CLINICAL STUDY

Peripheral Blood Regulatory T-Cell and Type 1 Helper T-Cell Population Decrease after Hepatic Artery Embolization

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ABSTRACT

Purpose: To evaluate changes in T-cell populations in peripheral blood after bland hepatic artery embolization (HAE).

Materials and Methods: Bland HAE was performed in 12 patients to treat primary (n = 5) or metastatic (n = 7) liver tumors, using microspheres and polyvinyl alcohol (n = 8) or microspheres alone (n = 4). Patient peripheral blood samples were collected within 1 month before HAE, within 1 week after HAE (early period after HAE), and 2–8 weeks after HAE (follow-up period). Peripheral blood populations of cytotoxic T lymphocytes, $CD4^+$ T cells, type 1 helper T cells (T_h1) and type 2 helper T cells (T_h2), and regulatory T cells (T_{reg}) were evaluated using flow cytometry. Changes in T-cell populations before and after bland HAE were compared using paired *t* tests.

Results: Peripheral blood $CD4^+$ T-cell populations decreased significantly in the early period after HAE (44.0% ± 2.2 to 34.4% ± 3.6, $P < .01$) and in the follow-up period (44.0% ± 2.2 to 36.3% ± 3.0, $P < .01$). Among the individual $CD4^+$ T-cell subtypes, T_{reg} (2.5% ± 0.3 to 1.7% ± 0.2, $P < .02$) and T_h1 (8.1% ± 1.8 to 5.6% ± 1.6, $P < .02$) decreased significantly in the early period after HAE only. The presence of extrahepatic disease was associated with decreasing T_{reg} ($P < .04$).

Conclusions: After HAE, the peripheral blood T-cell environment is changed with decreases in T_{reg} and T_h1.

ABBREVIATIONS

CD = cluster of differentiation, CTL = cytotoxic T lymphocytes, FOXP3 = forkhead box P3, HAE = hepatic artery embolization, IFN-γ = interferon-γ, IL = interleukin-4, PBMC = peripheral blood mononuclear cell, T_h1 = type 1 helper T cells, T_h2 = type 2 helper T cells, T_{reg} = regulatory T cells, WBC = white blood cell

Traditionally, the efficacy of hepatic artery embolization (HAE) has been attributed mainly to its direct ischemic tumoricidal effect (1,2). Little attention has been devoted to the potential for the immune environment. Actually, HAE induces tumor necrosis in situ by blocking the tumor blood supply. Therefore, it can create a source of tumor-associated antigen (3,4). Previous reports in the literature showed that tumor-specific T-cell response increases after transcatheter arterial chemoembolization (3,4). Moreover, HAE induces local inflammation within the liver leading to the release of various cytokines and chemokines (5–8). Induction of tumor-associated antigens and the release of cytokines and chemokines might change the systemic T-cell environment. We hypothesized that HAE can alter the peripheral blood T-cell environment. Elucidating the changes in the T-cell environment is important because cumulative evidence suggests that T cell–mediated immune response affects the disease progression and patient prognosis for cancer of several types (9–15). However, the effects of HAE on the T-cell environment were not elucidated satisfactorily

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None of the authors have identified a conflict of interest.

J Vasc Interv Radiol 2016; XX:▮▮▮–▮▮▮

http://dx.doi.org/10.1016/j.jvir.2016.01.150

in earlier reports in the literature. In this study, we evaluated changes in peripheral blood T-cell subtypes after bland HAE.

MATERIALS AND METHODS

Patients

This single-center prospective study was approved by our institutional review board. Written informed consent was obtained from all participants who underwent HAE for the treatment of primary or secondary malignancy. Patients with prior ablation or embolization procedures within 30 days and patients who did not require a blood draw before the procedure at the time they were evaluated for eligibility were excluded.

Between January 2014 and November 2014, five interventional radiologists (A.M.C., G.I.G., K.T.B., S.B.S., and J.P.E.) and one research assistant (T.T.C.) recruited study participants, and 20 patients were enrolled. In seven of these 20 patients, scheduled laboratory testing was not performed after the procedure. In addition, the blood sample was insufficient for analysis in one patient, leaving 12 patients who formed the cohort of this study. There were nine men (75.0%) and three women (25.0%) with a mean age of 56.2 years ± 3.6 (range, 39–75 y). The most common primary diagnosis was neuroendocrine tumor (50.0%; n = 6 of 12), followed by hepatocellular carcinoma (41.7%; n = 5 of 12) and leiomyosarcoma (8.3%; n = 1 of 12). Extrahepatic metastases were present in six patients (50.0%; n = 6 of 12). Table 1 summarizes patient and tumor characteristics. No patient received other cancer therapy for ≥ 30 days before study enrollment until the end of follow-up.

Table 1. Patient Backgrounds, Tumor Characteristics, and HAE Details

Parameter	Value
No. patients	12
Age, y	56.2 ± 3.6
≤ 60	7 (58.3)
> 60	5 (41.7)
Sex	
Male	9 (75.0)
Female	3 (25.0)
Primary diagnosis	
Neuroendocrine tumor	6 (50.0)
Hepatocellular carcinoma	5 (41.7)
Leiomyosarcoma	1 (8.3)
Child-Pugh score	
5	10 (83.3)
≥ 6	2 (16.7)
Tumor number	
Single	2 (16.7)
Multiple	10 (83.3)
Maximum tumor diameter (cm)	
≤ 5	9 (75.0)
> 5	3 (25.0)
Extrahepatic lesion	
No	6 (50.0)
Yes	6 (50.0)
Range of HAE	
Lobar	8 (66.7)
Segmental	4 (33.3)
Maximum AST after HAE (IU/L)	
≤ 100	6 (50.0)
> 100	6 (50.0)
Initial therapeutic response on mRECIST	
CR or PR	9 (75.0)
SD or PD	3 (25.0)

Note–Continuous data are presented as mean and SE. Numbers in parentheses are percentages.
AST = aspartate aminotransferase; CR = complete response; HAE = hepatic artery embolization; mRECIST = modified Response Evaluation Criteria in Solid Tumors; PD = progressive disease; PR = partial response; SD = stable disease.

HAE Procedure

Bland HAE was performed by five interventional radiologists (A.M.C., G.I.G., K.T.B., S.B.S., and J.P.E.). After routine hepatic angiography with 4-F or 5-F angiographic catheters to identify hepatic arterial anatomy, tumor location, and feeding arteries, bland HAE was performed via the common femoral artery. Feeding arteries that supplied the target lesion were catheterized as selectively as possible using microcatheters. Bland HAE was conducted using 40–100 μm microspheres (Embosphere; BioSphere Medical, Inc, Rockland, Massachusetts) in five patients, 100–300 μm microspheres in four patients, and both 40–100 μm and 100–300 μm microspheres in three patients. The endpoint of embolization was complete stasis of anterograde blood flow in the feeding arteries. To achieve complete stasis, additional embolization by polyvinyl alcohol embolization particles (Cook, Inc, Bloomington, Indiana) was performed in four of five patients who received HAE by 40–100 μm microspheres, one of four patients who received HAE by 100–300 μm microspheres, and all three patients who received HAE by both 40–100 μm and 100–300 μm microspheres. If multiple lesions were present in the liver and selection of multiple feeding arteries was difficult, lobar HAE was performed. Four patients received segmental HAE by 40–100 μm microspheres plus polyvinyl alcohol (n = 3) or 40–100 μm microspheres alone (n = 1). The remaining eight patients received lobar HAE.

Blood Collection

Peripheral blood of patients was collected within 1 month before HAE, during the early period after HAE (ie, within 1 week after HAE), and during the follow-up period (ie, 2–8 weeks after HAE). This timing of blood