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Optimizing outcomes in HCC: Comment on "optimal timing of combining sorafenib with trans-arterial chemoembolization in patients with hepatocellular carcinoma: A meta-analysis" by Jiang et al.

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ABSTRACT

Recent years have witnessed notable advances in the management of intermediate and advanced hepatocellular carcinoma (HCC). However, several questions remain unanswered, including the timely transition from locoregional to systemic therapies and the lack of data on sequencing. In this Commentary, we critically discuss the results of the interesting meta-analysis conducted by Jiang and colleagues on the role of the combination therapy of trans-arterial chemoembolization (TACE) and sorafenib in this setting.

Hepatocellular carcinoma remains a common cause of cancer-related death, representing one of the most frequent malignancies worldwide and accounting for approximately 80% of all primary liver tumors [1]. Historically, treatments for HCC are stratified according to the concomitant liver function and the disease stage [2]. Recent years have witnessed the emerging of several novel therapeutic options for patients with advanced HCC, including multikinase inhibitors, as well as immune-checkpoint inhibitors (ICIs) and combinations of both strategies [3,4]. In particular, following the results of landmark clinical trials, four targeted treatments have been recently approved for advanced or metastatic disease, including lenvatinib in treatment-naïve HCC and ramucirumab, cabozantinib and regorafenib in previously treated patients [5,6]. In addition, outstanding advances in the comprehension of immunogenicity of HCC have been achieved over the last years, leading to the evaluation of immune checkpoint inhibitors (ICIs) as front-line treatment in this setting [7]. In fact, the role of ICIs – as monotherapy or in combination with other anticancer agents - in unresectable, treatment-naïve HCC has been explored in several phase I to III clinical trials, and the results of the IMbrave150 trial conducted by Finn and colleagues have suggested a novel standard of care in treatment-naïve patients [8]. In fact, in this phase III study randomizing 501 HCC patients to atezolizumab plus bevacizumab or to sorafenib monotherapy, superior overall survival (OS) and independent review facility-assessed progression-free survival (PFS) were observed in HCCs receiving the immune-based combination, starting a new era in this setting. However, several questions remain unanswered, including the timely transition from locoregional to systemic therapies and the lack of data on sequencing.

According to the Barcelona Clinic Liver Cancer (BCLC) staging system, transarterial chemoembolization (TACE) represents the first-line treatment for intermediate stage HCC, including patients with multinodular or large disease, well-preserved liver function, and no evidence of extrahepatic spread or vascular invasion (Fig. 1). In particular, two main TACE techniques have been used in recent years: conventional TACE and TACE with drug-eluting beads (DEB-TACE).

In the current systemic review and meta-analysis conducted by Jiang and colleagues, the authors pulled together seven randomized controlled trials (RCTs) for a total of 1464 patients with unresectable HCC [9]. According to the results of this study, Jiang et al. suggested that the combination of TACE and sorafenib may improve time to progression (TTP) and progression-free survival (PFS). Jiang and colleagues used well-accepted and rigorous methods to compare evidence across clinical trials, also reporting and acknowledging some limitations.

The present meta-analysis holds its own strengths and caveats to be highlighted. The strengths of this analysis include the inclusion of only phase III RCTs, the overall number of patients ($n = 1464$; 734 in TACE + sorafenib and 730 in TACE + placebo or alone group) and the high quality of statistical analysis. Nonetheless, the results of the meta-analysis should be interpreted with caution, due to the presence of some limitations. First, although the authors used random-effects modeling to address heterogeneity, some analyses (e.g., diarrhea, hypertension, rash, etc.) were burdened by substantial heterogeneity, with

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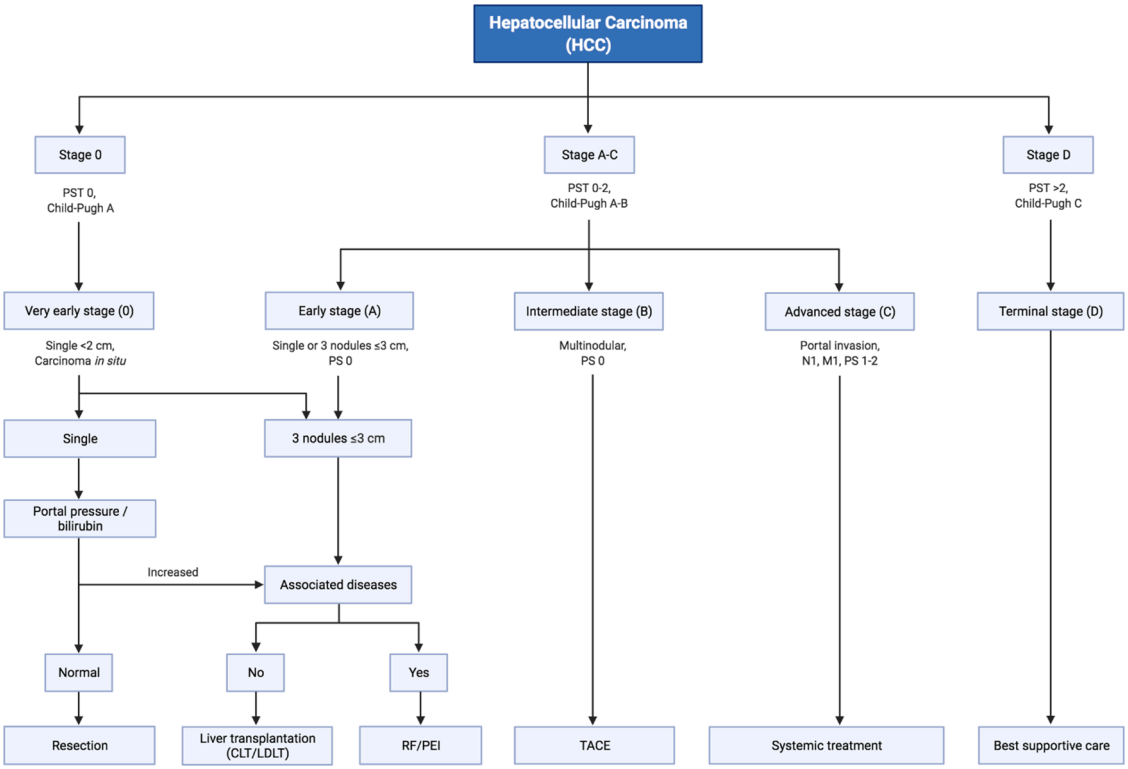

Fig. 1. Schematic figure representing the Barcelona Clinic Liver Cancer (BCLC) Staging System. Abbreviations: CLT: cadaveric liver transplantation; LDLT: living donor liver transplantation; PEI: percutaneous ethanol injection; PS: performance status; PST: performance status test; RF: radiofrequency ablation; TACE: trans-arterial chemoembolization.

I^2 ranging from 72 to 92%. Second, individual patient data were not available, and thus, aggregate data included in the analysis were extracted from clinical trials results. Third, differences in demographics across the included trials should be considered, including the proportion of Asian and non-Asian patients as well as the higher proportion of HBV-positive patients in some trials [9,10]. In addition, the majority of the included studies compared TACE plus sorafenib versus TACE plus placebo or alone in patients with ECOG-PS 0 or 1, and thus, these patient populations may only partially be representative of all HCC patients receiving these treatments in everyday clinical practice.

However, we think the authors are to be acknowledged for their work. Given the impressive development of ICIs in this setting and since there is paucity of data on the integration of TACE and immunotherapy, this should be explored in future research, in order to improve clinical outcomes of patients with HCC, a common and aggressive malignancy with several unanswered questions.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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