Editorial
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How to optimize the treatment strategy for advanced-stage hepatocellular carcinoma with macrovascular invasion

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See Article "Subclassification of advanced-stage hepatocellular carcinoma with macrovascular invasion: combined transarterial chemoembolization and radiotherapy as an alternative first-line treatment" on Pages 177-188.

To date, the Barcelona Clinic Liver Cancer (BCLC) staging system for hepatocellular carcinoma (HCC) has been widely adopted in real-world clinical practice, primarily owing to its simplicity to use and ability to predict prognosis and clearly guide treatment strategy.[1] However, BCLC stage C HCC encompasses a variety of disease burdens including HCC with macrovascular invasion (MVI), lymph node involvement, and/or extrahepatic spread (EHS). Despite the distinct overall prognosis according to the presence or extent of various tumor factors, the BCLC staging system has only recommended systemic treatment for patients with BCLC stage C HCC.[1] Before the release of positive results from the IMbrave150 trial,[2] the first-line treatment for patients with BCLC stage C HCC had been systemic chemotherapy based upon multi-kinase inhibitors (i.e., sorafenib or lenvatinib). Due to the better overall survival outcomes in patients treated with atezolizumab plus bevacizumab compared to those treated with sorafenib, the combined regimen is currently the most preferred treatment (considering both a better overall survival and a more acceptable safety profile).[3-5]

In contrast, in some regions, such as East Asia, patients with BCLC stage C HCC have been traditionally treated with a variety of modalities in addition to systemic treatment. These modalities include transarterial chemoembolization (TACE), transarterial radioembolization (TARE), surgical resection, radiation therapy (RT), and other multidisciplinary approaches. Notably, for selected patient groups, such active loco-regional treatments (LRTs) have shown a better prognosis than systemic treatment alone.[6,7] In particular, a significant proportion of patients treated with active LRTs, have experienced successful down-staging, and subsequently, underwent successful surgical resection or orthotopic liver transplantation, leading to a better long-term overall survival outcome.[8,9]

Similarly, some studies have sub-classified patients with BCLC stage C HCC for a more delicate prognostication based on clinical considerations (e.g., Child-Pugh score) and tumor factors (e.g., tumor size, presence or type of vascular invasion, bile duct invasion, tumor morphology, presence or type of EHS, and tumor markers).[10-12]

In this issue of the *Journal of Liver Cancer*, Jin et al.[13] in their study of 1,419 consecutive patients with HCC and MVI, comprehensively compared prognosis between patients treated with combined TACE and RT and those treated with systemic treatment alone, after stratification by prognostic factors. Based on their findings, Jin et al.[13] proposed a simple prognosis model based on the sum of scores from the following parameters: Child-Pugh class B (score 2),

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main or bilateral vascular invasion (score 1), presence of extrahepatic metastasis (score 2), and tumor size ≥10 cm or infiltrative-type tumor (score 2).[13] Of the 1,419 patients, those treated with combined TACE and RT showed a significantly longer median overall survival than patients treated with systemic treatment. In contrast, when the patients were stratified, patients treated with combined TACE and RT exhibited significantly longer median overall survival (24.2 and 9.5 months, respectively) than those who received systemic treatment (6.4 and 5.1 months, respectively) in the low (points ≤1) and intermediate (points=2) risk groups, while there was no statistical difference between the two modalities in the high-risk group. Therefore, Jin et al.[13] concluded that combined TACE and RT, rather than systemic treatment alone (as proposed by the BCLC staging system),[1] may be considered a first-line treatment option for patients with HCC and MVI, provided that they were classified into low and intermediate-risk groups.

Combined TACE and RT may be regarded as a viable option for treating patients with BCLC stage C HCC. Since most MVI is due to portal vein invasion, its presence can compromise perfusion of the portal flow into the liver, thereby, decreasing liver function. For this situation, additional RT can be used to overcome unfavorable conditions by decreasing tumor thrombus in the portal vein to recover the portal flow and TACE can be used to control the intrahepatic tumor burden. However, the best option for active LRTs remains to be determined. Considering that TARE, liver-directed concurrent chemoradiotherapy based on hepatic arterial infusion chemotherapy, or other combined LRT methods are also viable options, further studies are required. The availability of the combined atezolizumab plus bevacizumab regimen in the current practice also warrants further discussion. According to updated data,[5] the median overall and progression-free survival of patients treated with atezolizumab plus bevacizumab was 19.2 and 6.9 months, respectively, compared to 13.4 and 4.3 months in patients treated with sorafenib (both $P<0.001$). Therefore, the results of the study by Jin et al.[13] should be externally validated based on more recent data.

Lastly, Casadei-Gardini et al.[14] compared the overall survival between patients treated with atezolizumab plus bevacizumab vs. lenvatinib, and found no significant differences between the two groups. This is a noteworthy finding, considering extrapolations from the REFLECT study which indicated a non-inferior overall survival outcome in the lenvatinib arm compared to the sorafenib arm.[15] Although the exact mechanisms have not been fully elucidated, the favorable outcome in the atezolizumab plus bevacizumab arm compared to the lenvatinib arm among patients with viral hepatitis and the conversely unfavorable outcomes among patients with non-alcoholic fatty liver disease may in part contribute to the overall similar outcomes between the two groups. In the future, additional studies to verify the conclusion, optimized for the current practice milieu, are necessary.

In conclusion, even though the optimal treatment strategy for advanced-stage HCC with MVI remains to be determined, a subset of patients with BCLC stage C HCC, that is, those in the low and intermediate-risk groups (defined using Child-Pugh class B, main or bilateral vascular invasion, the presence of extrahepatic metastasis, and tumor size ≥10 cm or infiltrative-type tumor), may benefit from combined TACE and RT, as opposed to systemic treatment alone. Further studies in independent populations, considering other LRTs, the new chemotherapeutic regimen, and different patients' demographic characteristics are required to validate this hypothesis.

Conflict of Interest

The author declares no conflict of interest to disclose.

Ethics Statement

This editorial is fully based on the articles which were already published and did not involve additional patient participants. Therefore, IRB approval is not necessary.

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Data Availability

Data sharing not applicable to this article as no datasets were generated or analyzed during this study.

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Author Contribution

Conceptualization, Methodology, Writing–original draft, approval of final manuscript: BKK

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