Immunoembolization of Malignant Liver Tumors, Including Uveal Melanoma, Using Granulocyte-Macrophage Colony-Stimulating Factor

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A B S T R A C T

Purpose

We conducted a phase I study to investigate the feasibility and safety of immunoembolization with granulocyte-macrophage colony-stimulating factor (GM-CSF; sargramostim) for malignant liver tumors, predominantly hepatic metastases from patients with primary uveal melanoma.

Patients and Methods

Thirty-nine patients with surgically unresectable malignant liver tumors, including 34 patients with primary uveal melanoma, were enrolled. Hepatic artery embolization accompanied an infusion of dose-escalated GM-CSF (25 to 2,000 μ g) given every 4 weeks. Primary end points included dose-limiting toxicity and maximum tolerated dose (MTD). Patients who completed two cycles of treatments were monitored for hepatic antitumor response. Survival rates of patients were also monitored.

Results

MTD was not reached up to the dose level of 2,000 μ g, and there were no treatment-related deaths. Thirty-one assessable patients with uveal melanoma demonstrated two complete responses, eight partial responses, and 10 occurrences of stable disease in their hepatic metastases. The median overall survival of intent-to-treat patients who had metastatic uveal melanoma was 14.4 months. Multivariate analyses indicated that female sex, high doses of GM-CSF ($\geq 1,500$ μ g), and regression of hepatic metastases (complete and partial responses) were correlated to longer overall survival. Moreover, high doses of GM-CSF were associated with prolonged progression-free survival in extrahepatic sites.

Conclusion

Immunoembolization with GM-CSF is safe and feasible in patients with hepatic metastasis from primary uveal melanoma. Encouraging preliminary efficacy and safety results warrant additional clinical study in metastatic uveal melanoma.

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INTRODUCTION

Management of hepatic metastases from chemotherapy-resistant tumors, such as metastatic uveal melanoma, is always challenging, and the overall survival (OS) of patients is generally short. Uveal melanoma is a rare eye tumor, and there is an age-adjusted incidence in most countries of five to seven per million people.¹ Despite the availability of effective treatments for primary uveal melanoma, up to 50% of patients subsequently develop metastasis, most commonly in the liver.²⁻⁴ Because survival after liver metastasis is reportedly less than 6 months without treatment,⁵ control of hepatic metastases is critical.

Chemoembolization, a procedure that combines disruption of the tumor blood supply with

infusion of cytotoxic drugs, has been used to treat primary hepatocellular carcinoma with successful local control and potential survival benefit.^{6,7} In patients who had uveal melanoma metastatic to the liver,⁸ stabilization or regression of liver lesions was achieved by chemoembolization in up to 66% of patients enrolled on nonrandomized clinical trials.⁹⁻¹² However, most patients with an initial response to chemoembolization developed subsequent extrahepatic (ie, systemic) metastases.¹² Because metastatic uveal melanoma is highly resistant to systemic chemotherapy,¹³ a modified approach to control liver metastases and to prevent or delay extrahepatic spread was developed by incorporating embolization of the hepatic artery with granulocyte-macrophage colony-stimulating factor (GM-CSF)—immunoembolization—instead

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of cytotoxic drugs. In theory, immunoembolization provides several advantages beyond the ischemic damage consequent to embolization,¹⁴ which include attraction and stimulation of antigen-presenting cells in liver tumors and improved uptake of tumor antigens released from necrotic tumor cells. Inflammatory responses that develop in or near the tumor may eliminate residual tumor cells. In addition, local stimulation of the immune system may produce a systemic immune response against tumor cells, which thereby suppresses the growth of extrahepatic metastases.

GM-CSF is a glycoprotein that is secreted principally by activated T cells and that stimulates immune cells, such as macrophages and dendritic cells.¹⁵ Although recombinant human GM-CSF is used clinically as a marrow supportive agent,¹⁶ it also stimulates macrophages and increases the cytotoxicity of monocytes toward malignant melanoma cells in vitro.¹⁷ In addition, tumor cells genetically engineered to produce GM-CSF induce specific, long-lasting antitumor immunity in animal models¹⁸ and have provided efficacy as immunoadjuvants for cancer vaccines.^{19,20} Clinical studies have shown significant inflammatory responses in remote metastases and the development of

tumor-specific T- and B-cell responses after patients received GM-CSF-transduced melanoma cell vaccines.^{19,21}

In this phase I study, we examined the use of immunoembolization to treat unresectable liver tumors, the majority of which originated from primary uveal melanomas. We demonstrated that immunoembolization with GM-CSF is safe and causes regression of hepatic metastases that is associated with a long OS.

PATIENTS AND METHODS

Patient Enrollment and Eligibility

Patients who had surgically unresectable malignant liver tumors were enrolled from 2000 to 2004 after approval by the Clinical Cancer Research Review Committee and the institutional review board of Thomas Jefferson University, under the auspices of an investigational new drug application (BB-IND 8260) and with monitoring by the US Food and Drug Administration (US FDA).

The major inclusion criteria consisted of one or more hepatic tumors with less than 50% involvement of total liver volume and adequate renal, bone

Table 1. Patient Demographics

Characteristic	All Patients (N = 39)*		Uveal Melanoma (n = 34)			
			Low-Dose GM-CSF (≤ 1,000 μg; n = 18)		High-Dose GM-CSF (≥ 1,500 μg; n = 16)	
	No.	%	No.	%	No.	%
Sex						
Male	14	36	5	28	7	44
Female	25	64	13	72	9	56
Age, years						
Median	56.1		56.5		55.4	
Range	25.8-79.8		32.3-79.8		37.3-77.3	
ECOG performance status						
0	37	95	17	94	16	100
1	2	5	1	6	0	0
2	0	0	0	0	0	0
Primary disease site						
Uveal melanoma	34	87	18	100	16	100
Skin melanoma	3	8	NA	NA	NA	NA
Conjunctival melanoma	1	3	NA	NA	NA	NA
Hepatocellular carcinoma	1	3	NA	NA	NA	NA
Prior therapy for hepatic tumor	11	28	5	28†	1	6‡
Pre-existing extrahepatic metastases						
Yes	14	36	7	39	3	21
No	25	64	11	61	13	79
Liver involvement, %						
< 20	12	31	5	28	5	31
20-50	27	69	13	72	11	69
LDH at enrollment						
Normal	27	69	13	72	9	56
Abnormal	12	31	5	28	7	44
No. of treatments received						
Median	6		5.5		6	
Range	1-14		1-12		1-14	

Abbreviations: GM-CSF, granulocyte-macrophage colony-stimulating factor; ECOG, Eastern Cooperative Oncology Group; NA, not applicable; LDH, lactate dehydrogenase. *In addition to 34 patients who had metastatic uveal melanoma, four patients had hepatic metastases from non-uveal melanoma (granulocyte-macrophage colony-stimulating factor doses: 125 μg [n = 1]; 250 μg [n = 2]; 1,000 μg [n = 1]), and one had primary hepatocellular carcinoma (granulocyte-macrophage colony-stimulating factor dose: 1,000 μg).

†Therapies were systemic chemotherapy (n = 1), interferon (n = 1), surgery + cancer vaccine (n = 2), cancer vaccine + interleukin-2 + chemotherapy (n = 1).

‡Surgery (n = 1).

marrow, and liver function (total bilirubin ≤ 2.0 mg/mL and no sign of hepatic failure). Major exclusion criteria included main portal vein occlusion and biliary obstruction or prior biliary surgery except cholecystectomy.

Immunoembolization Treatment

One of the hepatic arteries was cannulated on the basis of the locations of the tumors. Yeast-derived GM-CSF (sargramostim, Leukine; Bayer HealthCare Pharmaceuticals, Wayne, NJ) was emulsified with ethiodized oil to increase its dwell time in the tumor vicinity and to enhance the ischemic effects of the gelatin sponge particles.^{22,23} The amount of ethiodized oil used in the emulsion was calculated as 1 mL per centimeter of summed tumor diameters (10 mL maximum). The ethiodized oil/GM-CSF emulsion was slowly injected into the hepatic artery. The perfusion pattern to the targeted tumors was confirmed during the injection. After administration of the emulsion, gelatin sponge particles were injected until hemostasis was obtained. Treatments were given every 4 weeks. In patients who had disease confined to one lobe, the treatment was repeated to the same lobe. Each lobe was treated alternately in patients who had tumors in both lobes. After every two treatments, radiographic response in hepatic tumors was assessed by computed tomography (CT) scan and magnetic resonance imaging (MRI) of the abdomen. Patients with stable or responsive disease received a total of six procedures in the involved lobes. After the first six treatments, patients who showed clinical benefit (complete response [CR], partial response [PR], or stable disease [SD]) were permitted to continue their treatments until disease progression. Those patients who achieved CR, PR, or SD and who elected to discontinue immunoembolization after six cycles could be re-treated with up to the maximum GM-CSF dose tested if they experienced liver tumor progression.

Evaluation

Systemic and local toxicities from immunoembolization were assessed by using WHO criteria (<http://www.fda.gov/cder/cancer/toxicityframe.htm>). Because embolization itself can cause significant toxicity, patients may develop significant procedure-related adverse events independent of study medication. Our institutional experience indicates that the majority of procedure-related toxicity is resolved within 7 days after embolization, except for mild elevation of hepatic enzymes without symptoms. On the basis of this experience, we arbitrarily defined abnormal symptoms and laboratory test results between days 1 to 6 after the procedure as related to the embolization procedure, whereas toxicities experienced on day 7 or later were attributed to GM-CSF. Dose-limiting toxicity (DLT) was defined as grade 3 or greater symptomatic adverse events present on day 7 or later. The maximum-tolerated dose (MTD) of GM-CSF was defined as one dose level lower than the dose in which at least one third of patients experienced DLT. Patients who developed an adverse event were followed until resolution. In addition to symptom assessment, laboratory tests were

ordered before individual treatments, on the following day, and then weekly thereafter.

The DLT and the MTD of GM-CSF were evaluated in a two-step dose schedule. The first step included inpatient dose escalation for every two treatments. This step consisted of three patients, in whom the doses of GM-CSF were escalated during treatment: patient 1 (25, 50, and 125 μ g), patient 2 (50, 50, and 125 μ g), and patient 3 (125, 125, and 250 μ g). The second step consisted of dose escalation administered in serial cohorts of patients, and the cohorts consisted of GM-CSF doses of 250, 500, 750, 1,000, 1,500, and 2,000 μ g.

Efficacy

Tumor response was assessed after every two treatment procedures by using CT scans and MRI. Liver tumors were evaluated by independent radiologists by using Response Evaluation Criteria in Solid Tumors (RECIST),²⁴ including diameters from up to six hepatic lesions. The best overall response of liver metastases, from the start of immunoembolization until hepatic progression, was used for the efficacy analysis.

OS for patients in the intent-to-treat population was calculated from the first immunoembolization procedure until death. Progression-free survival (PFS) was calculated from the first immunoembolization to confirmation of metastatic progression or death; hepatic (PFS-L) and extrahepatic (PFS-S) progressions were evaluated separately.

Statistical Analysis

Information about sex, age, preexisting extrahepatic metastases (EHM), lactate dehydrogenase (LDH), tumor volume in the liver ($< 20\%$ v 20% to 50% involvement), and the dose of GM-CSF were collected at baseline. Categorical data (ie, sex, EHM, tumor volume) were summarized with frequencies and percentages. LDH values were dichotomized into two groups (values greater than the normal limit v values equal to or less than the normal limit). Age was dichotomized into two groups (< 60 v ≥ 60 years). OS and PFS were calculated by using Kaplan-Meier analysis for the subset of 34 patients who had hepatic metastases from uveal melanoma. These patients were additionally subcategorized on the basis of the dose of GM-CSF ($< 1,000$, 1,000, 1,500, and 2,000 μ g). The dose levels of GM-CSF were also subcategorized as high ($\geq 1,500$ μ g) or low dose ($\leq 1,000$ μ g). Additionally, patients were categorized on the basis of radiographic response in the hepatic metastases (CR + PR v SD + PD). Differences in survival between the subgroups were evaluated by using the log-rank test in univariate analysis. Multivariate analyses were performed by using the Cox proportional hazards model that involved the above-mentioned variables. The results of statistical analyses were considered significant if P was $< .05$. The statistical analyses were performed with SAS version 9.1 (SAS Institute, Cary, NC).

Table 2. Dose Escalations and GM-CSF–Related Grade 3 or 4 Adverse Events (N = 38)

GM-CSF Dose, μ g	No. of Patients	Adverse Event	Details
25*	1	—	—
50*	2	—	—
125*	2	—	—
250	3	—	—
500	3	Grade 3 elevation of hepatic enzyme AST (n = 1)	Asymptomatic
750	3		
1,000	10	Grade 3 elevation of hepatic enzyme ALP (n = 1)	Asymptomatic
1,500	6	Grade 3 abdominal pain > 7 days (n = 1)	Possibly related to study drug; patient dropped out and was placed in hospice care; three more patients were accrued at this dose level
2,000	10	Grade 3 elevation of hepatic enzyme ALP (n = 1)	Asymptomatic
		Grade 4 acute respiratory failure (n = 1)	Related to narcotics

Abbreviations: GM-CSF, granulocyte-macrophage colony-stimulating factor; ALP, alkaline phosphatase.

*Inpatient dose escalation (n = 3).

Table 3. GM-CSF–Related Adverse Events at 2,000- μ g Dose Level

Adverse Event	Grade				
	0	1	2	3	4
AST/ALT elevation	42	11	2	—	—
Alkaline phosphatase elevation	44	9	1	1*	—
Pain	49	5	1	—	—
Nausea/emesis	50	3	2	—	—
Anemia	52	3	—	—	—
Constipation	53	2	—	—	—
Fever	53	2	—	—	—
Bilirubin	54	1	—	—	—
Pulmonary	53	1	—	—	1†

NOTE. Adverse events reported were measured on day 7 or later. N = 55 procedures in 10 patients. Grade 0 signifies no adverse event in the respective number of immunoembolization procedures.

Abbreviations: ALT, alanine aminotransferase; GM-CSF, granulocyte-macrophage colony-stimulating factor.

*Asymptomatic; resolved to grade 1 at day 14.

†Shortness of breath; resolved to grade 0 by day 15.

RESULTS

Patient Demographics

The demographic characteristics of 39 patients enrolled on this study are listed in Table 1. The focus of this report was on the 34 patients who had hepatic metastases from primary uveal melanoma.

Embolization Procedures

Multiple embolization procedures were performed in the majority of patients with uveal melanoma who had hepatic metastases (median number of procedures, six; range, 1 to 14; Table 1). All but three patients who achieved CR, PR, or SD after the completion of the initial six treatments continued their treatments. These patients (125- μ g dose level, n = 1; 500- μ g dose level, n = 2) who did not continue their treatment because of practical considerations subsequently received re-treatment for their progression of hepatic metastases more than 6 months after completion of the initial series of treatment.

MTD and Safety

One patient who had metastatic uveal melanoma (750- μ g dose level) was excluded from the safety analysis because of placement of a biliary stent before treatment (protocol violation). The summary of

grade 3 or greater toxicity on day 7 or later is listed in Table 2. Because no DLT was experienced at GM-CSF doses of up to 1,000 μ g, a total of 10 patients were accrued to the 1,000- μ g dose level to additionally evaluate toxicity. As no DLT occurred at 1,000 μ g, the US FDA approved two additional dose levels (1,500 and 2,000 μ g) to additionally assess the MTD. One of the first three patients who received GM-CSF 1,500 μ g developed grade 3 abdominal pain that lasted greater than 7 days. This patient subsequently discontinued the study and was placed in hospice care. Because of this DLT, three additional patients were accrued at the 1,500- μ g dose level. No additional grade 3 toxicity was observed, and the GM-CSF dose was increased to 2,000 μ g. There were no DLT for the first three patients at the 2,000- μ g dose level; therefore, seven additional patients were accrued to additionally investigate the toxicity of immunoembolization.

Of the 10 patients who received GM-CSF 2,000 μ g, the majority reported only mild symptoms (eg, fever, upper abdominal pain, and nausea) for 1 to 2 days after immunoembolization. Grades 3 to 4 toxicities experienced during days 1 to 6 (ie, procedure related) were mainly asymptomatic transient elevation of liver enzymes (grade 3 in three patients; grade 4 in two patients). One patient developed intractable liver pain (grade 3) at 3 days after treatment and was readmitted for pain control with narcotics. He subsequently developed respiratory suppression on day 4 as a result of narcotic use. He continued to have grade 4 respiratory failure on day 7. However, this patient did not require mechanical ventilation, and he completely recovered from this DLT. There was no other DLT at this highest dose level (Table 3). Thus, the MTD for GM-CSF was not reached up to the dose level of 2,000 μ g, and the study was closed as planned.

Subset Analysis of Efficacy

Although not a primary objective, patients were monitored for tumor response as mandated by good medical practice. Because the majority of patients (n = 34; 87%) had uveal melanoma metastatic to the liver, we limited the analysis of GM-CSF dose-related efficacy to this population.

Radiographic Response in Hepatic Metastases

Three patients did not receive the two immunoembolization treatments required for assessment of response because of development of brain metastasis (750- μ g dose level), study withdrawal and placement on hospice care because of significant liver pain (1,500- μ g dose level), and protocol violation (ie, pre-existing significant liver dysfunction; 750- μ g dose level). Therefore, 31 of 34 patients were assessable for radiographic response of liver metastases. The overall response rate was 32%, which included two patients who experienced

Table 4. Radiographic Response of Liver Metastases in Patients With Uveal Melanoma

GM-CSF Dose (μ g)	No. of Patients (N = 31)	Response			
		Complete (n = 2)	Partial (n = 8)	Stable Disease (n = 10)	Progressive Disease (n = 11)
< 1,000	8	0	3	3	2
1,000	8	1*	2	3	2
1,500	5	0	0	3	2
2,000	10	1	3	1	5

Abbreviation: GM-CSF, granulocyte-macrophage colony-stimulating factor.

*Scar tissue with no positron emission tomography scan activity in > 12 months.

CR and eight patients who experienced PR (Table 4). In this modest data set, no trend was observed between GM-CSF dose and radiographic response in hepatic metastases.

OS and PFS

OS in the intent-to-treat population of metastatic uveal melanoma ($n = 34$; GM-CSF 25- to 2,000- μg dose levels) was assessed. One patient was alive at 40.8 months of follow-up. The median OS was 14.4 months (95% CI, 11.2 to 22.3 months). One and 2-year survival rates were 62% (95% CI, 45.0 to 78.1%) and 26% (95% CI, 11.2 to 41.0%), respectively. The median PFS-L was 4.8 months (95% CI, 3.6 to 11.5 months), and the median PFS-S was 10.4 months (95% CI, 6.8 to 12.4 months). Seven patients developed progression of extrahepatic metastasis before the progression of hepatic metastases. Ten patients died as a result of hepatic metastases without progression of extrahepatic metastases. The rest of the patients developed progression of hepatic metastases either before ($n = 11$) or at the same time ($n = 6$) of extrahepatic progression.

Radiographic responses in the hepatic metastases were correlated to OS. The OS rates of patients who achieved CR or PR were much longer than that of patients who experienced SD or PD (33.7 months ν 12.4 months; $P = .0043$; Fig 1A). Interestingly, PFS-S correlated with GM-CSF dose (Fig 1B). Survival curves for the two higher doses were similar, as were the two for the lower doses. Therefore, dose level was categorized as high ($\geq 1,500 \mu\text{g}$) or low ($\leq 1,000 \mu\text{g}$) in additional analyses. Patients who received immunoembolization with high-dose GM-CSF had a significantly longer PFS-S of 12.4 months (95% CI, 11.2 to 18.4 months) compared with patients who received low-dose GM-CSF, for whom the PFS-S was 5.6 months (95% CI, 4.9 to 10.0 months; Fig 1C; $P = .006$).

To additionally evaluate findings observed in the univariate analyses, the Cox multivariate analysis was performed. After analysis was adjusted for confounding factors, female sex, a higher dose of GM-CSF (ie, 1,500 and 2,000 μg), and regression of hepatic metastases (CR and PR) were associated with longer OS (Table 5). In addition, a higher dose of GM-CSF is related to prolonged PFS in extrahepatic (systemic) sites. As expected, regression of hepatic metastases was related to longer PFS in the liver.

Inflammatory Response in Remote EHM

During this study, EHM were removed from six patients who had metastatic uveal melanoma after immunoembolization as needed for their medical management. Among these patients, two patients had significant inflammation in remote extrahepatic metastases.

DISCUSSION

The results of the present study demonstrate that immunoembolization of liver lesions with GM-CSF was feasible and well tolerated. MTD was not reached at the 2,000- μg GM-CSF dose level. The most striking observation of this phase I study is the seeming efficacy of treatment in patients who have hepatic metastases from primary uveal melanoma. Notably, the overall response rate (CR + PR) in hepatic metastases was 32%. This is in stark contrast to the less than 5% response rate seen with systemic therapies in patients who have uveal melanoma metastatic to hepatic and/or nonhepatic sites.¹³ The observed median OS of 14.4 months is especially encouraging compared

Fig 1. Kaplan-Meier curves for survival: (A) overall survival by hepatic response (complete [CR] + partial response [PR] ν stable [SD] + progressive disease [PD]); (B) systemic progression-free survival by four dose categories of granulocyte-macrophage colony-stimulating factor (GM-CSF); and (C) low-dose GM-CSF ($\leq 1,000 \mu\text{g}$) versus high-dose GM-CSF ($\geq 1,500 \mu\text{g}$).

with our institutional historical control of uveal melanoma patients who received chemoembolization with 1,3-bis (2-chloroethyl)-1-nitrosourea (BCNU).¹² In patients who had less than 50% involvement of the liver with metastases, the median OS in patients treated with chemoembolization was 9.8 months (95% CI, 4.6 to 14.1 months) and was shorter than that observed in this study ($P = .0085$). Although direct comparison may not be appropriate, this is also one of the longest OS among similar sets of patients who received chemoembolization (OS range, 5 to 15 months).^{11,25-27} It also is interesting that

Table 5. Multivariate Survival Analyses

Covariate by Survival Type	Analyses		
	Hazard Ratio	95% CI	P
Overall			
Sex, male	3.089	1.206 to 7.911	.0188
GM-CSF, low-dose	3.110	1.313 to 7.363	.0099
Age > 60 years	2.535	0.971 to 6.618	.0574
Hepatic response, CR or PR	0.126	0.039 to 0.408	.0005
Systemic PFS			
GM-CSF, low-dose	4.210	1.788 to 9.910	.0010
Hepatic response, CR or PR	0.483	0.204 to 1.144	.0981
Hepatic PFS			
GM-CSF, low-dose	2.258	0.954 to 5.347	.0640
Hepatic response, CR or PR	0.238	0.092 to 0.619	.0032

NOTE. $P < .05$ was statistically significant.

Abbreviations: PFS, progression-free survival; CR, complete response; PR, partial response.

patients who received immunoembolization with higher doses of GM-CSF showed substantially longer PFS-S compared with patients who received lower doses of GM-CSF.

Despite our hypothesis, it is possible that GM-CSF released into the systemic circulation after intrahepatic arterial infusion directly stimulated the systemic immune system. In fact, Spittler et al²⁸ reported that subcutaneous injection of yeast-derived recombinant human GM-CSF (ie, sargramostim) at 125 $\mu\text{g}/\text{m}^2$ per day for 14 days followed by 14 days of rest for 1 year prolonged OS and disease-free survival in stages III and IV cutaneous melanoma patients compared with historical controls. In comparison to their approach, the peak concentration of GM-CSF in the systemic circulation in the current study was high but of short duration, and the GM-CSF was given only once every 4 weeks. The serum concentration measured 1 hour after immunoembolization with 1,000 mcg GM-CSF was $4.6 \pm 4.0 \times 10^3$ pg/mL and was comparable to the peak serum concentrations after a single intravenous injection of GM-CSF at 250 $\mu\text{g}/\text{m}^2$ to healthy volunteers (C_{max} , 5.0 to 5.4×10^3 pg/mL). This is higher than the peak serum GM-CSF levels in healthy volunteers who received a single subcutaneous injection at 250 $\mu\text{g}/\text{m}^2$ (C_{max} , 1.5×10^3 pg/mL; data on file, Bayer HealthCare Pharmaceuticals, Wayne, NJ). It remains to be seen whether several hours of exposure to high-dose GM-CSF could induce a systemic antitumor response.

In summary, immunoembolization of hepatic metastases from uveal melanoma with GM-CSF is feasible and safe up to the dose level

of 2,000 μg . Although not directly comparable to other studies, the median OS of 14.4 months and the delay in progression of EHM in higher-dose cohorts warrants additional study at these dose levels in a larger group of patients who have uveal melanoma and hepatic metastases. In fact, we have initiated a double-blind, randomized, phase II clinical trial, in which patients who have uveal melanoma and hepatic metastases are randomly assigned to either embolization of the hepatic artery with GM-CSF 2,000 μg or plain embolization without GM-CSF. Also, our novel immunoembolization procedure may be applicable to other types of chemotherapy-resistant hepatic tumors, such as primary hepatocellular carcinoma and hepatic metastases from renal cell carcinoma.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).