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Changes of tryptase in patients with hepatocellular carcinoma after transarterial chemoembolization

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Background: To explore the dynamic changes of tryptase in hepatocellular carcinoma (HCC) after transarterial chemoembolization (TACE) treatment and to determine whether the tryptase level changes in response to TACE.

Methods: The serum levels of tryptase were detected in 40 patients with HCC 1 day prior to TACE procedure, as well as 1, 7, and 28 days after TACE treatment by using enzyme-linked immune-sorbent assays (ELISAs). The difference in serum tryptase levels before and after chemoembolization therapy was examined using analysis of variance. A *t*-test was performed for comparisons between two response groups.

Results: The levels of tryptase in this group 1 day before TACE, and 1, 7 and 28 days after TACE were 4.85±2.46, 3.32±1.76, 3.15±1.67 and 4.85±2.50 ng/mL, respectively. The tryptase levels before and after TACE treatment were significantly different (F=48.461, P=0.000). The levels of tryptase decreased markedly on day 1 and 7 after TACE and were recovered to the pre-TACE level on day 28 after TACE. Partial response (PR), stable disease (SD) and progressive disease (PD) were observed in 13 (32.5%), 12 (30.0%) and 15 (37.5%) patients, respectively; none of the patients achieved a complete response (CR). The serum levels of tryptase in responsive group (CR + PR) were significantly lower than those in non-responsive group (SD + PD) 28 days after TACE (3.54±1.16 *vs.* 5.48±2.74 ng/mL, respectively; t=2.426, P=0.020).

Conclusions: The level of serum tryptase in patients with HCC after TACE shows a dynamic change that may be used to evaluate the response to TACE.

Keywords: Hepatocellular carcinoma (HCC); transarterial chemoembolization (TACE); tryptase; angiogenesis; treatment response

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in the world (1). Because of the typically advanced nature of the occult disease at the time of diagnosis, the majority of patients with HCC have no chance to accept surgical resection. Transarterial chemoembolization (TACE) can improve the quality of life and survival time of patients with HCC (2-7). At present, TACE has become the main therapeutic method for patients with HCC without the option for surgical resection. However, tumor angiogenesis of residual lesions seriously

affects the efficacy of TACE in the locoregional treatment of HCC (8-11). A variety of studies have demonstrated the classical regulatory factors and the vital inducing factors involved in all stages of tumor angiogenesis; changes in the expression of these factors after TACE treatment for HCC were also observed (8-14). In recent years, a few studies have shown that tryptase released by mast cells (MCs) correlates with tumor angiogenesis in several types of malignancies (15-27); however, few studies have addressed the dynamic changes of tryptase after TACE and the use of monitoring the treatment response to TACE in HCC patients. Therefore, the present study aimed to detect the serum tryptase levels in patients with HCC 1 day before and 1, 7 and 28 days after TACE to explore the dynamic changes of tryptase in HCC after TACE treatment and to determine whether the tryptase level changes in response to TACE.

Methods

Clinical data

During the period from October 2013 to November 2014, a total of 40 HCC patients were selected, including 36 males and 4 females. All cases were confirmed by percutaneous liver biopsy or typical imaging findings (dynamic enhanced computed tomography or magnetic resonance imaging) for HCC associated with a pathological increase of serum alpha-fetoprotein levels. The ages of the patients ranged from 35 to 70 years (mean age 56.3±9.9 years). None of the patients received any other anti-tumor therapy prior to the TACE procedure. Four weeks after chemoembolization procedure, the overall tumor response was evaluated according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) (28).

TACE procedure

In 40 patients, the chemoembolization procedure was conducted according to the method reported in our previous study (29). A 5-F RH angiographic catheter (Terumo Corporation, 44-1, 2-Chome, Hatagaya, Shibuya-ku, Tokyo 151-0072, Japan) was placed in the common or proper hepatic artery for diagnostic arteriography. Following the superselective catheterization procedure with a microcatheter (3F SP microcatheter, Terumo Corporation, 44-1, 2-Chome, Hatagaya, Shibuya-ku, Tokyo 151-0072, Japan), TACE was performed by the administration of 5-fluorouracil (1,000 mg) and hydroxycamptothecine (30 mg), followed by lipiodol with adriamycin (50 mg) emulsion and gelfoam particles.

Experimental methods

Fasting peripheral venous blood samples (3–5 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 TACE treatment. All of the samples were placed in sterile tubes and were allowed to stand for 30–60 min. Then, the samples were centrifuged at 3,000 r/min for 15 min; the serum samples were collected and stored in a –80 ℃ freezer for future use. Tryptase levels were determined using enzyme-linked immunosorbent assays (ELISAs) according to the ELISA kit instructions.

Statistical methods

SPSS 20.0 was used to conduct the statistical analysis. The level of serum tryptase was expressed as the mean ± standard deviation. The difference in serum tryptase levels before and after chemoembolization therapy was examined using analysis of variance. A *t*-test was performed for comparisons between two response groups, $P<0.05$ was considered statistically significant.

Results

Liver function in HCC patients was evaluated using the Child-Pugh grading scale. Twenty-nine patients (72.5%) were classified as Child-Pugh grade A, while 11 patients (27.5%) were classified as Child-Pugh grade B. The levels of tryptase in this group 1 day before TACE, and 1, 7 and 28 days after TACE were 4.85±2.46, 3.32±1.76, 3.15±1.67 and 4.85±2.50 ng/mL, respectively. The tryptase levels before and after TACE treatment were significantly different ($F=48.461$, $P=0.000$) (*Figure 1*). The levels of tryptase decreased markedly on day 1 and 7 after TACE and were recovered to the pre-TACE level on day 28 after TACE. Partial response (PR), stable disease (SD) and progressive disease (PD) were observed in 13 (32.5%), 12 (30.0%) and 15 (37.5%) patients, respectively; none of the patients achieved a complete response (CR). Patients with CR + PR constituted the responsive group, and patients with SD + PD constituted the non-responsive group. The serum levels of tryptase in responsive group were significantly lower

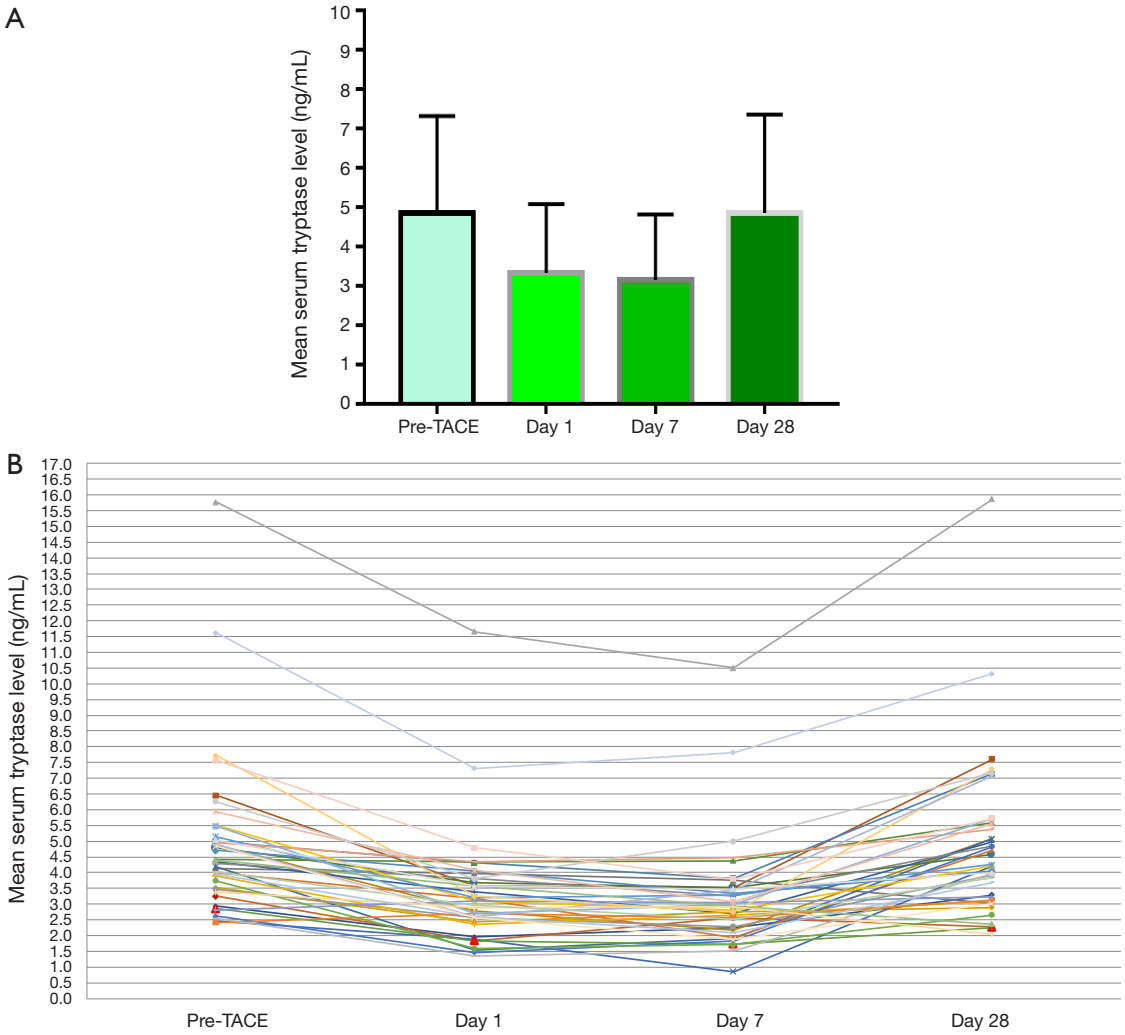

Figure 1 Changes in tryptase level that occurred in HCC patients before and after TACE therapy. (A) Mean and standard deviation of all patients; (B) dynamic change of individual patients. Serum levels of tryptase decreased 1 and 7 days after TACE therapy. At day 28 after TACE therapy, serum tryptase returned to the pre-TACE levels. HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization.

than those in non-responsive group 28 days after TACE (3.54±1.16 *vs.* 5.48±2.74 ng/mL, respectively; t=2.426, P=0.020) (*Figure 2*).

Discussion

The normal liver receives a dual supply of blood from both the portal vein and the hepatic artery. The portal vein is responsible for 80% of the blood supply to normal liver tissue. In contrast, the blood supply to hepatic tumors is mainly delivered by the hepatic artery. TACE involves both anti-cancer chemotherapy and embolization of tumor-feeding arteries. Recently, the Barcelona Clinic Liver Cancer (BCLC) classification emerged as the standard classification system for the clinical management of patients with HCC. According to this staging system, TACE is recommended as standard therapy for patients with intermediate-stage HCC (B stage of BCLC staging criteria) (4,30,31).

Previous research has shown that MCs are present in both normal and pathological livers (32-36). MC density is highly correlated with angiogenesis in chronic inflammatory diseases and tumors (37-41). Human MCs are categorized into those positive only for tryptase and those positive for both tryptase and chymase, and tryptase appears to play a more significant role in tumor progression than chymase (42). However, the role of tryptase in tumor angiogenesis is not

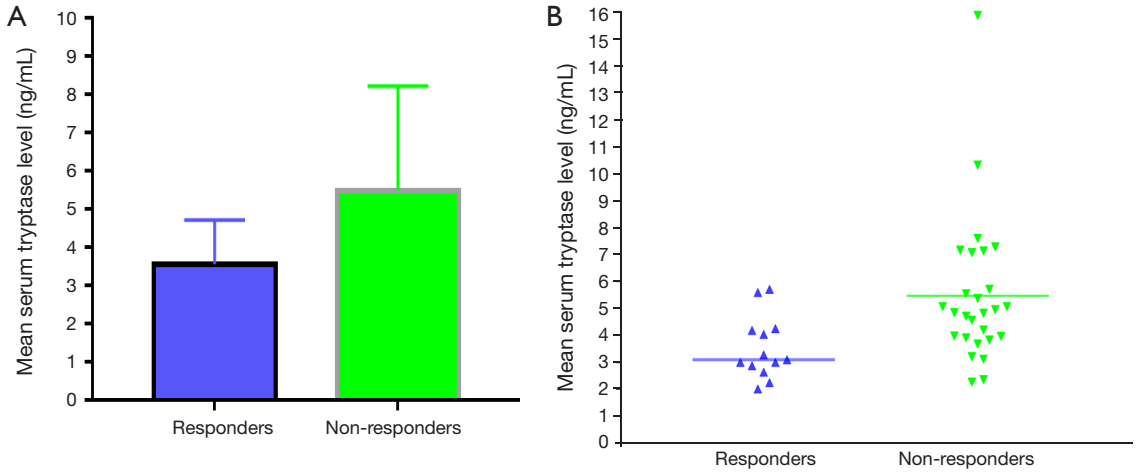

Figure 2 The difference of serum tryptase levels between responder group and non-responder group 28 days after TACE. (A) Mean and standard deviation; (B) mean and scattered plot. The mean serum level of tryptase in responder group was significantly lower than those in non-responder group. TACE, transarterial chemoembolization.

entirely clear. Previous studies have shown that tryptase may induce tumor angiogenesis through the following mechanisms (42-48). First, tryptase interacts directly with endothelial cells via an unidentified mechanism to induce angiogenesis, and second, tryptase activates latent metalloproteinases and plasminogen activator to degrade the extracellular matrix, and this degradation is critical in the early stages of angiogenesis.

The process of tumor angiogenesis is very complex. There are many factors involved in tumor angiogenesis. Vascular endothelial growth factor (VEGF), a classical angiogenesis stimulating factor, plays a key role in tumor angiogenesis (8). Bai *et al.* (49) found that addition of tryptase to human dermal microvascular endothelial cells (HDMECs) caused an obvious increase of mRNA and protein levels of VEGF and its receptors. Yang *et al.* (50) investigated the correlation between beta-tryptase and VEGF in bone marrow stromal cells in acute myeloid leukemia. They found that VEGF mRNA and protein expression was significantly up-regulated by beta-tryptase in a dose-dependent manner. These results suggest that tryptase significantly increased the expressions of VEGF. However, Ranieri *et al.* (51) evaluated serum levels of both VEGF and tryptase in 71 HCC patients. Their results demonstrated the lack of correlation between serum VEGF and tryptase levels suggesting an independent role of VEGF and tryptase in the angiogenic process.

Goffredo *et al.* (52) reported a study about the potential significance of serum tryptase in HCC patients in 2013. These authors assessed serum tryptase levels in 30 HCC patients 1 day before, and 1 day after TACE. In their study, a statistically significant difference was detected between pre- and post-TACE tryptase levels. Ranieri *et al.* (51) reported similar results. These results demonstrated that tryptase was a potential biomarker of the response to TACE treatment in HCC patients. In the present study, the serum tryptase levels decreased significantly 1 day after TACE treatment compared with those measured before TACE treatment, and the levels remained low at 7 days after TACE; however, the serum levels of tryptase in this group returned to pre-TACE levels at 28 days after TACE. Moreover, the tryptase levels in different response groups 28 days after TACE treatment were significantly different. The change in tryptase level observed 1 day after TACE was consistent with the results of Goffredo *et al.* (52) and Ranieri *et al.* (51). One possible reason for why the tryptase level decreased significantly 1 day and 7 days after TACE treatment may be that TACE causes tumor tissue ischemia and necrosis, leading to decreased numbers of MCs and less secretion of tryptase. However, TACE also causes local hypoxia and stimulates angiogenesis via VEGF expression that in turns may help residual cancer cells to survival. Thus, serum tryptase may be a surrogate indicator of the magnitude of the angiogenic process and of the presence of HCC tumor tissues (51). It may be used to evaluate therapeutic responses to TACE in combination of other serum biomarkers as well as imaging biomarkers (4,53-58).

However, the present study has several limitations. First, the number of cases was small. Second, the serum tryptase levels in patients with HCC after TACE are known to change dynamically at different times; however, in this study, the serum levels of tryptase were detected only at limited time points. Third, the relationship between tryptase and other classical tumor angiogenesis regulatory factors, such as VEGF, was not studied.

In summary, the level of serum tryptase in patients with HCC after TACE shows a dynamic change that may be used to evaluate the response to TACE.

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Footnote

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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 our institutional review board, and patient informed consent (written consent) was obtained.

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