the cisplatin on day 8 concurrent with continued CSF therapy might actually have worsened myelotoxicity by exposing rapidly cycling progenitor cells to the cytotoxic agent. Other investigators have evaluated the use of G-CSF [31, 32] or GM-CSF [17–19, 33] in support of agents such as cyclophosphamide, 5-FU/LV, oral etoposide or topotecan, and have observed a potential worsening of neutropenia with concurrent chemotherapy–CSF as compared to sequential administration. In this trial, however, we found that administering standard EAP doses but adjusting the schedule to give all chemotherapy prior to starting GM-CSF (dose level 3) did not shorten the median duration of grade IV neutropenia. In fact, it is evident from Table 3 that in groups with similar total doses but altered schedules (levels 1 and 3, and levels 2 and 4), the toxicity appears more severe when all the treatment is delivered in the first 3 days. Clearly treatment with a dose of cisplatin on day 8 does not impair any protective effect of GM-CSF. Compared to historical data, the toxicity at standard doses of EAP was relatively mild, and while grade IV neutropenia was common, the mean duration in all patients at levels 1 and 3 was only 4 days.

In this, as in previous trials, EAP therapy proved to have substantial haematological toxicity. Although no deaths owing to chemotherapy-induced toxicity occurred, grade 4 neutropenia (19/23 courses) and grade 4 thrombocytopenia (14/23 courses) were frequent at dose levels 3 and 4. Admission to hospital was required in association with seven of the 23 courses of therapy administered at these dose levels. The severity of myelosuppression still precluded dose escalation on either schedule of EAP administered, despite GM-CSF support.

Although not designed to answer the question of therapeutic outcome, there were no responses observed in our patients. In conclusion, myelosuppression remains the major dose-limiting toxicity associated with the EAP regimen despite the addition of GM-CSF. While these results suggest that the use of a growth factor may decrease the duration of neutropenia with standard EAP doses, the goal of chemotherapy dose intensification could not be realised.

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