Commentary

Combination therapies for advanced hepatocellular carcinoma: a beacon of light or a castle in the air

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The review article by Zhang *et al.* (1) critically discussed the efficacy of combination therapies for advanced hepatocellular carcinoma (HCC) and the factors affecting efficacy and overall survival (OS) with a particular emphasis on timing and sequence of combination therapies to improve OS. The role of interventional therapies such as radio-frequency ablation (RFA) and chemoembolization were also discussed—although ablation is well-established for the treatment of small tumors, cancer, it may not be appropriate for tumors near the liver capsule or adjacent to blood vessels due to a higher risk of complications and local recurrence from untreated perivascular cells. Although microwave ablation mitigates the limitations of RFA and can also be used for larger tumors, there is no compelling data favoring one modality over the other when evaluating risk of local recurrence or OS.

Fortunately, the availability of three-dimensional visual surgical planning systems has increased the applicability of ablation for larger and high-risk-location tumors (2). Selecting the patient for subtypes of chemoembolization such as bland embolization, transarterial chemoembolization, drug-eluting bead chemoembolization or transarterial radioembolization in the treatment of advanced HCC is challenging and should be carefully determined by a multispecialty group of experts (2). Increased OS with combination therapies along with interventional therapy overcome the challenges of translating objective response rate (ORR) and progression free survival (PFS) benefits to OS benefits and support the notion of improved outcomes with a combination of immunotherapy + targeted therapy + interventional therapy compared to single-agent therapy in cases of advanced HCC (1). Combination immunotherapies are beneficial via attenuating time to response (TTR) and increasing ORR but are associated with adverse events and should be used cautiously while monitoring liver function and adverse events. The role of combination therapies for advanced HCC was supported by a recent report in which TACE, ablation, tyrosine kinase inhibitor therapy (with apatinib) and immunotherapy (with camrelizumab) applied sequentially (TATI modality) were associated with improved clinical outcomes with a survival of 17–32 months and no serious adverse (3). TATI increases the survival by facilitating tumor immunogenicity and host immune response (*Figure 1*).

Another important aspect discussed in this article is the sequence of therapeutic agents. Determining the optimal sequence for various therapies in patients with advanced HCC is a major challenge in clinics. The American Society of Clinical Oncology's framework of scoring (ASCO-NHB version 2) stratifies treatment options based on clinical benefit, toxicities, improvement in survival, cancer-related symptoms, quality of life, and/or treatment-free interval to calculate the overall Net Health Benefit (NHB) of cancer

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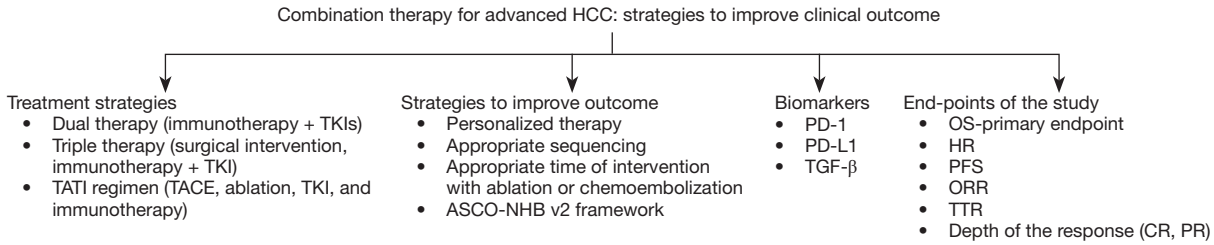

Figure 1 Combination therapies and proposed strategies to be considered for better clinical outcome. HCC, hepatocellular carcinoma; TKI, tyrosine kinase inhibition; TACE, transarterial chemoembolization; TATI, transarterial chemoembolization, ablation, tyrosine kinase inhibition, immunotherapy; ASCO-NHB, American Society of Clinical Oncology-Net Health Benefit; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; TGF-β, transforming growth factor beta; OS, overall survival; HR, hazard ratio; PFS, progression free survival; ORR, objective response rate; TTR, time to response; CR, complete response; PR, partial response.

treatment. Patient-oriented ASCO-NHB v2 approach is critical as it involves patients' preferences and increases their role in determining treatment protocols which in turn may lead to enhanced quality of life in parallel with improved compliance and outcomes (*Figure 1*). The combination of atezolizumab plus bevacizumab followed by regorafenib and atezolizumab plus bevacizumab followed by cabozantinib appears promising but interactions between these first- and second-line therapies warrant prospective trials and prognostic data (4-6). Another important aspect to be considered in combination therapy is to choose treatment for those patients refractory to first-line therapy with atezolizumab and bevacizumab of which regorafenib and cabozantinib are the preferred options (7). Similarly, combination therapy for the patient with no response to atezolizumab plus bevacizumab are candidates for second-line therapy, and a sequence of therapeutic agents such as sorafenib, lenvatinib, regorafenib, ramucirumab, and cabozantinib should be considered carefully with a patient-oriented approach (8). This underscores the importance of choosing the appropriate sequence of therapeutic agents of combination therapy for such patients while also keeping it patient-oriented. This approach may lead to advances in personalized precision therapy, an evolving therapeutic approach associated with a better outcome with patient selection based on Barcelona Clinic Liver Cancer (BCLC) staging (*Figure 1*). The BCLS system recommends HCC treatment should be based on multiple factors not limited to tumor heterogeneity, presence or absence of vascular invasion and extrahepatic metastasis but also liver function (presence or absence of hepatic decompensation) and overall health (1,9).

The timing of intervention is another key aspect of combination therapy for advanced HCC. Timing of intervention with ablation and chemoembolization before or during combination therapy is pivotal with randomized control trials reporting variable outcomes partly due to tumor heterogeneity (9). This reaffirms that considering the therapy for each patient based on HCC stage is a prerequisite with other institution-specific criteria complementing the established ASCO-NHB v2 and BCLC to determine personalized precision therapy. Overall the three important factors associated with the most optimal clinical outcome are (I) selecting the most responsive patient, (II) choosing the correct sequence and (III) timing of therapies (*Figure 1*). The promising results of combination therapies suggest that the inclusion of multiple therapies with a timely and subsequent administration can improve OS with their synergistic effect, but more prognostic data of long-term survival from larger multicenter, prospective, randomized clinical trials with more robust criteria for OS is urgently required.

Although combination therapies have promising results, patient selection, time of transition between the treatments, monitoring the adverse effects, protection of major organ functions, and confirmation of the safety, feasibility, and effectiveness of combined systemic locoregional therapies are major challenges while starting combination therapy. In addition to the OS as an endpoint, the addition of PFS, ORR, follow-up time, and sample size should be considered while estimating the efficacy of a treatment. Including multiple endpoints have been proposed to increase the estimation of drug efficacy but statistical considerations in trials with multiple primary endpoints might be challenging. Another important factor is the consideration of biomarkers for predicting efficacy and the selecting the most responsive tumors. This is important as the presence of different criteria for evaluation may have a different effect on the outcome of PFS and ORR compared to OS, and the

presence of cancer heterogeneity has also led to equivocal results (1,2,5,10). Furthermore, for the best outcome of the study, study objectives should be carefully optimized, and the study endpoints should be selected carefully to best reflect patient survival benefits with quality of life scores and OS as appropriate endpoints of the study. Overall, there is a need for more robust data to establish a patient-centric framework for an ideal improved treatment strategy for advanced HCC.

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