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HIF-1α and VEGF levels for monitoring hepatocellular carcinoma treatment response to transcatheter arterial chemoembolization

Kang Liu[1,2], Lin Yang[2], Xiao-Ming Zhang[2], Yi Zhou[2], Tao Zhu[3], Nan-Dong Miao[2], Yong-Jun Ren[2], Hao Xu[2], Xu-Li Min[2], Juan Peng[2], Ke Yang[2], Shi Yang[2]

[1]Department of Pain Management, Xianyang Hospital of Yan'an University, Xianyang 712000, China; [2]Sichuan Key Laboratory of Medical Imaging, Department of Radiology, Affiliated Hospital of North Sichuan Medical College, Nanchong 637000, China; [3]Department of Preventive Medicine, North Sichuan Medical College, Nanchong 637000, China

Contributions: (I) Conception and design: K Liu, L Yang; (II) Administrative support: K Liu; (III) Provision of study materials or patients: ND Miao, YJ Ren, H Xu; (IV) Collection and assembly of data: K Liu, H Xu, XL Min, J Peng, K Yang, S Yang; (V) Data analysis and interpretation: K Liu, T Zhu, L Yang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Lin Yang, MD. Sichuan Key Laboratory of Medical Imaging, Department of Radiology, Affiliated Hospital of North Sichuan Medical College, Nanchong 637000, China. Email: linyangmd@163.com.

Background: The purpose of the present study was to investigate the use of hypoxia-inducible factor-1 alpha (HIF-1α) and vascular endothelial growth factor (VEGF) levels to monitor the treatment response to transcatheter arterial chemoembolization (TACE) in hepatocellular carcinoma (HCC).

Methods: A total of 41 consecutive HCC patients underwent TACE were enrolled into this study. The serum levels of HIF-1α and VEGF were measured using enzyme-linked immunosorbent assays (ELISAs) 1 day before, and 1, 7 and 28 days after TACE therapy. The overall tumor response was evaluated according to the modified Response Evaluation Criteria in Solid Tumors criteria. Patients with a complete response or partial response comprised the responding group, whereas those with stable disease or progressive disease comprised the non-responding group. The differences in serum HIF-1α and VEGF levels before and after TACE therapy were subjected to analysis of nonparametric test, while correlations between serum HIF-1α and VEGF levels were examined using Pearson's correlation analysis. Receiver-operating characteristic (ROC) curve was applied to analyze the evaluation value of factors for the response of TACE on the treatment of HCC. $P<0.05$ was considered statistically significant.

Results: In the present study, the serum levels of HIF-1α correlated positively with the serum levels of VEGF 1 day before TACE ($r=0.546$, $P=0.000$). The levels of HIF-1α and VEGF 1 day before, and 1, 7 and 28 days after TACE were significantly different, respectively ($\chi^2=90.688$, $P=0.000$ and $\chi^2=45.585$, $P=0.000$). The levels of the HIF-1α and VEGF increased markedly on day 1 and 7 after TACE and recovered to the pre-TACE level on day 28 after TACE. The levels of serum VEGF in responder group 28 days after TACE were significantly lower than those in non-responder group ($Z=2.774$, $P=0.006$), but the difference of HIF-1α levels between the two groups was not significant ($Z=1.905$, $P=0.057$). ROC curve analysis indicated that the sensitivity and specificity were 76.9% and 78.6%, when the threshold value was set at VEGF =254.5 pg/mL for predicting the response of TACE in patients with HCC; the corresponding area under the curve (AUC) was 0.772, respectively.

Conclusions: The levels of both HIF-1α and VEGF in patients with HCC after TACE exhibit dynamic changes. However, HIF-1α and VEGF may be insufficient for predicting tumor response to TACE treatment.

Keywords: Liver; cancer; chemoembolization; angiogenesis; treatment response

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common human malignancies. Because of the insidious pathogenesis of HCC, most patients with HCC are already in advanced stages when seeking treatment and have lost the opportunity for surgical resection. Transcatheter arterial chemoembolization (TACE) is the most common treatment option in HCC patients who cannot receive potentially curative therapies such as resection and transplantation. Chemoembolization for HCC has been proven to be useful in local tumor control, to prevent tumor progression, prolong patients' life and control patient symptoms (1-6). However, the long-term efficacy of TACE therapy against HCC is far from ideal. Tumor angiogenesis of the residual disease is one of the important factors that affect the efficacy of TACE in the treatment of HCC (7-10). There is ample evidence that tumor angiogenesis is the pathological basis of and a necessary condition for solid tumor growth and metastasis (11-13). Among the many regulatory factors in tumor angiogenesis, hypoxia-inducible factor-1 alpha (HIF-lα) and vascular endothelial growth factor (VEGF) are the key inducing factors of tumor angiogenesis and are involved in all stages of the process (14-18). Some researchers have studied the changes in VEGF expression that occurred in patients with HCC after TACE (19-26); however, few studies addressed the dynamic changes in the serum levels of HIF-1α that occur in patients with HCC after TACE. This prospective study aimed to assess the dynamic changes in the serum levels of both HIF-1α and VEGF in HCC patients after TACE and to determine whether the levels of the above-listed factors change in response to TACE. In addition, the correlation between HIF-1α and VEGF was also analyzed.

Methods

Clinical data

This study was approved by our institutional review board, and patient informed consent was obtained. A total of 41 HCC patients were selected, including 36 males and 5 females. All cases were confirmed by percutaneous biopsy or typical imaging findings (dynamic enhanced computed tomography or magnetic resonance imaging) for HCC associated with a pathological increase of serum alpha-fetoprotein (AFP) levels. The ages of the patients ranged from 26 to 69 years (mean age 52.6±11.1 years). All of the patients in this group cannot receive surgical resection. None of the patients received any other anti-tumor therapy prior to the TACE procedure. Four weeks after TACE treatments, the overall tumor response was evaluated according to the modified Response Evaluation Criteria in Solid Tumors criteria (27). Patients with a complete response (CR) or partial response (PR) comprised the responding group, whereas those with stable disease (SD) or progressive disease (PD) comprised the non-responding group.

TACE procedure

In 41 patients, the chemoembolization procedure was conducted according to the method reported in our previous study (28). After diagnostic digital subtraction angiography and superselective catheterization, TACE was performed by administration of 5-fluorouracil (1,000 to 1,500 mg) and hydroxycamptothecine (30 to 40 mg), followed by lipiodol (3 to 20 mL) with adriamycin (40 to 50 mg) emulsion and gelfoam particles. The volume of embolus was determined by taking into account the hepatic functional indices, the diameter of the lesion and the vascularity of the tumor.

Biomarker assessment

Fasting peripheral venous blood samples (4 mL) were collected from each patient in the morning 1 day prior to the TACE procedure, as well as 1, 7 and 28 days after the TACE treatment. The blood samples were placed in sterile tubes and allowed to stand for 30–60 min. The blood samples were then centrifuged at 3,000 r/min for 15 min. After centrifugation, serum was collected and stored in a –80 ℃ freezer for future assays. Serum HIF-1α and VEGF levels were determined using enzyme-linked immunosorbent assays (ELISAs) [human total HIF-lα Elisa kit (DYC1935-2), human VEGF Elisa kit (DVE00); R & D Systems, Inc., Minneapolis, MN 55413, USA].

Statistical methods

Serum HIF-1α and VEGF levels were statistically analyzed using SPSS 21.0 statistical software (SPSS Inc., Chicago, Illinois, USA). In the statistical analysis, values of serum HIF-1α and VEGF levels were expressed as median, first and third quartiles. The differences in serum HIF-1α and VEGF levels before and after TACE therapy were subjected to analysis of nonparametric test, while correlations were examined using Pearson's correlation analysis. Receiver-

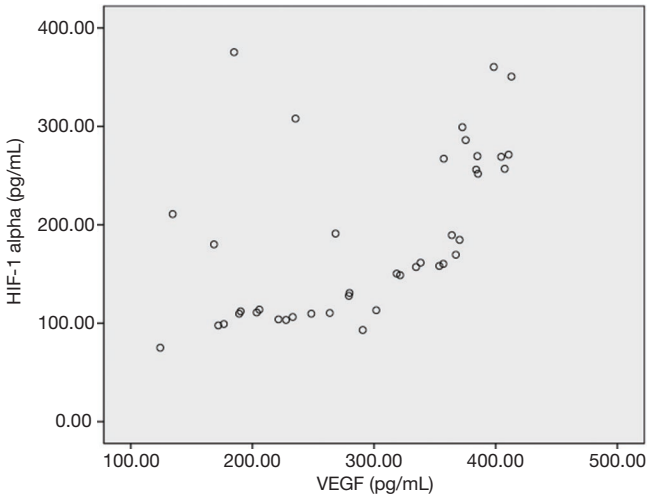

Figure 1 Scatter plot showing the correlation between serum HIF-1α levels and VEGF levels pre-TACE in HCC patients. Serum HIF-1α levels correlated positively with VEGF levels. HIF-1α, hypoxia-inducible factor-1 alpha; VEGF, vascular endothelial growth factor; TACE, transcatheter arterial chemoembolization; HCC, hepatocellular carcinoma.

operating characteristic (ROC) curve was applied to analyze the evaluation value of the factors for the response of TACE on the treatment of HCC. P<0.05 was considered statistically significant.

Results

Preoperative AFP was positive in 31 subjects (75.6%) and negative in 10 subjects (24.4%). HBsAg (+) occurred in 38 subjects (92.7%) and HBsAg (–) occurred in 3 subjects (7.3%). Liver function in the HCC patients was evaluated using the Child-Pugh grading scale. Twenty-nine patients (70.7%) were classified as Child-Pugh grade A, while 12 patients (29.3%) were classified as Child-Pugh grade B. All patients' diseases were staged using Barcelona Clinic Liver Cancer's (BCLC) scheme: 32 patients (78.0%) had stage B, and 9 patients (22.0%) had stage C tumors. Nine patients (22.0%) were confirmed with presence of portal vein invasion, and 5 patients (12.2%) were confirmed with presence of metastasis. Sixteen subjects (39.0%) had an intact capsule and 25 subjects (61.0%) had no capsule or infiltration. The maximum tumor diameters ranged from 4.1 to 13.2 cm (mean 7.2±3.7 cm).

After treatment, PR was achieved in 13 patients (31.7%), SD was achieved in 18 patients (43.9%), and PD was achieved in 10 patients (24.4%), none of the patients achieved CR. The serum levels of HIF-1α correlated positively with the serum levels of VEGF 1 day before TACE (r=0.546, P=0.000) (*Figure 1*). The levels of HIF-1α and VEGF 1 day before, and 1, 7 and 28 days after TACE were significantly different, respectively (χ^2=90.688, P=0.000 and χ^2=45.585, P=0.000). The levels of the HIF-1α and VEGF increased markedly on day 1 and 7 after TACE and recovered to the pre-TACE level on day 28 after TACE (*Table 1*, *Figure 2*). The levels of serum VEGF in responder group 28 days after TACE were significantly lower than those in non-responder group (Z=2.774, P=0.006), but the difference of HIF-1α levels between the two groups was not significant (Z=1.905, P=0.057) (*Figure 3*, *Table 2*). ROC curve analysis indicated that the sensitivity and specificity were 76.9% and 78.6%, when the threshold value was set at VEGF =254.5 pg/mL for predicting the response of TACE in patients with HCC; the corresponding area under the curve (AUC) was 0.772, respectively.

Discussion

Tumor angiogenesis is closely related to the development, progression and metastasis of solid tumors. Among the numerous angiogenesis-related factors, HIF-1α and VEGF have attracted considerable attention due to their key roles in promoting angiogenesis. HIF-1α is overexpressed under hypoxic conditions, which induces the transcription of the VEGF gene and upregulates the expression of VEGF and its receptor, thereby promoting tumor angiogenesis (29-31). The cognate DNA recognition site of HIF-1α is hypoxia response element (HRE). The binding of HIF-1α to HRE in the VEGF promoter is a predominant enhancer of VEGF production (29,30). VEGF was reported to promote angiogenesis by inducing migration and proliferation of endothelial cells. VEGF protein binds to VEGF receptors on endothelial cells, and these mediate its physiological functions (29,30).

In recent years, some scholars investigated the post-TACE changes in serum VEGF levels that occur in patients with HCC and explored the significance of those changes in evaluating the response to TACE therapy (19-26). Li *et al.* (19) measured plasma VEGF levels in 45 HCC patients prior to TACE therapy and 1, 3, 7 days and 1 month after TACE therapy. The results showed that the plasma VEGF level was significantly higher in patients with HCC than in patients with benign lesions and healthy volunteers. In addition, plasma VEGF levels were drastically increased

Table 1 Comparison of serum HIF-1α and VEGF levels in HCC patients before and after TACE therapy

Indicators	1 day before TACE therapy	1 day after TACE therapy	7 days after TACE therapy	28 days after TACE therapy	χ^2	P
HIF-1α (pg/mL)	160.3 (110.7–262.1)[a]	452.4 (401.5–577.5)[b]	245.9 (210.4–350.7)[c]	170.3 (137.0–194.3)[a]	90.688	0.000
VEGF (pg/mL)	301.8 (213.6–371.5)[a]	428.6 (387.4–475.4)[b]	378.3 (345.3–435.4)[c]	272.6 (235.4–323.5)[a]	45.585	0.000

Different letters at the upper right corner of the numbers indicate that statistically significant differences existed between the groups (all P<0.05). TACE, transcatheter arterial chemoembolization; HIF-1α, hypoxia-inducible factor-1 alpha; VEGF, vascular endothelial growth factor; HCC, hepatocellular carcinoma.

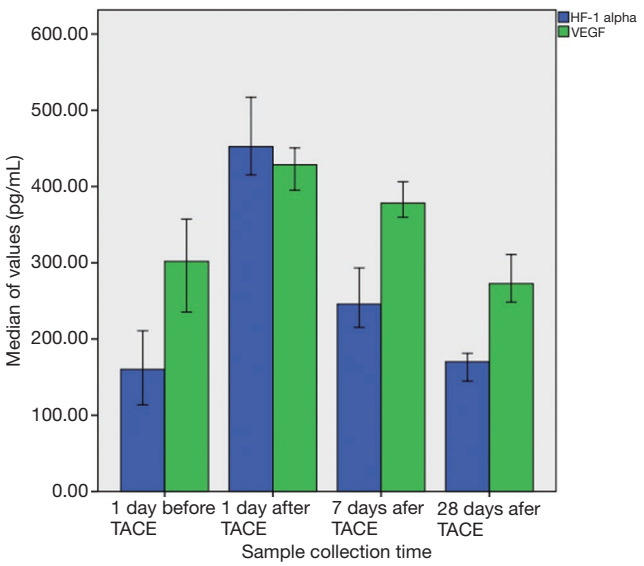

Figure 2 Bar graph showing the changes in serum HIF-1α and VEGF levels that occurred in HCC patients before and after TACE therapy. Serum levels of HIF-1α and VEGF rose to a peak value at 1 day after TACE therapy and then decreased markedly by 7 days after TACE therapy. However, serum HIF-1α and VEGF levels remained significantly higher at 7 days after TACE therapy than the serum HIF-1α and VEGF levels observed prior to TACE therapy. At 28 days after TACE therapy, serum HIF-1α and VEGF returned to the pre-TACE level. HIF-1α, hypoxia-inducible factor-1 alpha; VEGF, vascular endothelial growth factor; TACE, transcatheter arterial chemoembolization; HCC, hepatocellular carcinoma.

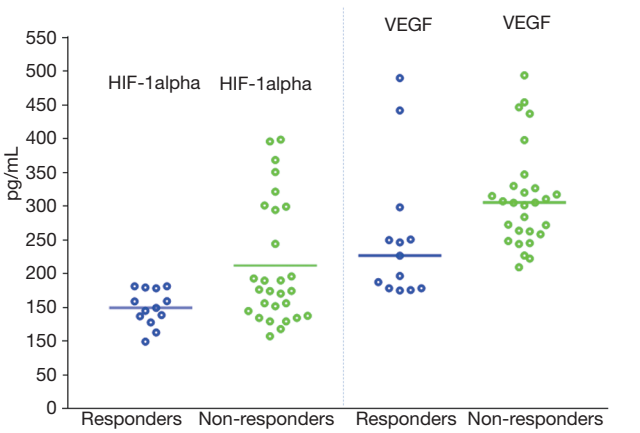

Figure 3 Scatter plot shows the differences in serum HIF-1α and VEGF levels between responder group and non-responder group. The levels of VEGF in responder group 28 days after TACE were significantly lower than those in non-responder group, but the difference of HIF-1α levels between the two groups was not significant. In addition, the values of responders and non-responders overlap. HIF-1α, hypoxia-inducible factor-1 alpha; VEGF, vascular endothelial growth factor; TACE, transcatheter arterial chemoembolization.

in HCC patients after TACE therapy. Plasma VEGF levels reached a peak value on the first day after therapy and then decreased gradually. Moreover, VEGF levels were related to therapeutic efficacy; TACE yielded better therapeutic efficacy in patients with low pre-TACE levels of VEGF, whereas TACE was less effective in patients with high pre-TACE levels of VEGF. Many other studies revealed similar dynamic changes in VEGF levels in patients with HCC after TACE therapy (20-26).

However, a number of studies yielded results that are not entirely consistent with the above findings (32,33). For example, Suzuki *et al.* (32) reported that in a group of 38 patients with HCC, VEGF levels did not increase until 1 week after TACE therapy. Chao *et al.* (33) examined post-TACE VEGF levels in 41 patients with HCC. Those authors found that VEGF levels increased even more slowly and reached a peak value 14 days after TACE therapy.

To date, few studies have focused on the dynamic changes in serum HIF-1α levels that occur in patients with HCC after TACE therapy, and the use of HIF-1α and VEGF levels to monitor the treatment response to TACE in HCC.

Table 2 Comparison of serum HIF-1α and VEGF levels 28 days after TACE between responders and non-responders

Indicators	Responding group	Non-responding group	Z	P
HIF-1α (pg/mL)	149.1 (132.2–178.9)	175.4 (139.1–298.2)	1.905	0.057
VEGF (pg/mL)	226.7 (178.3–274.5)	305.3 (259.5–329.3)	2.774	0.006

TACE, transcatheter arterial chemoembolization; HIF-1α, hypoxia-inducible factor-1 alpha; VEGF, vascular endothelial growth factor.

Jia *et al.* (34) performed ELISA to examine the changes in the expression of HIF-1α and VEGF in 40 patients with primary liver cancer (PLC) before and after TACE therapy. The results showed that serum HIF-1α and VEGF levels in patients with PLC rose significantly to a peak at 1 day after TACE therapy. Serum HIF-1α and VEGF levels were then markedly reduced 1 week after TACE therapy and remained higher than the pre-TACE levels. The present study simultaneously explored the dynamic changes in serum HIF-1α and VEGF levels that occur in HCC patients who received TACE therapy. The results showed that serum HIF-1α and VEGF levels in HCC patients both rose to peak values at 1 day after TACE therapy. The serum HIF-1α and VEGF levels then decreased gradually and finally returned to pre-TACE levels 28 days after TACE therapy. The levels of VEGF in responding group 28 days after TACE were significantly lower than those in non-responding group, but the difference of HIF-1α levels between the two groups was not significant. In addition, the values of responders and non-responders overlap.

The present study has the following limitations: first, the sample size was rather small; second, the serum levels of HIF-1α and VEGF in patients with HCC after TACE will changes dynamically at different times; however, in this experiment, the serum levels of HIF-1α and VEGF only detected 1, 7 and 28 days after TACE therapy, with no analysis of serum levels of HIF-1α and VEGF during other periods. Another limitation is that the relationship between the observed changes in HIF-1α and VEGF levels after TACE therapy and prognosis was not investigated in the HCC patients. In further studies, an increased number of medical cases should be examined and more time points should be selected to analyze serum HIF-1α and VEGF levels. In addition, the prognosis of the patients should be followed up. Hence, a deep understanding of the dynamic changes in HIF-1α and VEGF levels that occur in patients with HCC after TACE therapy and the relationship between those changes and prognosis could be achieved.

In summary, our results indicated that in patients with HCC, serum levels of HIF-1α and VEGF demonstrated dynamic changes after TACE therapy, first increasing and then decreasing. However, HIF-1α and VEGF may be insufficient for predicting tumor response to TACE treatment. As previous studies have shown that imaging examination play an important role in evaluating tumor treatment response (28,35-42). Therefore, for a specific individual, serum HIF-1α and VEGF changes combined with imaging changes are more conducive to accurately evaluate the TACE treatment response.

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Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Yì-Xiáng J. Wáng, Yong Wang) for the series "Translational Imaging in Cancer Patient Care" published in *Translational Cancer Research*. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2017.08.32). The series "Translational Imaging in Cancer Patient Care" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Affiliated Hospital of North Sichuan Medical College (No. ER2017A0213), and patient informed consent was obtained.

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