Editorial

Editorial on combination treatment beyond sorafenib alone for hepatocellular carcinoma with portal vein tumor thrombosis

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Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide and the third most common cause of cancer death with exceedingly high rates in Eastern/South-Eastern Asia, several areas of Africa and, historically, Southern Europe (1). Despite recent progress in screening programs and treatment for HCC, the prognosis is still poor because most cases are diagnosed at an advanced stage. The presence of portal vein tumor thrombosis (PVTT) in particular is considered an important prognostic factor of unfavorable survival. This is due to the combination of impaired hepatic reserves, intrinsic aggressiveness of the tumor, reduced tolerance to anti-neoplastic treatment, and a high rate of complications related to portal hypertension (2). The current practical guidelines for the treatment of advanced HCC including PVTT recommend sorafenib alone as the standard treatment but various treatment modalities are considered as alternative treatment options in the real world (3-9).

Standard management for HCC with PVTT

Sorafenib is an oral multikinase inhibitor that blocks both tumor cell proliferation by targeting the Raf/MAPK/ERK signaling pathway and tumor angiogenesis by targeting the tyrosine kinase VEGR-2, VEGFR-3 and PDGF receptor β (10). In 2008, the phase III Sorafenib Hepatocellular Carcinoma Assessment Randomised Protocol (SHARP) study was published (11). In this trial, 602 patients from Western countries with advanced HCC and Child-Pugh (CP) class A were randomized to receive either sorafenib 400 mg twice daily (BID, n=299) or a placebo (n=303). The median overall survival (OS) was significantly longer in the sorafenib group than in the placebo group (10.7 *vs.* 7.9 months, P<0.001). In subgroup analysis of patients with macrovascular invasion (MVI), the median OS was longer in the sorafenib group (n=108, 8.1 months) than in the placebo group (n=123, 4.9 months) [hazard ratio (HR) in the sorafenib group, 0.68; 95% confidence interval (CI), 0.49–0.93] (12). Following the SHARP trial, the ORIENTAL trial by Cheng *et al*. (13) from the Asia-Pacific region was reported. Total 226 patients from China, South Korea, and Taiwan were randomized to receive either sorafenib 400 mg BID (n=150) or a placebo (n=76) with similar aims and design as the SHARP trial to confirm the efficacy of sorafenib in different geographical regions and with varying underlying etiological factors. The median OS was significantly longer in the sorafenib group than in the placebo group (6.5 *vs.* 4.2 months, P=0.014). In subgroup analysis of patients with MVI and/or extrahepatic spread, the median OS was longer in the sorafenib group (n=108, 5.6 months) than in the placebo group (n=123, 4.1 months) (HR in the sorafenib group, 0.75; 95% CI, 0.54–1.05) (14). In comparison with the SHARP trial, the absolute median OS was shorter, which might have resulted from

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the difference in baseline characteristics between the patients, suggesting more advanced stages of HCC in the ORIENTAL trial (15). Based on the results of these 2 phase III randomized trials, the Barcelona Clinical Liver Cancer (BCLC) staging system recommends only sorafenib as the first-line treatment modality for advanced HCC (4).

For HCC patients with PVTT as advanced stage, however, the recommendation of sorafenib as the only remedy has been questionable. Firstly, the site of MVI from the SHARP trial and the ORIENTAL trial was unclear. Although PVTT is the most common type of MVI in HCC, MVI also includes gross invasion into hepatic veins or the inferior vena cava (16). In addition, PVTT was defined as follows according to the classification system of the Liver Cancer Study Group of Japan: vp1 as tumor thrombus distal to the second branch of the portal vein; vp2 as tumor thrombus in the second branch of the portal vein; vp3 as tumor thrombus in the first branch of the portal vein; and vp4 as tumor thrombus in the portal trunk or extending to a branch on the contralateral side (17). The prognosis of PVTT is different according to the proximity and its extent (18,19). Secondly, subgroup analysis from the SHARP trial and the ORIENTAL trial showed lower survival benefit in patients with PVTT. In particular, the median OS in patients with PVTT from the ORIENTAL trial was not significantly different between the sorafenib group and the placebo group. Lastly, sorafenib is expensive. Considering that the majority of cases occur in developing countries, especially in Asia where there are limited health resources, sorafenib paying approximately > US $ 5,000 a month is not a cost-effective option as the first-line treatment for HCC patients with PVTT (20,21). Based on these limitations, recent official recommendations of the American Association for the Study of Liver Disease (AASLD) state that it is not possible to make a recommendation for sorafenib alone over locoregional treatment as there was inadequate evidence to inform the balance of benefit versus harm (22). Therefore, the treatment of HCC patients with PVTT is still a challenging area.

Combination treatment for HCC with PVTT

To improve treatment outcome, various treatment modalities including transarterial chemoembolization (TACE), radioembolization, hepatic arterial-infusion chemotherapy, external beam radiotherapy (RT), surgery, or a combination of the above modalities have been used for HCC patients with PVTT. Among these, TACE is the most common treatment modality in Asian clinical practice. Historically, TACE was contraindicated in HCC with PVTT because it had a potent risk of liver failure. However, recent technical progress in the form of superselective TACE and improved patient' selection based on good liver functional reserve and the presence of collateral circulation following PVTT support the use of TACE for PVTT (23). Xue *et al*. (24) reported a meta-analysis comparing TACE with conservative treatment in HCC patients with PVTT. TACE significantly improved the 6-month OS (HR, 0.41; 95% CI, 0.32–0.53; P=0.000) and 1-year OS (HR, 0.44; 95% CI, 0.34–0.57; P=0.000) compared with conservative treatment. TACE refers to the injection of a chemotherapeutic agent, mixed with embolic material, administered selectively into the feeding arteries of the tumor to potentially obtain higher intra-tumor drug concentrations, with occlusion of the blood vessel causing tumor necrosis (25). However, TACE also enhances angiogenesis and up-regulates VEGF expression and results in a high rate of HCC recurrence (26). Theoretically, combination therapy of TACE and sorafenib might be beneficial due to tumor necrosis by TACE and inhibition of VEGF activity by sorafenib, but clinical results have been controversial. Therefore, five meta-analyses were conducted to evaluate the treatment benefit of combination therapy compared with TACE alone in patients with unresectable or advanced HCC (27-31). Three meta-analyses showed significantly longer OS in TACE combined with sorafenib than in TACE alone (27-29). On the other hand, two meta-analyses significantly improved time to progression (TTP) in TACE combined with sorafenib but OS was not different (30,31).

Recently, Zhang and colleagues evaluated the benefits of TACE combined with sorafenib compared with TACE alone in HCC patients with PVTT (32). The authors systematically reviewed eight high-quality, retrospective studies and conducted a meta-analysis using five retrospective studies. The number of treatment cycles of TACE using various chemotherapeutic agents ranged from 1 to 8 times and the time on sorafenib (400 mg BID) ranged from 1 to 7 days after the first TACE session, with no breaks before or after repeated TACE if toxicity of grade 3/4 did not occur. Meta-analysis from four studies showed better objective response rate (ORR) in the combination group [odds ratio (OR), 3.59; 95% CI, 1.74–7.39; P=0.0005]. The median OS ranged 7 to 13 months in the combination group and 4 to 6.1 months in the TACE group. Meta-analysis from five studies showed better 6-month OS (OR, 3.47; 95% CI, 2.47–4.89; P<0.00001) and 1-year OS (OR, 3.10;

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Table 1 Summary of meta-analyses for combination treatment in HCC patients with PVTT

Authors	No. of study	Study design	No. of patients	Treatment modality	ORR	Median OS (mo)	OS	Toxicity
Zhang *et al.* (32)	8 (5[a])	All retrospective studies	1,019	TACE and sorafenib *vs.* TACE	OR, 3.59; 95% CI, 1.74–7.39; P=0.0005	7–13 *vs.* 4–6.1	HR, 0.62; 95% CI, 0.51–0.75; P<0.00001	TACE and sorafenib group experienced more toxicity
Zhao *et al.* (33)	8	Retrospective studies (n=5); prospective studies (n=3)	1,760	TACE and RT *vs.* TACE	ORR of PVTT[b]: OR, 4.22; 95% CI, 3.07–5.80; P<0.001; ORR of HCC: OR, 1.37; 95% CI, 0.67–2.79; P=0.390	7.5–13 *vs.* 4.1–9.1	HR, 0.69; 95% CI, 0.57–0.83; P=0.001	TACE and RT group experienced more toxicities: OR, 3.38; 95% CI, 1.98–5.77; P<0.001

[a], among 8 studies, 5 studies were used for meta-analysis; [b], treatment target for RT was PVTT in 6 studies, and PVTT and HCC in 2 studies. Therefore, studies separately reported ORR to evaluate RT response and overall response. TACE, transarterial chemoembolization; RT, radiotherapy; ORR, objective response rate; OR, odds ratio; CI, confidence interval; OS, overall survival; HR, hazard ratio; HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombosis.

95% CI, 2.22–4.33; P<0.00001) in the combination group. In addition, HR for OS favored the combination group (HR, 0.62; 95% CI, 0.51–0.75; P<0.00001). The median TTP ranged from 3 to 7 months in the combination group and 2.4 to 3 months in the TACE group. Interestingly, all eight studies analyzed survival according to type of PVTT. TACE combined with sorafenib lead to better survival for PVTT above the first branch (vp1–3) than for that below the main portal trunk (vp4). The authors recommended TACE combined with RT in patients with vp4 PVTT. More toxicity was associated with the combination group.

Radiation oncologist' view

The efficacy of TACE would be reduced in extensive PVTT with worsening liver function or vp4 as Zhang and colleagues mentioned above. In this clinical setting, RT is considered an effective modality to kill tumor cells within the thrombus and rapidly relief PVTT. This could restore portal flow, improve liver functional reserve, and allow modest delivery of further TACE. One meta-analysis supported this combination approach. The study was designed to compare the efficacy and safety of TACE combined with RT versus TACE alone in HCC patients with PVTT (33). Among 8 studies, 6 studies targeted only PVTT for RT. The ORR of PVTT was significantly improved in the combination group (OR, 4.22; 95% CI, 3.07–5.80, P<0.001) but the ORR of HCC was not significantly different. HR for OS favored the combination group (HR, 0.69; 95% CI, 0.57–0.83; P=0.001). Overall toxicity of grade 3 or 4 was occurred more frequently in the combination group (OR, 3.38; 95% CI, 1.98–5.77, P<0.001). Two important meta-analyses are summarized in *Table 1*. In addition, research from our hospital demonstrated the benefit of TACE combined with RT for HCC with PVTT (34). Sixty-seven patients treated with TACE combined with RT were retrospectively compared with 35 patients treated with sorafenib: cases with huge HCCs beyond two-third of the whole liver volume or CP score <7, which are not feasible for combination treatment, were excluded from the sorafenib group by an experienced radiation oncologist. The OS in the combination group was significantly longer than that in the sorafenib group (14.1 *vs.* 3.3 months, P<0.001). After propensity score matching, the combination group showed prolonged OS compared to the sorafenib group (6.7 *vs.* 3.1 months, P<0.001). These clinical data suggest that patients with PVTT and limited tumor burden who can receive local modality may get

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beneficial effect from the combination treatment.

Another approach is combination of RT and sorafenib. Sublethal dose of RT in each fraction might induce VEGF expression and increase VEGF secretion *in vivo*; RT-induced VEGF could be a paracrine proliferative stimulus to accelerate the growth of HCC out of the RT field (35). Theoretically, addition of sorafenib might inhibit RT-induced VEGF overexpression and improve treatment outcome. A phase II study evaluated the efficacy of RT combined with sorafenib for advanced HCC; PVTT was present in 24 patients (60%). Intensity modulated RT was applied and sorafenib was initiated at the commencement of RT at a dose of 400 mg BID. The median OS was 14 months in the whole population and 10.6 months in patients with PVTT. In spite of promising survival, the incidence of hepatic toxicity was high. During RT, 4 patients (10%) experienced hepatic toxicity of grade 3. After RT, 6 patients (15%) developed hepatic toxicity ≥ grade 3, and 3 of them died. Similar treatment outcomes were reported from a phase I study of stereotactic body radiotherapy combined with sorafenib (36). Based on these studies, concurrent use of RT and sorafenib is not recommended in the clinical setting, and other sequences have been evaluated with the aim of reducing toxicity. However, preclinical studies showed inconsistent results with pre-RT and post-RT use of sorafenib. Li *et al*. (37) reported that sorafenib given 30 minutes before RT reduced the anti-proliferative effects in HCC, whereas sorafenib given 24 hours after RT increased the anti-tumor effects *in vitro*. Yu *et al*. (38) observed inconsistent outcomes with pre-RT and post-RT use of sorafenib in two different cell lines. Chen *et al*. (39) suggested that the use of sorafenib before RT could provide a better tumor growth inhibition than concurrent or the use of sorafenib after RT. Therefore, further studies are necessary to clarify the optimal sequence for use of RT and sorafenib.

Conclusions

In conclusion, PVTT is one of the unfavorable prognostic factors for survival in patients with HCC and presents heterogeneously. Although sorafenib is the only approved first-line treatment modality for advanced HCC, the treatment benefit in patients with PVTT is limited. In selected patients with PVTT, combination therapy, such as TACE and sorafenib, TACE and RT, RT and sorafenib, and so on, could result in better treatment outcomes. Further studies are warranted to evaluate the feasibility and efficacy of these combination treatments to achieve optimal results.

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Footnote

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