

Original Article

The effect of TACE in combination with thalidomide-mediated adjuvant therapy on the levels of VEGF and bFGF in patients with hepatocellular carcinoma

Chao Tong¹, Hui Liu¹, Rihui Chen¹, Fengting Zhu²

¹Department of Interventional Radiology, Central South University, Xiangya School of Medicine Affiliated Haikou Hospital, Haikou, Hainan Province, China; ²Department of Oncology, Hainan Hospital of Traditional Chinese Medicine, Haikou, Hainan Province, China

Received December 30, 2020; Accepted February 1, 2021; Epub May 15, 2021; Published May 30, 2021

Abstract: Objective: To investigate the efficacy of transcatheter arterial chemoembolization (TACE) combined with thalidomide-mediated adjuvant therapy on the expression levels of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) in hepatocellular carcinoma (HCC) patients. Methods: A prospective study was designed, by which 134 HCC patients from our hospital who underwent treatment were selected and randomly divided into an observation group and a control group, 67 participants per group. The control group was administered hepatic TACE, while the observation group was given TACE in combination with thalidomide. The total disease control rate (DCR) and the rate of adverse effects were analyzed and compared between the two groups of patients. The expression levels of CD3⁺, CD4⁺, CD8⁺, CD4⁺/CD8⁺, VEGF, VEGFA, and bFGF were measured between the two groups before and after treatment. The overall survival rate of the two groups were also compared after a follow-up for 3 years. Results: The rate of adverse effects and DCR in the control group were 44.78% and 61.19%, respectively, whereas these rates were 22.39% and 89.55% in the observation group, respectively. Of note, the differences in terms of the rate of adverse effects and DCR were statistically significant between the two groups ($P < 0.05$). Before treatment, no significant difference was shown regarding the expression levels of CD3⁺, CD4⁺, CD8⁺, CD4⁺/CD8⁺, VEGF, VEGFA, and bFGF between the two groups ($P > 0.05$). After treatment, the expression levels of CD3⁺, CD4⁺, and CD4⁺/CD8⁺ were significantly upregulated in the two groups, while the levels of CD8⁺, VEGF, VEGFA, and bFGF were considerably downregulated ($P < 0.05$). In addition, compared with the control group, the expression levels of CD3⁺, CD4⁺, and CD4⁺/CD8⁺ were significantly higher, whereas the levels of CD8⁺, VEGF, VEGFA, and bFGF were notably lower in the observation group ($P < 0.05$). After the follow-up for 3 years, the overall survival rate of the observation group was significantly higher in comparison to the control group ($P < 0.05$). Conclusion: TACE in combination with thalidomide-mediated adjuvant treatment has revealed a promising clinical outcome on HCC patients by downregulating the levels of VEGF and bFGF.

Keywords: Transcatheter arterial chemoembolization, thalidomide, hepatocellular carcinoma, vascular endothelial growth factor, basic fibroblast growth factor

Introduction

Liver cancer is a common malignancy in our digestive system. It has been shown that the incidence and the mortality of this disease rank the 5th and 3rd, respectively among the malignant tumors worldwide [1, 2]. With the development of our society, the morbidity of hepatocellular carcinoma (HCC) is becoming higher. The routine therapeutic strategy for liver cancer is the hepatectomy, which has made some progress for liver cancer treatment. However, post-

surgery disadvantages such as high chance of complications and pains are of concerns among patients. In clinical practice, the gold standard to treat advanced HCC is transcatheter arterial chemoembolization (TACE), which can slowly release the drug to the target organs and maintain a high blood concentration of the medication to control the rapid growth of tumors. However, studies have shown that TACE may have some negative impacts on the immune function of patients [3-6]. Thalidomide belongs to a group of immunosuppressants, which func-

tions by regulating T lymphocytes, preventing tumor angiogenesis, and inducing tumor apoptosis and has been widely used as an auxiliary anti-tumor medication in the treatment of intermediate and advanced malignant tumors [7]. Previous studies have elucidated the clinical effects of the TACE combined with thalidomide in the treatment of HCC, but the underlying mechanism remains elusive [8]. Angiogenesis is one of the fundamental steps for tumor initiation and progression, in which vascular endothelial growth factor (VEGF) is a key angiogenic mediator to drive the neovascularization [9-11]. The fibroblast growth factor (FGF) family and its related receptors are involved in a variety of biological functions, such as regulating cell proliferation, differentiation and migration, participating in the initiation and development of tumors, and playing roles in the tissue repair [12]. Based on previous studies, this study aimed to elucidate the efficacy of TACE in combination with thalidomide-mediated adjuvant therapy on the levels of VEGF and bFGF in patients with HCC and to provide therapeutic insights into HCC treatment.

Materials and methods

General information

A total of 134 HCC patients who underwent treatment in our hospital from January 2015 to January 2017 were selected in this prospective research and divided into an observation group and a control group based on a random number table method, with 67 participants in each group. Our study was approved by the ethics committee of our hospital, and patients as well as their family members were informed and signed the consent form.

Inclusion and exclusion criteria

Inclusion criteria: (1) Met the relevant diagnostic and staging criteria of HCC [13]; (2) Without targeted drug therapy, radiotherapy, chemotherapy or other drug treatments in the past; (3) No indication for surgery; (4) No history of liver surgery; (5) With complete clinical data; (6) No other malignant tumors; (7) Age >18 years.

Exclusion criteria: (1) Missing data or specimens; (2) With other severe diseases; (3) Pregnancy or lactation; (4) Poor compliance; (5) Intolerant with this treatment plan.

Methods

Both groups' patients were treated with TACE, which was conducted by a modified Seldinger method [14]. The chemotherapy regimen included 5-Fu (0.75-1.25 g) + cisplatin (80-120 mg) + oxaliplatin (200 mg) + episoft Bistar (80-120 mg). The embolization agent contained gelatin and super-liquefied lipiodol. The dosage of chemotherapy and embolization agents depended on the size of the tumor and blood supply.

The observation group was administered with thalidomide based on the therapy of the control group. Thalidomide (Changzhou Pharmaceutical Factory Co., Ltd., 25 mg × 20 tablets) was taken orally from 7 days after TACE, 100-200 mg each time, once per day, continuously for 3 months. The control group was given the placebo from 7 days after TACE, 100-200 mg each time, once per day for 3 months.

Outcome measurements

The levels of VEGF, VEGF-A, and bFGF: Two tubes of 5 mL fasting venous blood were collected from patients at one day before treatment and the morning after treatment. The sample was centrifuged for 5 min at 3,000 r/min to isolate the serum. One of the venous blood samples was subjected to the flow cytometry (BD FACSCalibur, US) to detect CD3⁺, CD4⁺, CD8⁺, and CD4⁺/CD8⁺ levels, while the other one was used for enzyme-linked immunosorbent assay (ELISA; Hamilton microlab star multi-functional microplate reader, Switzerland) to measure the levels of VEGF, VEGF-A and bFGF [15].

Tumor response rate: The clinical efficacy of the treatment was investigated based on the Response Evaluation Criteria in Solid Tumors (RECIST) [16]. Complete response (CR): the lesions disappeared completely and no new lesions generated; partial response (PR): no new lesions generated for 4 weeks and the sum of the longest diameter of the lesions reduced by more than 30%; stable disease (SD): the sum of the longest diameters of the lesions decreased less than 30%; progressive disease (PD): new lesions appeared or the sum of longest diameters of the lesions increased by more than 20%. Objective response rate (RR) = (CR + PR)/total number of patients of

Effects of TACE and thalidomide in the treatment of HCC

Table 1. Comparison of general information between the two groups of patients ($\bar{x} \pm sd, n$)

Indicator	Observation group (n=67)	Control group (n=67)	t/ χ^2	P
Age (years)	53.4±5.7	53.9±5.2	0.530	0.597
Gender			0.308	0.579
Male	44	47		
Female	23	20		
Pathological type			0.729	0.695
Nodular	33	31		
Bulky	28	32		
Diffuse	6	4		
Child-pugh staging [13]			0.121	0.728
A	31	29		
B	36	38		
Clinical stage			0.191	0.662
II b-III	53	55		
IV	14	12		

Table 2. Comparison of clinical efficacy between the two groups of patients (n, %)

Group	CR (%)	PR (%)	SD (%)	PD (%)	RR (%)	DCR (%)
Observation group (n=67)	1 (1.49)	27 (40.30)	32 (47.76)	7 (10.45)	28 (41.79)	60 (89.55)
Control group (n=67)	0 (0.00)	20 (29.85)	21 (31.34)	26 (33.81)	20 (29.85)	41 (61.19)
χ^2					2.078	4.787
P					0.150	0.029

this group $\times 100\%$; disease control rate (DCR) = (CR + PR + SD)/total number of patients of this group $\times 100\%$.

Adverse effects and survival: The occurrence of adverse effects such as gastrointestinal reactions, anemia, fever, fatigue, bone marrow suppression, and leukopenia were recorded in the two groups. Adverse effects rate = number of patients with adverse effects/total number of patients of each group $\times 100\%$.

After a follow-up for 3 years, the survival time and survival rate were calculated, which were compared between the two groups of patients.

Statistical analysis

Statistical analysis was processed using the SPSS 22.0 software. The counting data were presented as the number of cases and percentage (n, %), while the quantitative data was presented as mean \pm standard deviation ($\bar{x} \pm sd$). The quantitative data that followed normal distribution were analyzed by t test, whereas the

counting data were compared by χ^2 test. The Kaplan-Meier (K-M) analysis was applied to compare the overall survival rates of the two groups. $P < 0.05$ was considered as significantly different.

Results

Comparison of general information between the two groups of patients

The data demonstrated that no significant difference was found regarding the general information such as age and gender between the two groups of patients ($P > 0.05$, **Table 1**).

Comparison of clinical outcome between the two groups of patients

The results revealed that the RR and DCR of the observation group were 41.79% and 89.55%, respectively, while they were 29.85% and 61.19%, respectively in the control group. Compared with the control group, the DCR was significantly higher in the observation group ($P < 0.05$, **Table 2**).

Effects of TACE and thalidomide in the treatment of HCC

Table 3. Comparison of CD3⁺, CD4⁺, CD8⁺, and CD4⁺/CD8⁺ levels between the two groups before and after treatment ($\bar{x} \pm sd$)

Group	Observation group (n=67)	Control group (n=67)	t	P
CD3⁺				
Before treatment	42.34±5.57	42.78±5.24	0.471	0.638
After treatment	71.39±6.94*	53.28±6.71*	15.356	<0.001
CD4⁺				
Before treatment	31.25±3.51	31.74±3.22	0.842	0.401
After treatment	44.98±4.06*	38.21±4.03*	9.687	<0.001
CD8⁺				
Before treatment	37.83±4.42	37.91±4.34	0.106	0.916
After treatment	30.01±2.59*	33.56±2.71*	7.752	<0.001
CD4⁺/CD8⁺				
Before treatment	0.87±0.20	0.83±0.24	1.048	0.297
After treatment	1.44±0.31*	1.19±0.22*	5.383	<0.001

Note: compared with before treatment within the same group, *P<0.05.

Table 4. Comparison of VEGF, VEGFA and bFGF levels between the two groups before and after treatment ($\bar{x} \pm sd$)

Group	Observation group (n=67)	Control group (n=67)	t	P
VEGF (pg/mL)				
Before treatment	447.24±76.55	452.83±81.32	0.410	0.683
After treatment	208.79±43.11*	294.45±40.17*	11.899	<0.001
VEGFA (pg/mL)				
Before treatment	232.56±33.42	237.81±34.27	0.898	0.371
After treatment	154.89±21.03*	187.33±23.72*	8.376	<0.001
bFGF (pg/mL)				
Before treatment	121.46±13.35	124.51±14.76	1.254	0.212
After treatment	71.34±8.89*	92.75±8.02*	14.637	<0.001

Note: compared with before treatment within the same group, *P<0.05.

Comparison of CD3⁺, CD4⁺, CD8⁺, and CD4⁺/CD8⁺ levels between the two groups before and after treatment

Before treatment, the expression levels of CD3⁺, CD4⁺, CD8⁺, and CD4⁺/CD8⁺ between the two groups did not reveal any significant difference (P>0.05). After treatment, the expression levels of CD3⁺, CD4⁺, and CD4⁺/CD8⁺ were significantly increased in both groups, while the level of CD8⁺ was notably decreased (P<0.05). In comparison to the control group, the observation group showed significantly higher levels of CD3⁺, CD4⁺, and CD4⁺/CD8⁺, while significantly lower level of the CD8⁺ (P<0.001, **Table 3**).

Comparison of VEGF, VEGFA and bFGF levels between the two groups before and after treatment

Before treatment, no significant difference was found in terms of the levels of VEGF, VEGFA, and bFGF between the two groups (P>0.05). After treatment, the levels of VEGF, VEGFA, and bFGF were significantly decreased in both groups (P<0.05). Additionally, VEGF, VEGFA, and bFGF levels of the observation group were remarkably downregulated in comparison to those of the control group (P<0.001, **Table 4**).

Comparison of the rate of adverse effects between the two groups of patients

The results revealed that the incidence of adverse effects of the observation group was significantly lower in comparison to that of the control group (22.39% vs. 44.78%, P<0.05, **Table 5**).

Comparison of overall survival rate between the two groups of patients

After the follow-up for 3 years, the median survival time of the observation group was 32.86 months, with an overall survival rate of 61.19%, while the median survival time of the control group was 23.83 months, with an overall survival rate of 41.79%. Statistical analysis showed that the overall survival rate was significantly higher in the observation group than that of the control group ($\chi^2=21.150$, P=0.001, **Figure 1**).

Discussion

Due to the lack of specific biomarkers for early diagnosis of HCC, patients have already progressed to the intermediate and late-stage HCC when diagnosed, resulting in missing the best time for treatment. Currently, TACE is often

Effects of TACE and thalidomide in the treatment of HCC

Table 5. Comparison of the incidence of adverse effects between the two groups of patients (n, %)

Symptom	Observation group (n=67)	Control group (n=67)	X ²	P
Gastrointestinal reactions	4 (5.97)	7 (10.45)	0.891	0.345
Anemia	1 (1.49)	7 (10.45)	4.786	0.029
Fever	1 (1.49)	2 (2.98)	0.341	0.559
Fatigue	2 (2.98)	1 (1.49)	0.341	0.559
Bone marrow suppression	6 (8.96)	8 (11.94)	0.319	0.572
Leukopenia	1 (1.49)	5 (7.46)	2.792	0.095
Total	15 (22.39)	30 (44.78)	4.540	0.033

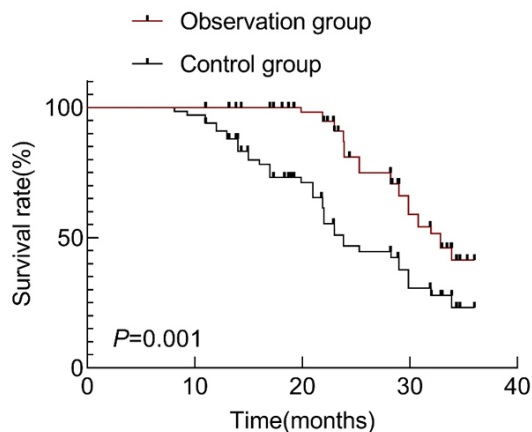


Figure 1. Comparison of overall survival rate between the two groups of patients.

applied to treat HCC in clinical practice. Although this approach has been approved to have promising outcome, it has been reported that tumors are prone to relapse after TACE treatment [17]. The possible reason is that TACE can cause hypoxia in tumor microenvironment, which favors the growth of tumors and induces the angiogenesis. Neovascularization is the fundamental step for the initiation and development of tumors, which is mediated by hypoxia in tumor microenvironment [18]. Studies have reported that when the body is under hypoxic conditions, hypoxia-inducible factor (HIF) upregulates VEGF expression, which in turn promotes the proliferation of vascular endothelial cells and the neovascularization, reduces extracellular matrix (EXM), and increases the permeability of tumor blood vessels [19]. VEGFA is a member of the VEGF family, which can interact with VEGFR2 to induce the tumor angiogenesis [20]. bFGF refer to a type of polypeptide with a wide range of biological functions. Studies have shown that bFGF

can promote the cell division and proliferation of mesoderm and ectoderm, thereby inducing the formation of new blood vessels [21]. In addition, studies have also revealed that bFGF can upregulate the expression of VEGF, increase the level of VEGF in vascular smooth muscle, and indirectly induce the angiogenesis [22]. Therefore, this study uses VEGF, VEGFA, and bFGF as biological indicators to evaluate clinical outcome of TACE in combination with thalidomide-mediated adjuvant therapy in the treatment of HCC.

can promote the cell division and proliferation of mesoderm and ectoderm, thereby inducing the formation of new blood vessels [21]. In addition, studies have also revealed that bFGF can upregulate the expression of VEGF, increase the level of VEGF in vascular smooth muscle, and indirectly induce the angiogenesis [22]. Therefore, this study uses VEGF, VEGFA, and bFGF as biological indicators to evaluate clinical outcome of TACE in combination with thalidomide-mediated adjuvant therapy in the treatment of HCC.

Thalidomide is a class of glutamic acid derivatives with sedative and antiemetic effects, which has been initially used to control early pregnancy reactions. However, with the occurrence of serious adverse effects, its use during pregnancy has been banned. Recently, researchers have demonstrated that thalidomide can effectively inhibit the expression of VEGF and bFGF, thereby suggesting an anti-angiogenic effect [23]. In addition, thalidomide can also regulate the expression of some cytokines, improve the body's immune function, and play an anti-tumor effect. Therefore, studies have been conducted in exploring its clinical effects in the treatment of cancer [24, 25]. This study has applied thalidomide combined with TACE to treat HCC, which demonstrates that compared with the control group, the DCR is significantly higher in the observation group. By either TACE alone or combined therapy, the levels of VEGF, VEGFA, and bFGF in patients are considerably downregulated, and the combined therapy has revealed more reduction regarding the levels of these biological indicators. Our data indicate that thalidomide combined with TACE can suppress the tumor angiogenesis by significantly inhibiting the expression levels of VEGF and bFGF. In addition, the occurrence of adverse effects has also been compared between the two groups during the treatment, which shows that adverse effects such as gastrointestinal reactions, anemia, fever, fatigue, bone marrow suppression, and leukopenia are found among some patients in both groups. However, the total adverse effects are significantly higher in the control group than those of the observation group, which suggests that in order to have the timely treatment abnormal

responses of patients should be taken into account.

T lymphocytes play important roles in our body's immune function. CD3⁺ represents the total T lymphocytes, which can be divided into CD4⁺ and CD8⁺ subgroups. CD4⁺CD25⁺ Tr of CD4⁺ cells are regulatory T cells, which mainly function in the modulation of the immune system. On the contrary, CD8⁺ cells together with CD4⁺ cells maintain the balance of the immune response. Our data have shown that the level of T lymphocyte subgroups in patients has been improved after treatment, and the improvement is more significant for the treatment via thalidomide combined with TACE, suggesting that the combined treatment can significantly improve patients' immune function. In addition, this study has compared the overall survival rate through a 3-year follow-up between the two groups, which reveals that the median survival time of the observation group is 32.86 months (overall survival rate of 61.19%), while the median survival time of patients treated with TACE alone is 23.83 months (overall survival rate of 41.79%), indicating a better long-term outcome with combined treatment.

In summary, TACE in combination with thalidomide-mediated adjuvant treatment of patients with HCC has shown a promising clinical outcome via downregulating the levels of VEGF and bFGF. However, this study has not observed the dynamic changes of various biological indicators, the sample size is small, and other indicators are not included to comprehensively evaluate the effect of this combined approach, leading to limitations of this study. Therefore, follow-up studies are warranted.

Disclosure of conflict of interest

None.

Address correspondence to: Fengting Zhu, Department of Oncology, Hainan Hospital of Traditional Chinese Medicine, No. 47 Heping North Road, Haikou 570203, Hainan Province, China. Tel: +86-0898-66151369; Fax: +86-0898-66151369; E-mail: zhufengting68er@163.com

References

[1] Wu FX, Chen J, Bal T, Zhu SL, Yang TB, Qi LN, Zou L, Li ZH, Ye JZ and Li LQ. The safety and

efficacy of transarterial chemoembolization combined with sorafenib and sorafenib monotherapy in patients with BCLC Stage B/C hepatocellular carcinoma. *BMC Cancer* 2017; 17: 645.

- [2] Zhao J, Gray SG, Wabitsch M, Greene CM and Lawless MW. The therapeutic properties of resminostat for hepatocellular carcinoma. *Oncoscience* 2018; 5: 196.
- [3] Kwan SW, Harris WP, Gold LS and Hebert PL. Comparative effectiveness of transarterial embolization and sorafenib for hepatocellular carcinoma: a population-based study. *AJR Am J Roentgenol* 2018; 210: 1359.
- [4] Wu X, Chen R, Zheng W and Hu J. Comprehensive analysis of factors affecting clinical response and short-term survival to drug-eluting bead transarterial chemoembolization for treatment in patients with liver cancer. *Technol Cancer Res Treat* 2018; 17: 1533033818759878.
- [5] Wang H, Du PC, Wu MC and Cong WM. Postoperative adjuvant transarterial chemoembolization for multinodular hepatocellular carcinoma within the barcelona clinic liver cancer early stage and microvascular invasion. *Hepatobiliary Surg Nutr* 2018; 7: 418-428.
- [6] Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, Zhu AX, Murad H and Marrero JA. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology* 2018; 67: 358.
- [7] Liang PC, Ch'ang HJ, Hsu C, Chen LT, Shih TTF and Liu TW. Perfusion parameters of dynamic contrast-enhanced magnetic resonance imaging predict outcomes of hepatocellular carcinoma receiving radiotherapy with or without thalidomide. *Hepatol Int* 2015; 9: 258-268.
- [8] Wu J, Ng J, Christos PJ, Goldenberg AS, Sparano J, Sung MW, Hochster HS and Muggia FM. Chronic thalidomide and chemoembolization for hepatocellular carcinoma. *Oncologist* 2014; 19: 1229-1230.
- [9] Ramjiawan RR, Griffioen AW and Duda DG. Anti-angiogenesis for cancer revisited: is there a role for combinations with immunotherapy? *Angiogenesis* 2017; 20: 185-204.
- [10] Yu S, Sun J, Zhang J, Xu XF, Li H, Shan BZ, Tian T, Wang HC, Ma DX and Ji CY. Aberrant expression and association of VEGF and Dll4/notch pathway molecules under hypoxia in patients with lung cancer. *Histol Histopathol* 2013; 28: 277-284.
- [11] Zhang S, Gao X, Fu W, Li SW and Yue LM. Immunoglobulin-like domain 4-mediated ligand-independent dimerization triggers VEGFR-2 activation in HUVECs and VEGFR2- positive breast cancer cells. *Breast Cancer Res Treat* 2017; 163: 423-434.

Effects of TACE and thalidomide in the treatment of HCC

- [12] Chen YC, Zhang L, Li EN, Ding LX, Zhang GA, Hou Y and Yuan W. Association of the insulin-like growth factor-1 single nucleotide polymorphisms rs35767, rs2288377, and rs5742612 with osteoporosis risk: a meta-analysis. *Medicine (Baltimore)* 2017; 96: e9229-e9231.
- [13] Ministry of Health of the People's Republic of China. Standards for diagnosis and treatment of hepatocellular carcinoma (2011). *J Clin Oncol* 2011; 16: 929-946.
- [14] Ao M, Xiao X, Yan Y, Shi Y and Lv XY. The effect of thalidomide on vascular endothelial growth factor and quality of life after interventional primary liver cancer. *Adv Mod Biomed* 2017; 17: 4928-4931.
- [15] Spagnuolo RD, Brich S, Bozzi F, Conca E, Castelli C, Tazzari M, Maestro R, Brenca M, Gualemi AV, Gloghini A, Stacchiotti S, Pierotti MA, Pillotti S and Negri T. Sunitinib-induced morphofunctional changes and drug effectiveness in malignant solitary fibrous tumours. *Oncotarget* 2016; 7: 45015-45026.
- [16] Yang XN and Wu YL. Evaluation criteria for therapeutic efficacy of solid tumors-recist. *Evidence-Based Med* 2004; 4: 85-90, 111.
- [17] Huang WK, Yang SF, You LN, Liu M, Liu DY, Gu P and Fan XW. Transcatheter arterial chemoembolisation (TACE) plus S-1 for the treatment of BCLC Stage B hepatocellular carcinoma refractory to TACE. *Contemp Oncol (Pozn)* 2016; 20: 468-474.
- [18] Tohme S, Chidi AP, Sud V and Tsung A. Prognostic nutritional index is associated with survival in patients with unresectable hepatocellular carcinoma treated with radioembolization. *J Vasc Interv Radiol* 2017; 28: 470-472.
- [19] Poluzzi C, Iozzo RV and Schaefer L. Endostatin and endorepellin: a common route of action for similar angiostatic cancer avengers. *Adv Drug Deliv Rev* 2016; 97: 156-173.
- [20] Zhang S, Tang D, Zang W, Yin G, Dai JG, Sun YU, Yang ZJ, Hoffman RM and Guo XX. Synergistic inhibitory effect of traditional Chinese medicine astragaloside IV and curcumin on tumor growth and angiogenesis in an orthotopic nude-mouse model of human hepatocellular carcinoma. *Anticancer Res* 2017; 37: 465-473.
- [21] El-Raggal NM, El-Farrash RA, Saad AA, Attia EAS, Saafan HA and Shaaban IS. Circulating levels of vascular endothelial growth factor and basic fibroblastic growth factor in infantile hemangioma versus vascular malformations. *Clin Appl Thromb Hemost* 2017; 24: 663-668.
- [22] Zhang JQ, Song HL, Lu YQ, Chen HY, Jiang S and Li LL. Effects of Estradiol on VEGF and bFGF by Akt in endometrial cancer cells are mediated through the NF- κ B pathway. *Oncol Rep* 2016; 36: 705-714.
- [23] Decourt B, Drumm-Gurnee D, Wilson J, Jacobson S, Belden C, Sirrel S, Ahmadi M, Shill H, Powell J, Walker A, Gonzales A, Macias M and Sabbagh MN. Poor safety and tolerability hamper reaching a potentially therapeutic dose in the use of thalidomide for Alzheimer's disease: results from a double-blind, placebo-controlled trial. *Curr Alzheimer Res* 2017; 14: 403-411.
- [24] Raturi R, Patel AA and Carter JD. Two cases demonstrating thalidomide's efficacy in refractory lupus nephritis. *Clin Rheumatol* 2017; 36: 725-728.
- [25] Tokida H, Kanaya Y, Shimoe Y, Yamori S, Tagawa K and Kuriyama M. Lateral geniculate body presenting only hemorrhage homonymous hemianopia—a case report. *Rinsho Shinkeigaku* 2016; 56: 781-784.