Original Article

Impact of Serum Vascular Endothelial Growth Factor on Prognosis in Patients with Unresectable Hepatocellular Carcinoma after Transarterial Chemoembolization

Jian-hai Guo*, Xu Zhu*, Xiao-ting Li, Ren-jie Yang**

Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Interventional Therapy, Peking University School of Oncology, Beijing Cancer Hospital & Institute, Beijing 100142, China

DOI: 10.1007/s11670-012-0036-8

ABSTRACT

Objective: To investigate the expression level of serum vascular endothelial growth factor (VEGF) in patients with unresectable hepatocellular carcinoma (HCC) and its relationship with the clinicopathological characteristics, and to assess the impact of serum VEGF as a predictive factor for HCC prognosis during transarterial chemoembolization (TACE) treatments.

Methods: Serum VEGF levels were measured using enzyme-linked immunosorbent assay (ELISA) in 60 random patients who underwent TACE or transarterial infusion (TAI) for unresectable HCC between May and September 2008 and 12 healthy volunteers were also involved in this study to serve as control. All patients' clinicopathological features were retrospectively analyzed. Serum VEGF levels were correlated with clinicopathological features of the HCC patients. The patients' survival rates were analyzed with Kaplan-Meier survival curves and compared by the log-rank test. The prognostic significance of serum VEGF levels and factors related to survival rate were evaluated by univariate and multivariate analysis.

Results: The median serum VEGF level in the HCC patients was 285 pg/ml (range 14–1,207 pg/ml), significantly higher than that of healthy controls (P=0.021). The serum VEGF levels were significantly correlated with platelet counts (r=0.396, P=0.002) but not other clinicopathological features. Patients with serum VEGF level >285 pg/ml had worse overall survival compared with those with serum VEGF level <285 pg/ml (P=0.002). By multivariate analysis, the serum VEGF level was a significant prognostic factor.

Conclusion: High serum VEGF levels may predict poor prognosis of HCC after TACE. This study highlights the importance of tumor biomarker as a prognostic predictor in TACE therapy for HCC, which has an intrinsic problem of unavailability of histopathological prognostic features.

Key words: Hepatocellular carcinoma; Vascular endothelial growth factor; TACE; ELISA

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, which cause approximately 600,000 to 1,000,000 deaths annually[1]. It has been the second cancer killer in China since 1990s. As the disease is often advanced at the first manifestation, there is a 5-year survival rate of less than 5% without treatment. Surgical resection and liver transplantation are the only potentially curative therapies. However, only few patients (11.9%–30.1%) at clinical presentation of tumors are suitable candidates for surgery because of multicentricity or poor hepatic functional reserve due to pre-existing cirrhosis. In clinical practice, therefore, transarterial chemoembolization (TACE) or transarterial embolization (TAE) is considered standard palliative treatment[2-4]. However, TACE or TAE, as all currently available systemic options for HCC therapy, usually induce only short-termed disease stabilizations in majority of the patients, early identification of potential treatment responders would be useful to both oncologists and patients.

Received 2011–07–15; **Accepted** 2011–12–09
This work was supported by National Science & Technology Major Project of China (No. 2008ZX10002-026).
*Contributed equally to this study.
**Corresponding author.
E-mail: renjieyang2007@163.com

Current determination of survival and prognosis in patients treated with TACE or TAE for unresectable HCC is mainly based on clinical assessment. Serum alpha-fetoprotein (AFP) as a well accepted tumor marker is only expressed by 60% of our patients. Thus, for more than one-third of the patients, AFP could not be linked to prognosis. Apart from well-known clinical factors related to tumor stage or liver function, remarkably few data are available upon other measurable prognostic or predictive factors for TACE or TAE treatment response in HCC.

Because HCC is a highly vascular tumor, it has been studied screening patients for markers of increased angiogenesis, which may be detected even before HCC, is clinically significant. Vascular endothelial growth factor (VEGF) has successfully been correlated with stimulation of angiogenesis and does therefore reflect functional tumor activity, which is otherwise often difficult to be assessed by conventional imaging modalities[5]. Tumor expression of VEGF has been shown to be related to microscopic venous invasion, metastasis spread and poor prognosis of HCC[6-8]. The elevation of VEGF in blood implies a promotion of tumor angiogenesis, and several studies have shown that high serum VEGF levels predicted poor survival results independent of clinicopathological features in patients with various types of cancer undergoing resection or receiving chemotherapy[9-11]. In this prospective study, we analyzed the serum VEGF levels in patients with HCC prior to TACE to determine the clinicopathological significance of VEGF, and to assess the clinical usefulness of VEGF as a predictor of outcome in patients undergoing TACE therapy for HCC.

MATERIALS AND METHODS

Patients

Between May and September 2008, serum VEGF levels were measured using enzyme-linked immunosorbent assay (ELISA) in 60 random patients with diagnosed HCC undergoing at least one course of TACE or transarterial infusion (TAI) in Beijing Cancer Hospital. Diagnosis was based on histological or cytological examination by ultrasound guided biopsy for 28 patients. For the remaining 32 patients, diagnosis was based on the guidelines of American Association for the Study of Liver Diseases (AASLD) criteria. Indications for TACE or TAI were: (1) patient's refusal resection; (2) unresectable tumors because of multicentricity, topography conditions or poor hepatic functional reserve; (3) positive margin or vascular invasion; (4) recurrence after resection or locoregional therapy [i.e. radiofrequency ablation (RFA)]; and (5) persistent high AFP level after hepatectomy. Exclusion criteria for treatment were poor liver function, portal obstruction of at least three segmental branches, advanced cardiac or pulmonary disease and severe renal function impairment.

Of the 60 patients, 27 patients did not undergo TACE or TAI before blood collection, the remaining 33 patients underwent at least one course of TACE or TAI before blood collection. Each patient's disease was staged using Barcelona Clinic Liver Cancer's (BCLC) scheme: 17 patients had Stage A, 28 Stage B, and 15 Stage C tumors. To determine the severity of underlying cirrhosis, the Child-Pugh classification was used: 51 patients had Child's A class cirrhosis and 9 Child's B class. The type of the tumor was considered as paucifocal with no more than three distinct lesions, and as multifocal with more than three lesions and infiltrated or diffused nonfocal lesions. Of the 12 patients after resection, 9 patients received TACE because of HCC recurrence, and 3 patients received TAI because of HCC vascular invasion. Two patients received TACE because of HCC recurrence after RFA.

The study was approved by the institutional review board of the hospital and conducted according to the standards of the Declaration of Helsinki, and informed written consent was obtained from all patients before their treatment.

TACE Procedure

The chemoembolization procedure consisted of injecting iodized oil (Lipiodol; Laboratoire Andre Guerbet, Aulnaysous-Bois, France) mixed with epirubicin hydrochloride (20–60 mg; Main Luck Pharmaceutical, Shenzhen, China) as an emulsion into segmental or subsegmental tumor-feeding arteries. Sometimes subsequent embolization was obtained by using Spongostan particles (Jinling, Nanjing, China) as an alternative in some cases. For those with hepatic arteriovenous fistula, Spongostan particles were used to block the fistula before iodized oil was used. Before or after iodized oil embolization, two to three chemotherapeutic regimens of 5-fluorouracil (750–1,000 mg; Xudong Haipu, Shanghai, China), cisplatin (50–100 mg; Keding, Nanjing, China) or carboplatin (200–300 mg; Qilu, Jinan, China), and mitomycin (8–12 mg; Kyowa Hakko Kogyo, Tokyo, Japan) were diluted in 50–100 ml sodium chloride solution or glucose injection and infused through the catheter. The TAI procedure was adopted when the tumor mass was too superficial, and the arterial anatomy precluded a super selective injection, or when significant arteriovenous fistulas or intrahepatic portal thrombosis presented. In each case, the decision to repeat TACE or TAI was based on computed