Editorial

Transarterial chemoembolization (TACE) combined with Sorafenib is more effective than TACE for hepatocellular carcinoma with portal vein tumor thrombus

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Hepatocellular carcinoma (HCC) is one of the most common and malignant tumor with poor prognosis in the world. Most HCC patients were diagnosed in progressive stage, especially patients with portal vein tumor thrombus (PVTT), with a median survival time (MST) of 2.7 months (1). According to Barcelona Clinic Liver Cancer (BCLC) treatment guidelines, Sorafenib is recommended as the first-line treatment to HCC patients with PVTT (2). However, the effect of Sorafenib is limited. Studies have shown that the MST of patients using Sorafenib is only 5.5 months, accompanied with many side effects, and life quality of patients is non-ideal (3). While Chinese scholars have made some beneficial explorations (4,5), using transarterial chemoembolization (TACE) or transarterial chemoembolization combined with Sorafenib (TACE-S) therapy to treat HCC patients accompanied with PVTT, receiving better effects. However, due to the lack of large-sample, multi-center and prospective-study, whether TACE-S has a better effect than TACE can't perorate.

We read the paper by Zhang *et al*. (6) that published in *Oncotarget*, which compared the effectiveness and safety between TACE-S and TACE for HCC with PVTT. In this article, 1,091 patients (TACE-S =356, TACE =735) from eight high-quality retrospective studies were included in the review, and 973 patients (TACE-S =238, TACE =735) from five retrospective studies were included in the meta-analysis. In the meta-analysis of retrospective studies, the objective response rate (ORR) (OR =3.59, 95% CI: 1.74–7.39; I^2 =21%, P=0.0005) and disease control rate (DCR) (OR =4.72, 95% CI: 1.75–12.72; I^2 =56%, P=0.002) indicated that the TACE-S therapy is more effective than TACE therapy, and TACE-S significantly improved 6-month overall survival (OS) (OR =3.47, 95% CI: 2.47–4.89; I^2 =0%, P<0.00001) and 1-year OS (OR =3.10, 95% CI: 2.22–4.33; I^2 =41%, P<0.00001). In the meta-analysis of HR for OS, compared with TACE-alone therapy, the TACE-S significantly extended the survival time (HR =0.62, 95% CI: 0.51–0.75; I^2 =30%, P<0.0000). As for the adverse events (AEs), hand-foot skin reaction (HFSR) (178; 73%), diarrhea (142; 58%) and alopecia (76; 31%) are the most common, while the TACE-S group and the TACE-alone group showed no obvious difference in AEs related to TACE therapy. These results also indicated that TACE-S treating for PVTT had better outcomes in the first-order portal vein branch and lower-order portal vein branches than in the main portal vein and upper branches to superior mesenteric vein. At least, the researchers suggested

that the TACE-S is more effective than TACE for the improvement of OS, ORR, time to progression (TTP) and DCR for HCC patients with PVTT. This systematic review and meta-analysis is about TACE-S and TACE for HCC patients with PVTT. In China, HCC is the one of the most lethal cancers, clinicians and researchers of China have rich experience in diagnosis and treatments for PVTT. Thus, both the quality of the included studies and the reliability of this paper by Zhang X *et al*. are quite high. It may provide available references for the treatment of PVTT patients. Defects also resists, the lack of RCTs and prospective nature of studies included may increase the bias, and the further bias test may need to make this article more convinced.

A lot of articles about TACE-S and TACE for HCC patients with PVTT have been reported, and most of them are from Asian countries. In an article (7) published in 2014, Zhu *et al*. retrospectively evaluated a total 91 HCC patients with PVTT who underwent TACE-S or TACE from January 2010 to December 2012. They found that TACE-S group (n=46) showed significant survival benefits compared with TACE group (n=45), especially patients with type B (median survival, 13 *vs.* 6 months; P=0.002) or type C (median survival, 15 *vs.* 10 months; P=0.003) PVTT, and the median TTP for TACE-S group (6.0 months, 95% CI: 4.9–7.1) was 3.0 months longer than for the TACE group (3.0 months, 95% CI: 2.2–3.8), the survival rate for group (6 months, 82.6%; 1 year, 60%) was better than TACE group (6 months, 45.7%; 1 year, 17.8%). In another article, Wang *et al*. (8) compared the effectiveness of TACE (n=604) and TACE-S (n=113) for each subtype of PVTT based on Cheng's Classification, the MST for patients after TACE-S (n=113) for type I, II, and III patients (95% CI) were 12.0 (6.6–17.4), 8.9 (6.7–11.1), and 7.0 (3.0–10.9) months, respectively; for TACE (n=604), 9.3 (5.6–12.9), 4.9 (4.1–5.7), and 4.0 (3.1–4.9) months respectively; the 6-month and 1-year survival rates were 67.88% *vs*. 41.56%, 37.36% *vs*. 24.16%, showed that TACE-S provides significantly better long-term survival than TACE. Bai *et al*. (9) found that the TACE-S was generally well tolerated and significantly improved OS and TTP compared with TACE alone in patients with intermediate or advanced HCC. In conclusion, the TACE-S therapy was more effective than TACE alone for patients with intermediate or advanced HCC.

The increase of vascular endothelial growth factor (VEGF) expression may be associated with recurrence and distant metastasis of PVTT after TACE (10). As an oral multi-tyrosine kinase inhibitor, Sorafenib may play the role of anti-tumor cell proliferation and anti-angiogenesis by inhibiting tyrosine kinase of VEGF receptor and platelet-derived growth factor receptor. This may be the reason why TACE-S has a preferable effect than TACE. Although there exists some debates about the adverse reaction of TACE-S such as HFSR, diarrhea, alopecia and liver dysfunction (7,11,12). According to current statistical data, TACE-S didn't increase the probabilities. Hence, we can preliminarily conclude that compared with TACE, TACE-S has more positive effects on HCC with PVTT. Also, because of the limited research quantity and cases adopted, further multicenter RCTs with large samples are imperative to assess the long-term curative effects and improve the stability of TACE-S for PVTT.

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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.

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