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A randomized phase I study of oral etoposide with or without granulocyte-macrophage colony-stimulating factor for the treatment of patients with advanced cancer

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The purpose of this study was to evaluate the feasibility of chronic oral administration of etoposide with granulocyte-macrophage colony-stimulating factor (GM-CSF) [sargramostim (Immunex)] coadministration or premedication; to estimate and compare the frequency of toxicities accompanying etoposide administration alone, etoposide/GM-CSF coadministration and etoposide with GM-CSF premedication. Thirty-nine patients with advanced treatment-refractory malignancies were enrolled to this study. Eligible patients were randomized to one of three treatment arms: daily oral etoposide alone for 21 days (arm A); daily oral etoposide for 21 days with GM-CSF, 250 $\mu g/m^2$, s.c. twice daily for the first 10 days of etoposide administration (arm B); or daily oral etoposide for 21 days with GM-CSF twice daily for the sixth through second days preceding etoposide administration (arm C). Courses of treatment were repeated every 28 days. Etoposide dosages for each arm were 25, 50, 75 and 100 mg/m^2/day. At least three patients were treated at each dosage level until dose-limiting toxicity was observed. Patients had twice weekly blood counts and weekly clinical examinations to assess toxicity. Patients with measurable or evaluable evidence of cancer were assessed for antitumor response after every other course of therapy. Nadir neutrophil counts at each dosage level were compared between treatment arms by non-parametric Wilcoxen rank sum tests. GM-CSF coadministration (arm B) or premedication (arm C) with daily chronic oral etoposide was feasible and did not lead to excessive hematological toxicity. Pairwise comparisons of neutrophil nadirs for the first course of therapy for each treatment arm did not demonstrate any significant differences and, at most, a slight trend favoring improved neutrophil nadirs was shown for arm C compared to arm A ($p = 0.07$). Dose intensity as measured by mean days of etoposide administered per patient for each arm suggested only slight improvement in etoposide tolerance for treatment arms B and C. The conclusion, GM-CSF can be safely administered to patients receiving chronic daily oral etoposide. It appears that GM-CSF provides no clinically useful improvement in granulocyte tolerance of therapy.

Key words: Etoposide, granulocyte-macrophage colony stimulating factor (sargramostim), phase I trial.

Introduction

The application of hematopoietic colony-stimulating factors to the management of patients receiving intensive chemotherapy or high-dose chemotherapy with bone marrow or peripheral stem cell rescue has become an accepted method for shortening the duration of chemotherapy-related neutropenia and for the prevention of febrile neutropenia.[1–4] At the present time, two recombinant colony stimulating factors, filgrastim [Neupogen (Amgen)] and sargramostim [Leukine (Immunex)], are the only preparations approved for clinical use in the US. A third preparation, molgramostim [Leucomax (Schering-Plough/Sandoz)], is under evaluation by the Food and Drug Administration. Although each of these agents has very potent effects upon post-chemotherapy neutropenia, their comparative efficacy and toxicity have not been examined. In addition, the use of colony-stimulating factors to enhance chemotherapy dose-intensity remains within the domain of clinical research trials.

Etoposide is a semisynthetic epipodophyllotoxin whose anticancer activity appears to be mediated by topoisomerase II inhibition.[5] In the US, it is approved for the treatment of patients with refractory testicular carcinomas or with small cell lung cancer.[6] Etoposide is available in preparations for parenteral and for oral administration. The oral bioavailability of the drug is approximately 50% with wide individual variation.[7] In a phase I trial of oral etoposide administered at a dosage of 50 mg/

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m^2/day for 21 consecutive days every 4 weeks, Hainsworth *et al.* exploited the schedule dependency of this agent and observed noteworthy antitumor activity.[8] Chronic oral administration of etoposide has shown efficacy against metastatic breast cancer, lymphoma, non-small cell lung cancer, small cell lung cancer and germ cell tumors.[9–12]

Guidelines for the use of the colony-stimulating factors recommend the administration of these agents after chemotherapy administration. Premedication or concurrent administration is not recommended due to concern for enhancement of chemotherapy-induced toxicity, inhibition of chemotherapeutic activity or even stimulation of the growth of cancer cells. In studies of the tumor growth potentiating properties of granulocyte-macrophage colony stimulating factor (GM-CSF), Salmon and Liu[13] and Foulke *et al.*[14] observed no enhancement of tumor growth in the human tumor cloning assay. Utilizing this same assay, Von Hoff *et al.* have identified synergistic antitumor activity of etoposide and GM-CSF.[15] We have recently completed a randomized phase I trial of chronic 21-day oral administration of etoposide alone, coadministered with GM-CSF [molgramostim (Schering-Plough)] for 10 days or preceded by 5 days' administration of GM-CSF.[16] Neither combination arm allowed administration of etoposide exceeding the amount administered alone. Indeed, earlier and deeper neutropenia was observed in patients receiving concomitant etoposide and GM-CSF.

Sargramostim (Immunex) is a recombinant GM-CSF product derived from the yeast *Saccharomyces cerevisiae*. It is a glycosylated molecule, unlike the recombinant non-glycosylated GM-CSF, molgramostim (Schering-Plough), derived from *Escherichia coli*. Sargramostim differs from the natural human protein by substitution of leucine for arginine at position 23. To evaluate whether sargramostim may influence dose intensity, toxicity and perhaps antitumor activity of oral etoposide differently than the effect of molgramostim in our earlier trial, we embarked on this randomized phase I study of etoposide administered alone, preceded by or coadministered with sargramostim (for the purposes of this study, GM-CSF refers to sargramostim).

Materials and methods

Patient entry criteria

Patients with microscopically confirmed diagnosis of metastatic or locally advanced solid cancer refractory to conventional therapy or for which no effective therapy was known were candidates for enrollment in this study. Eligible patients were 18 years of age or older, and had an estimated life expectancy of 12 weeks, a SWOG performance status of 2 or better and had recovered from toxicities of all prior anticancer therapy. Prior to therapy, all patients underwent physical examination, two-view chest X-ray, electrocardiogram, complete blood count and differential (CBC), 20-channel blood chemistry panel, urinalysis and, if applicable, scans or X-rays to document measurable or evaluable disease. Pretreatment clinical and laboratory analysis had to show adequate organ function including WBC $\geq 3000/\mu l$, granulocytes $\geq 1500/\mu l$, platelets $\geq 100\,000/\mu l$, hemoglobin ≥ 9.0 g/dl, serum bilirubin < 2.0 mg/dl, aspartate aminotransferase < 3 times the institutional upper limit of normal, serum creatinine < 2.0 mg/dl or calculated creatinine clearance > 60 ml/min. Patients must have completed all prior anticancer therapy 3 weeks or more preceding onset of investigational therapy (6 weeks or more for prior mitomycin C or nitrosoureas). Patients must not have had a myocardial infarction within the preceding 6 months, must not be taking antiarrhythmic medication and must have had no symptomatic peripheral neuropathy. Women of child-bearing potential must have had a negative pregnancy test. All patients provided written informed consent consistent with federal and institutional requirements.

Study methods

Patients were randomly assigned to one of three treatment arms: arm A, oral etoposide daily for up to 21 days; arm B, oral etoposide daily for up to 21 days and GM-CSF (sargramostim) s.c. twice daily for the first 10 days of etoposide administration; arm C, oral etoposide daily for up to 21 days preceded by GM-CSF s.c. twice daily for 5 days from the sixth through second days before initiation of etoposide. The starting dosage of etoposide was 25 mg/m^2/day; subsequent dosage levels were 50, 75 and 100 mg/m^2/day. Because etoposide is formulated as a 50 mg capsule, all patients received their calculated dose as the best approximated dose distributed over 3 days, e.g. if the calculated dose of etoposide was 85 mg/day, the cumulative dose for 3 days was 255 mg and the actual dose administered was 100 mg/day for the first 2 days, 50 mg for the third day administered repetitively every 3 days. No intrapatient dosage escalation was allowed. GM-

CSF was administered at a fixed dosage of 250 μg/m^2 s.c. twice daily. Courses of treatment were repeated every 28 days if all toxicity of the preceding course had resolved. CBC was obtained twice weekly; blood chemistry, body weight, physical examination and toxicity query were obtained weekly for all patients. Both etoposide and GM-CSF were discontinued if granulocytes fell below 500/μl or platelets below 75000/μl within the 21-day drug administration level. Both drugs were resumed upon recovery of blood counts and were continued until 21 consecutive days since the start of etoposide administration had elapsed. The first patient at each dosage level for each arm was observed for a full 4 weeks following onset of treatment. Two additional patients were added to that arm at that dosage level if the first patient completed all planned therapy without interruption or did not develop life-threatening or fatal toxicity despite treatment interruption. If patients required treatment interruption for toxicity at a given dosage level, subsequent courses of treatment were administered at the next lower dosage level for that arm. Any patient intolerant of treatment at the lowest dosage level was withdrawn from the study.

If at least one of three patients treated at a given dosage level experienced an episode of unacceptable toxicity (grade 4 hematological toxicity or grade 3 or greater non-hematological toxicity; NCI Common Toxicity Criteria), at least three patients were treated at that dosage level to better characterize the observed toxicity before dosage escalation was allowed. If two or more episodes of unacceptable toxicity were observed among six patients, that dosage level defined the maximum tolerated dosage and that treatment arm was closed to further patient accrual. Patients were assessed for antitumor response to therapy (as applicable) following every other course of treatment. Standard criteria for response were utilized: complete response—complete disappearance of all evidence of cancer of at least 1 month's duration and no appearance of new lesions; partial response—$\geq$ 50% reduction in the sums of the products of the largest perpendicular diameters of all measurable lesions for at least 1 month and no appearance of new lesions; progressive disease—$\geq$ 25% growth in the sums of the products of the largest perpendicular diameters of all measurable lesions or the appearance of new lesions; stable disease—does not meet the criteria for partial response or progressive disease.

Both GM-CSF (sargramostim) and etoposide were obtained from commercially available sources. GM-CSF was supplied in glass vials as sterile lyophilized powder (500 μg) admixed with mannitol, sucrose and tromethamine. It was drawn into 1 ml tuberculin syringes for s.c. administration following reconstitution with 1 ml sterile water. If desired, patients were instructed in the technique of drug reconstitution and self-administration. Etoposide was supplied as 50 mg soft gelatin capsules. Patients were provided sufficient drug for 1 week's use.

Statistical methods

Non-parametric Wilcoxen rank sum tests were used to compare nadirs of neutrophils.

Results

Thirty-nine patients were enrolled to this three-armed randomized trial, all of whom were eligible for study. Eighty-six evaluable courses of treatment were administered to this patient sample. Patient characteristics are shown in Table 1.

Hematological toxicity

For arm A (etoposide alone), patients were treated at two dosage levels of oral etoposide (25 and 50 mg/m^2/day); dose-limiting neutropenia prevented further dosage escalation beyond 50 mg/m^2/day. At the first dosage level (25 mg/m^2/day), three

Table 1. Patient characteristics

Characteristic	Arm A (n=7)	Arm B (n=16)	Arm C (n=16)
Males/females	3/4	10/6	10/6
Median age (range)	62 (42–74)	67 (45–84)	62 (33–75)
Performance status			
0	1	6	3
1	5	8	12
2	1	2	1
Prior therapy			
surgery	2	13	10
radiation	3	4	7
chemotherapy	7	16	15
biological therapy	1	1	2
Disease types			
colorectal	0	7	4
lung, non-small cell	4	3	3
lung, small cell	1	2	2
breast	0	0	2
other	2	4	5
Evaluable courses of treatment	22	24	40

patients tolerated eight courses of treatment without developing dose-limiting hematological toxicity. Two of four patients treated at 50 mg/m^2 developed grade 4 neutropenia (60 and 200 granulocytes/μl), one of whom became febrile and required hospitalization. One patient at the 50 mg/m^2/day dosage level required interruption of treatment on the 16th day of oral etoposide due to grade 3 neutropenia (546 granulocytes/μl). This patient suffered early death from pneumonia shortly after discontinuance of therapy. At the 50 mg/m^2/day dosage level, three patients manifested anemia with hemoglobin values of 6.1, 7.4 and 7.9 g/dl.

For arm B (GM-CSF coadministered with oral etoposide), patients were treated at four dosage levels of oral etoposide (25, 50, 75 and 100 mg/m^2/day). Three patients treated with four evaluable courses of oral etoposide at the first dosage level developed no dose-limiting toxicity. Of six patients receiving treatment at a dosage of 50 mg/m^2/day, only two of 13 courses of treatment were complicated by grade 3 or greater neutropenia (18 and 950 granulocytes/μl) and grade 3 thrombocytopenia (35 000 platelets/μl). One patient developed fever with neutropenia of 18 granulocytes/μl and died 24 days after onset of therapy. Three patients displayed grade 3 anemia during treatment. Of four patients receiving more than one course of treatment at 50 mg/m^2/day, none required dosage reduction for hematological toxicity. Six patients commenced treatment at 75 mg/m^2/day; only seven courses of treatment were administered and only one patient tolerated a second course at this dosage level. Five courses of treatment were complicated by grade 4 neutropenia (0, 4, 148, 464 and 480 granulocytes/μl) or grade 4 thrombocytopenia (19 000 platelets/μl). None of these patients suffered febrile neutropenia. Four courses of treatment required early interruption due to onset of hematological toxicity (11, 12, 14 and 15 days). A single patient was treated at an etoposide dosage of 100 mg/m^2/day. This patient developed grade 4 neutropenia (40 granulocytes/μl), grade 4 thrombocytopenia (18 000 platelets/μl) and grade 3 anemia (hemoglobin 7.5 g/dl) promptly after only 10 days of treatment, became septic and died.

For arm C (oral etoposide preceded by GM-CSF treatment), patients were treated at three dosage levels (25, 50 and 75 mg/m^2/day). Three patients received 11 courses of treatment at the first dosage level, none of whom experienced dose-limiting hematological toxicity. Only one patient at this dosage level developed grade 2 anemia (hemoglobin 8.3 g/dl). At the 50 mg/m^2/day dosage level, seven patients received 21 courses of treatment, only one course interrupted after 8 days due to the development of nausea and vomiting from malignant hypercalcemia. Of this group, only two patients developed grade 4 neutropenia (360 and 210 granulocytes/μl) and grade 3 thrombocytopenia (38 000 platelets/μl). Of six patients enrolled at the 75 mg/m^2/day dosage level, two patients received no etoposide because of illness and early death related to complications of cancer. Four evaluable courses of treatment were administered to the remaining four patients; three of these patients developed grade 4 neutropenia (0, 70 and 221 granulocytes/μl) and grade 4 thrombocytopenia (23 000 platelets/μl). None developed febrile neutropenia. None of the patients required interruption of therapy since the onset of myelosuppression was delayed. Two patients received a second course of therapy at the next lower dosage level. Two patients acquired grade 3 anemia (hemoglobin 7.0 and 7.8 g/dl).

The hematological toxicities for only the first treatment course of each treatment arm are shown in Tables 2–4. Review and comparison of the toxicities by arm suggest a modest gain in etoposide dosage tolerance for the arms in which GM-CSF was administered, yet no GM-CSF schedule [GM-CSF coadministration (arm B) or GM-CSF premedication (arm C)] emerged as the more favorable. Pairwise comparisons of neutrophil nadirs for the first course of treatment within dosage levels revealed no statistically significant differences between the treatment arms. However, a nearly significant improvement in neutrophil nadirs was observed for arm C relative to arm A at the dosage level 50 mg/m^2 ($p=0.07$). Figure 1 demonstrates graphically the modest etoposide dosing advantage gained for arms B and C (GM-CSF coadministration and GM-CSF preadministration, respectively).

Table 5 indicates the preservation of dose intensity with coadministration (arm B) or premedication (arm C) of GM-CSF. Compared to our previous study in which non-glycosylated GM-CSF coadministration or premedication yielded diminished hematological tolerance of etoposide, this effect is striking. It is noteworthy that the administration schedule for arm C GM-CSF premedication seems most likely to sustain etoposide dose intensity despite the accompanying hematological toxicity.

Other toxicities

Treatment on all arms of this study induced a variety of relatively mild non-hematological toxicities. Mild

Table 2. Hematology toxicity:[a] neutropenia

Treatment arm	Dosage level (mg/m^2)	No. of patients	Patients with nadir cell count (cells/μl)		Median (cells/μl)
			500–999	<500	
A (etoposide alone)					
	25	3	0	0	4320
	50	4	2	1	1770
B (etoposide/GM-CSF)					
	25	3	0	0	5640
	50	6	1	1	2210
	75	6	1	5	464
	100	1	0	1	40
C (GM-CSF → etoposide)					
	25	3	0	0	3000
	50	7	2	2	2272
	75	4	1	3	221

[a] First course of treatment only.

Table 3. Hematological toxicity:[a] thrombocytopenia

Treatment arm	Dosage level (mg/m^2)	No. of patients	Patients with nadir cell count (cells/μl)		Median (cells/μl)
			25–49 000	<25 000	
A (etoposide alone)					
	25	3	0	0	426 000
	50	4	0	0	86 000
B (etoposide/GM-CSF)					
	25	3	0	0	316 000
	50	6	2	0	233 000
	75	6	0	1	150 000
	100	1	0	1	18 000
C (GM-CSF → etoposide)					
	25	3	0	0	137 000
	50	7	1	0	139 000
	75	4	0	1	72 000

[a] First course of treatment only.

nausea and anorexia were observed in six of the seven patients treated on arm A (etoposide alone). Fatigue and lethargy occurred in three of the patients. None of these toxicities seemed to be dose related. For arm B (GM-CSF with etoposide), seven of 16 treated patients experienced mild nausea, vomiting and/or anorexia, five of 16 patients reporting weakness or fatigue with therapy. Of possible GM-CSF-related toxicities, only one patient complained of myalgias, two patients developed chills or night sweats, but no fever was reported by any patient. Single episodes of diminished reflexes, paresthesias, oral mucositis and diarrhea were reported by individual patients. For arm C (GM-CSF before etoposide), eight of 14 evaluable patients complained of nausea or anorexia, six of malaise or weakness. GM-CSF-related toxicities included myalgias in five and fever in five. Other toxicities in this group included skin rash, oral mucositis and sensory neuropathy each in a single patient.

Table 4. Hematological toxicity: anemia

Treatment arm	Dosage level (mg/m^2)	No. of patients	Patients with nadir hemoglobin (g/dl)	
			6.5–7.9	<6
A (etoposide alone)				
	25	3	0	0
	50	4	2	1
B (etoposide/GM-CSF)				
	25	3	0	0
	50	6	3	0
	75	6	2	0
	100	1	1	-
C (GM-CSF → etoposide)				
	25	3	0	0
	50	7	3	0
	75	4	2	0

Table 5. Etoposide dose intensity [mean days of etoposide/course (no. of patients)]

Dosage level (mg/m^2)	Arm A	Arm B	Arm C
25	21.0 (3)	21.0 (3)	21.0 (3)
50	19.8 (4)	21.0 (6)	21.0 (6)
75		15.7 (6)	21.0 (4)
100		10.0 (1)	

Antitumor response

No patients in any arm manifested a confirmed antitumor response to therapy. Stable disease was commonly observed (two of seven patients in arm A; two of 16 patients in arm B; eight of 16 patients in arm C), but all patients' disease eventually progressed.

Discussion

Chronic oral administration of etoposide has generated increasing interest for its ease of delivery and exploitation of bioavailability more favorable than that accompanying oral administration of larger doses. Hande has demonstrated that the bioavailability of oral etoposide at dosages exceeding 200 mg/m^2 is approximately 50% or less.[7] At lower dosages of etoposide, oral bioavailability is substantially greater and may reflect saturation of a gastrointestinal transport system at high etoposide doses. These observations may, in part, explain the important clinical activity of chronic oral etoposide, including its utility as salvage therapy for patients with progressive cancer after higher doses of the drug.[9] If the therapeutic index of chronic oral etoposide can be improved, greater clinical activity may be one of the expected dividends.

The use of colony-stimulating factors for the prevention of chemotherapy-related neutropenia is an accepted treatment principle. However, the timing of colony-stimulating factor (CSF) administration remains a matter of convention rather than proven maxim. This study has shown that GM-CSF coadministration (arm B) or premedication (arm C) induced no detectable adverse hematological consequences.

The most noteworthy observation of this study was the feasibility of GM-CSF [Immunex; sargramostim (glycosylated)] administration prior to or with oral etoposide. GM-CSF treatment could be accomplished during escalation of etoposide dosage without inducing excessive hematological toxicity. These observations are in contrast to our previous study wherein GM-CSF [Schering-Plough; molgramostim (non-glycosylated)] administered on an identical schedule failed to allow escalation of oral

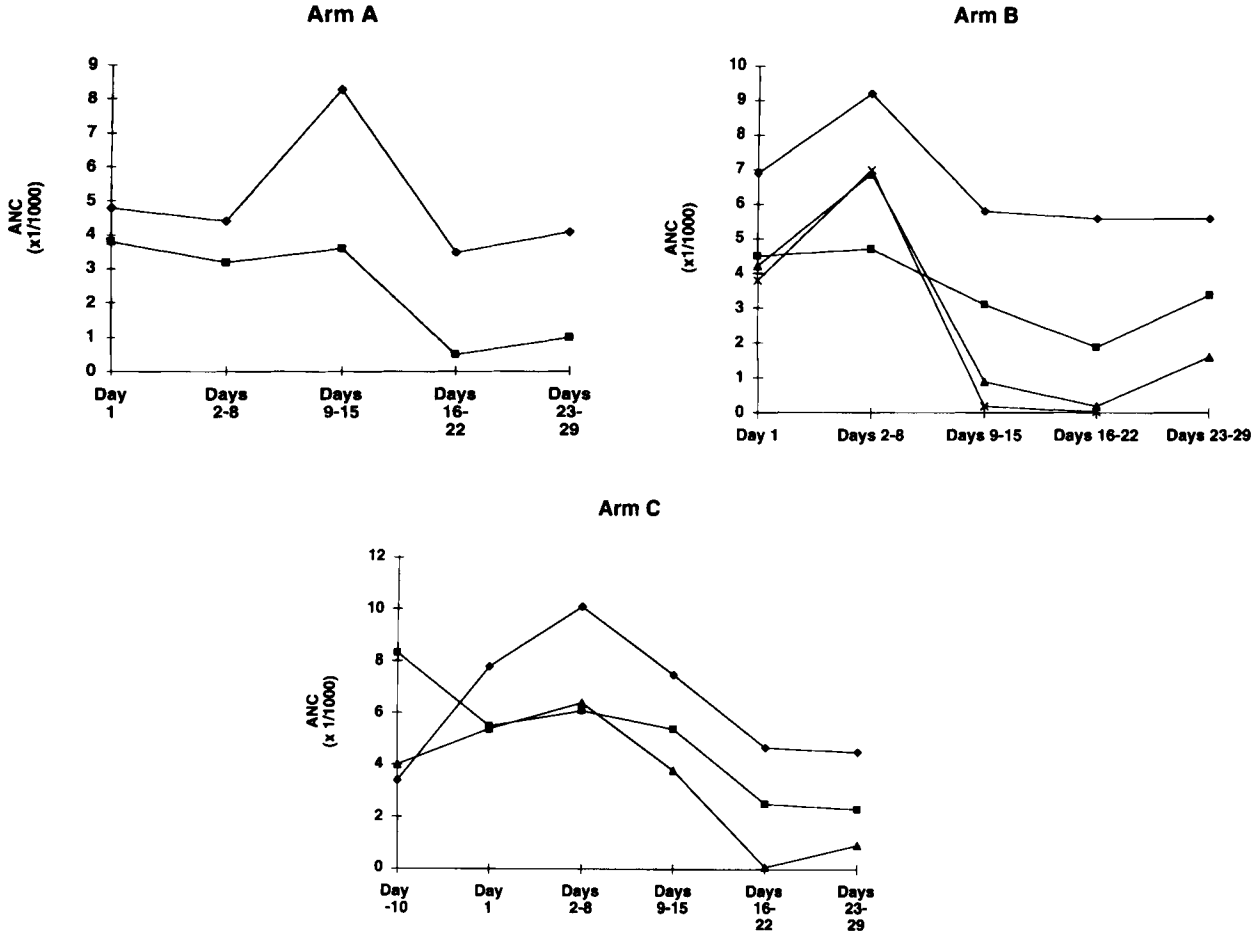

Figure 1. The median absolute neutrophil count by treatment arm for the first course of treatment: arm A (etoposide alone); arm B (etoposide/GM-CSF coadministration); arm C (GM-CSF premedication followed by etoposide). Etoposide dosages: ◆, level 1 (25 mg/m^2); ■, level 2 (50 mg/m^2); ▲, level 3 (75 mg/m^2); X, level 4 (100 mg/m^2). The plotted value is the lowest neutrophil count for the follow-up interval indicated on the *x*-axis.

etoposide dosage.[16] However, the effects of GM-CSF upon etoposide dose enhancement were admittedly modest. As another measure of the effect of GM-CSF in the setting of this study, dose intensity (calculated as the average number of days of etoposide administration at each dosage level) (Table 5) seems best preserved on arm C wherein patients were premedicated with GM-CSF for 5 days prior to etoposide. The judgment that such effects might translate into benefit for the cancer patient must be made cautiously. Proof of such benefit would be better served by a clinical trial investigating each schedule in diseases shown to be responsive to chronic oral etoposide. In addition, this study failed to discern evidence for or against enhancement of tumor growth of GM-CSF on either administration schedule.

The explanation for the different effects of sargramostim and molgramostim upon hematological tolerance of chronic oral etoposide is speculative. Molgramostim is identical in its molecular structure to the native protein but lacks glycosylation. The molecular structure of sargramostim differs from the native protein by an amino acid substitution, Arg^{23} to Leu^{23}. In addition, the clinical preparation includes three *N*-glycosylation species in roughly equal proportions.[17] It is unlikely that the amino acid change would adequately explain the difference in hematological effects since this site on the protein is not critical for retention of myelopoietic activity. However, protein glycosylation may be one structural difference that may account for differences in hematological effects. Highly glycosylated GM-CSF has lessened receptor affinity, reduced specific activity but a longer effective half-life. These phenomena seem a consequence of a prolonged elimination half-life for the glycosylated species.[18,19] In addition, the twice daily administration

schedule for GM-CSF utilized in this study may be a more effective method for promoting the clinical benefit of an agent with a relatively short half-life.

A direct clinical comparison of the two forms of GM-CSF has not been performed. It remains of obvious interest to exploit the dose intensifying potential of this class of colony-stimulating factor. Indeed, the Southwest Oncology Group attempted to utilize cisplatin and etoposide concurrently with radiotherapy, with and without glycosylated GM-CSF, for the induction therapy of limited small cell lung cancer.[20] GM-CSF was administered at a dosage of 250 $\mu g/m^2$ b.i.d., s.c. Despite a reduction in granulocytopenia, those patients receiving GM-CSF experienced more infections, more episodes of fever and more thrombocytopenia than control patients. As well, seven patients on the GM-CSF arm developed severe respiratory toxicity (dyspnea or pneumonia), resulting in early closure of the study.

Conclusion

In conclusion, we have shown that GM-CSF preadministration or coadministration to patients receiving chronic 21-day oral etoposide is feasible but accomplishes insignificant enhancement of etoposide dose intensity. This outcome may be dependent in part upon the GM-CSF preparation utilized (glycosylated) and frequency of administration insofar as sustained oral etoposide dose intensity is not observed with coadministration of the non-glycosylated GM-CSF preparation.

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