Editorial

Sorafenib plus transarterial chemoembolization for unresectable hepatocellular carcinoma

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This issue of the *Annals of Translational Medicine* features an important study by Li and colleagues titled "Efficacy evaluation of the combination therapy of sorafenib and transarterial chemoembolization for unresectable HCC: a systematic review and meta-analysis of comparative studies." (1). The authors performed a systematic review and summarized the current evidence related to the efficacy of combination therapy [i.e., sorafenib plus transarterial chemoembolization (TACE)] versus TACE monotherapy for unresectable hepatocellular carcinoma (HCC) (1). These data add to the current literature and provide the rationale for further research to evaluate the efficacy of combination therapy among patients with unresectable HCC.

According to the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) guidelines, TACE is recommended for Barcelona Clinic Liver Cancer (BCLC) stage B patients [i.e., patients with 2–3 nodules >3 cm, >4 nodules, preserved liver function, performance status (PS) 0], while sorafenib is recommended for individuals with BCLC stage C HCC (i.e., portal invasion, extrahepatic spread, preserved liver function, PS 1-2) (2,3). Several clinical trials have demonstrated a survival benefit with TACE over best supportive treatment among patients with unresectable HCC (4,5). TACE delivers anticancer therapy directly to the tumor feeding arteries and blocks the arterial blood supply of liver tumors. In turn, TACE creates a hypoxic tumor microenvironment, that leads to upregulation of the hypoxia inducible factor-1, which facilitates tumor angiogenesis with the release of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) (6,7). Of note, an increase in serum VEGF levels after TACE has been considered a possible mechanism responsible for high recurrence rates following TACE (6,7). In turn, there has been an interest in combining antiangiogenic agents with TACE to decrease TACE-induced angiogenesis aiming at decreasing recurrence rates. Sorafenib, a multi-kinase inhibitor, inhibits angiogenesis—a major mechanism of cancer progression—by targeting the VEGR receptor 2 (VEGFR2) and PDGF receptor (PDGFR), while also blocking cell proliferation by targeting the MAPK/ERK signaling pathway (8). As such, the addition of sorafenib has been hypothesized to enhance the efficacy of TACE when compared with TACE monotherapy.

In this context, Li and colleagues analyzed 14 studies published between 2011 to 2017 that compared combination therapy (i.e., sorafenib plus TACE) versus monotherapy with TACE (1). In their analysis, the authors included 4 prospective randomized controlled trials (RCTs) (9-12), while the remaining 10 were non-RCTs.(1) The authors demonstrated that the combination of sorafenib and TACE improved time-to-progression (TTP) (HR =0.72, 95% CI: 0.59–0.88, P=0.001) and overall survival (OS) (HR =0.65, 95% CI: 0.54–0.79, P<0.001) compared with TACE alone. Several points should be considered when interpreting the results of this meta-analysis (1).

First, half of the included studies were retrospective in

nature which was problematic, and may have introduced selection bias (1). Of note, there was large heterogeneity in the characteristics of patients included in each study. In particular, although the majority of studies analyzed BCLC-B and C stage patients, two studies included BCLC-A patients who—according to the latest BCLC guidelines—should be recommended resection, transplantation or ablation (2). In addition, three out of the 4 analyzed RCTs had negative results and did not demonstrate a significant benefit of combination therapy over TACE monotherapy (9-12). In turn, the survival benefit associated with combination therapy in the cumulative analysis was presumably mainly driven by the results of the non-RCTs. Although the results of the non-RCTs should not be ignored, the heterogeneity of these cohorts, as well as the chance of selection bias in retrospective studies, limit the significance of these findings. A subgroup analysis among RCTs or prospective studies (RCT and non-RCTs) could have provided a higher-level of evidence regarding the efficacy of combination therapy and could have enhanced the validity of the current meta-analysis (1).

Li *et al*. analyzed studies that reported on TACE in the form of both conventional TACE (cTACE) and drug eluting beads (DEB)-TACE (1). As previously demonstrated, DEB-TACE may enhance drug delivery, reduce systemic drug exposure and eventually reduce adverse events compared with cTACE (13,14). The authors reported that cTACE and DEB-TACE revealed comparable results relative to TTP (P=0.15), yet a subgroup analysis comparing combination therapy versus TACE monotherapy stratified by the type of TACE would have been informative. Performing such a subgroup analysis based on the type of TACE (i.e., cTACE or DEB-TACE) may provide more insight into which TACE approach provided the most benefit when combined with sorafenib.

In addition, the majority of the studies were conducted in Asian countries (10 out of 14) (1), where the etiology of HCC is somewhat different compared with Western countries. Indeed, hepatitis B virus (HBV) infection is the main predisposing factor for the development of HCC in Asia, while non-alcoholic fatty liver disease (NAFLD), alcohol-related cirrhosis and hepatitis C virus (HCV) infection are the main attributable factors for HCC in Western countries (2,3). Previous investigators have suggested that sorafenib may have a differential effect on outcomes according to the etiology of HCC (15). Indeed, a recent meta-analysis of randomized phase III trials demonstrated a sorafenib benefit only among HCV-positive and HBV-negative patients as opposed to any other combination of viral status (16). Of note, the relative impact of sorafenib across all other etiologies of HCC (i.e., NAFLD, alcohol-related cirrhosis etc.) is not well understood to date and warrants further investigation. As such, results from the present meta-analysis need to be interpreted in light of the population analyzed and not unequivocally extrapolated to other populations with different characteristics (i.e., Western populations).

Another factor that should be considered was the inclusion of studies that were published only up to December 2017. Since then, a number of studies have been published on the topic, yet the majority compared combination therapy versus sorafenib monotherapy and not TACE monotherapy (which was the objective of the present meta-analysis) (17-19). Of note, an important multicenter prospective RCT from Japan (TACTICS trial) was recently published that evaluated the combination of TACE plus sorafenib versus TACE alone (20). This trial was performed by the same group as the first trial by Kudo *et al*. that was published in 2011 (9), yet the TACTICS trial was a collaborative effort from multiple Japanese centers (20). The authors utilized a new protocol compared with the first trial that had yielded negative results (9). Specifically, patients in the combination group received sorafenib for 2–3 weeks prior to TACE, which was continued during on-demand cTACE sessions; in contrast, in the previous trial, 50% of patients had sorafenib >9 weeks following TACE. Furthermore, in the TACTICS trial, the investigators administered a higher dose of sorafenib (400 mg once daily for 2–3 weeks before TACE followed by 800 mg once daily during cTACE) versus the initial trial (400 mg) for a longer period of time (median time of sorafenib treatment: 38.7 *vs.* 17.1 weeks). Adverse events were consistent with previous TACE combination trials (21). The authors concluded that TACE plus sorafenib significantly improved progression-free survival (PFS) and TTP over TACE monotherapy among patients with unresectable HCC (20). As such, optimizing combination therapy protocols (i.e., timing of sorafenib administration, duration and dosage) may impact TTP and OS following combination therapy.

More recently, a number of other novel antiangiogenic agents have been investigated to treat advanced HCC. In the phase III REFLECT trial, lenvatinib demonstrated improved PFS and an objective response rate with equivalent OS compared with sorafenib in the setting of unresectable HCC (22). In addition, the phase III

IMbrave150 trial demonstrated that the combination of atezolizumab-bevacizumab resulted in better OS and PFS compared with sorafenib alone among patients with unresectable HCC (23). As such, newer agents such as lenvatinib and/or atezolizumab-bevacizumab may be even more potent anti-VEGF agents compared with sorafenib. In turn, these agents may more efficiently counteract the upregulation of hypoxia-induced angiogenesis caused by TACE. Although these novel treatments have yet to be approved as standard of care for individuals with advanced HCC, the combination of TACE along with these novel anti-angiogenic agents represents a promising field for future research.

In conclusion, the mechanistic background of TACE-induced angiogenesis provides a rationale for the implementation of anti-angiogenic agents along with TACE to reduce recurrence. The findings by Li *et al*. add to the current literature and suggest that the combination of TACE with sorafenib may provide a benefit over TACE alone for patients with unresectable HCC. The present meta-analysis provides a strong argument for the implementation of further large scale, prospective RCTs to validate the timing and the optimal dosage of sorafenib—or other more novel agents—to provide better outcomes when combined with TACE, while also evaluating adverse events and drug-related toxicity. The use of novel anti-angiogenic agents with TACE is a promising field for future research.

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