CLINICAL STUDY

Double-Blinded, Randomized Phase II Study Using Embolization with or without Granulocyte–Macrophage Colony-Stimulating Factor in Uveal Melanoma with Hepatic Metastases

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ABSTRACT

Purpose: To investigate the effects of immunoembolization with granulocyte–macrophage colony-stimulating factor (GM-CSF) in patients with uveal melanoma (UM) with liver-only metastasis.

Materials and Methods: In this double-blind phase II clinical trial, patients were randomized to undergo immunoembolization or bland embolization (BE). Lobar treatment was performed with GM-CSF or normal saline solution mixed with ethiodized oil followed by embolization with gelatin sponge emulsified with iodinated contrast medium. Fifty-two patients (immunoembolization, n = 25; BE, n = 27) were enrolled. Response was assessed after every two treatments. The primary endpoint was overall response rate (ORR) of liver metastases. Progression-free survival (PFS), overall survival (OS), and immunologic responses were secondary endpoints.

Results: There were five partial responses in the immunoembolization group (ORR, 21.2%; 90% confidence interval [CI], 10.3%–30.5%) and three in the BE group (ORR, 16.7%; 90% CI, 6.3%–26.9%). Stable disease was seen in 12 patients in the immunoembolization group and 19 in the BE group. OS times were 21.5 months (95% CI, 18.5–24.8 mo) with immunoembolization and 17.2 months (95% CI, 11.9–22.4 mo) with BE. The degree of proinflammatory cytokine production was more robust after immunoembolization and correlated with time to "systemic" extrahepatic progression. In the immunoembolization group, interleukin (IL)-6 levels at 1 hour ($P = .001$) and IL-8 levels at 18 hours after the procedure ($P < .001$) were significant predictors of longer systemic PFS. Moreover, a dose–response pattern was evident between posttreatment serum cytokine concentrations and systemic PFS.

Conclusions: Immunoembolization induced more robust inflammatory responses, which correlated with the delayed progression of extrahepatic systemic metastases.

ABBREVIATIONS

BE = bland embolization, CI = confidence interval, GM-CSF = granulocyte–macrophage colony-stimulating factor, HR = hazard ratio, IL = interleukin, ORR = overall response rate, OS = overall survival, PFS = progression-free survival, PR = partial response, SD = stable disease, TNF = tumor necrosis factor, UM = uveal melanoma

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None of the authors have identified a conflict of interest.

Tables E1–E6 are available online at *www.jvir.org*.

J Vasc Interv Radiol 2015; XX:■■■–■■■

http://dx.doi.org/10.1016/j.jvir.2014.11.037

Uveal melanoma (UM) is the most common primary intraocular malignant tumor in adults in the United Stated (1). As many as 50% of patients develop systemic metastases after successful treatment of the primary tumor (2). The liver is usually the first and only site of metastatic disease for a majority of patients (3). Treatment options for liver metastases include systemic chemotherapy, surgery, regional intra-arterial chemotherapy with or without embolization, and radioactive microsphere treatment (4).

The systemic chemotherapeutic regimens used in cutaneous melanoma generally are ineffective against this highly chemotherapy-resistant tumor, and only a minority of patients (<10%) are deemed eligible for treatment with surgical approaches (5). Hepatic intra-arterial chemotherapeutic infusion requires placement of implantable hepatic catheters, a technique not commonly used in the United States (6,7). Mavligit et al (8) reported a 46% response rate with the use of chemoembolization with cisplatin and polyvinyl alcohol sponge. However, these results were not consistently reproduced by others. In 2005, a phase II study consisting of 29 patients treated with chemoembolization using carmustine (9) demonstrated a median time to progression of 6.5 months. Nonetheless, despite control of hepatic metastases, progression of extrahepatic metastases was seen in two thirds of patients (9).

Therefore, a local/regional treatment that could potentially control growth of liver metastases and delay or prevent the development of systemic metastases would be an ideal treatment option. Immunoembolization with the use of granulocyte–macrophage colony-stimulating factor (GM-CSF) is a liver-directed treatment that may theoretically fulfill both goals.

The liver is the largest organ of the reticuloendothelial system and contains more than 70% of all tissue macrophages (ie, Kupffer cells). Hepatic sinusoidal lymphocytes, originally referred to as pit cells, have functions of natural killer cells. Natural killer T cells and $CD3^+$ γδ T cells are also present in the liver (10). GM-CSF is known to stimulate macrophages and dendritic cells and increase the cytotoxicity of monocytes toward tumor cell lines through release of tumor necrosis factor (TNF). Vaccination with genetically engineered irradiated tumor cells that produce GM-CSF has been shown to induce potent, specific, and long-lasting antitumor immunity in an animal model (11). Evidence has been accumulated that GM-CSF is useful as an immunoadjuvant agent for cancer vaccines (12).

The combination of ethiodized oil with GM-CSF is intended to increase the local concentration of GM-CSF to in turn trigger stimulation of the host immune system. The rationale behind immunoembolization with GM-CSF is that tumor cells would be killed by the ischemic effect of embolization. The local immunologic reaction evoked by GM-CSF in the presence of tumor antigens would induce systemic immunity against melanoma cells and delay the development of remote systemic metastases.

In 2008, a phase I trial that used human recombinant GM-CSF for immunoembolization was reported (13). There was no maximum-tolerated, dose-limiting dose or late toxicity found at doses as high as 2,000 μg of GM-CSF, and higher doses correlated with longer systemic progression-free survival (PFS). A subsequent retrospective analysis (14) that compared immunoembolization with carmustine chemoembolization showed a significantly longer survival with immunoembolization. To further investigate the immunologic mechanism of this approach, a randomized phase II clinical trial was designed intending to further explore the efficacy of this innovative treatment.

MATERIALS AND METHODS

Patient Enrollment and Eligibility

Patients with histologically confirmed metastatic UM to the liver with no extrahepatic metastasis and at least one measurable hepatic lesion were enrolled. The total tumor volume could not exceed 50% of the liver volume. Also required were Eastern Cooperative Oncology Group performance status no higher than 1 and the following laboratory parameters: serum creatinine level no greater than 2.0 mg/dL, granulocyte count of at least 1,000/mm^3, platelet count of at least 100,000/mm^3, bilirubin level no greater than 2.0 mg/mL, albumin level of at least 3.0 g/dL, prothrombin time/partial thromboplastin time less than 1.5 times the normal value, and alkaline aminotransferase, alanine aminotransferase, and alkaline phosphatase levels less than 5 times the normal value.

Exclusion criteria were uncontrolled hypertension and/or uncontrolled congestive heart failure, bleeding diathesis, life expectancy of 6 months or less, pregnancy or breastfeeding, HIV infection, need for immunosuppressive therapy, and severe allergy to iodinated contrast agent or GM-CSF judged by the study physicians based on their clinical assessment. In view of technical considerations, patients with occlusion of the main portal vein, inadequate collateral flow around an occluded portal vein as determined by angiography, biliary obstruction, stent or previous biliary surgery except cholecystectomy, and arteriovenous shunt identified on arteriography of the hepatic artery were also excluded.

Study Design and Interventions

This was a double-blinded and randomized phase II study in which patients assigned to undergo BE served as controls only for immunologic outcomes. The study design was not meant and did not have adequate power to formally compare arms in terms of the primary or secondary outcomes. A prespecified minimal overall response rate (ORR) was chosen as a selection process to consider the best arm for potential future clinical trials