Commentary

Approach to systemic therapy in advanced hepatocellular carcinoma

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Introduction

Systemic therapy is the mainstay of treatment in the management of unresectable or advanced hepatocellular carcinoma (HCC). Over the last two decades there has been a significant shift in the treatment paradigm for advanced HCC. Prior to 2007, cytotoxic chemotherapy was the standard of care with limited clinical benefit. The approval of sorafenib (1), a multi-targeted tyrosine kinase inhibitor (TKI), began the era of TKI treatment for HCC in 2007. While sorafenib was the first approved treatment in HCC to show overall survival (OS) benefit in a randomized control trial, several multi-targeted TKIs have been approved since, including lenvatinib (2), cabozantinib (3), and regorafenib (4). Recently, the shift has focused to immune checkpoint inhibitors (ICI) alone or in combination with other agents in the management of advanced HCC. This led to the approval of combination atezolizumab and bevacizumab (atezo-bev) (5) in 2020, and recently the combination of durvalumab and tremelimumab (durva-tremi) (6) in the first-line setting for patients with unresectable or metastatic HCC.

In a comprehensive review (7) published in 2021, Bruix *et al.* summarize the major clinical trials which have led to the currently approved systemic agents for patients with advanced HCC. They discuss candidacy for systemic therapy, contraindications to first-line agents and alternative options, timing of when to switch to second- or further-line therapies, paucity of data for treatment in patients with impaired liver function and concurrent comorbidities, and challenges in clinical trial design in HCC. Here, we will summarize the key points, discuss recent clinical trials in advanced HCC, and future directions.

Current approach to systemic therapy in HCC

Patients with advanced HCC should be started on systemic therapy. Systemic therapy may also be considered for patients with early or intermediate stage HCC where the usual first-line treatment option may be contraindicated or in patients who response to local therapies has been suboptimal. The randomized phase III clinical trials evaluating the currently approved systemic agents in HCC have notably only allowed patients with Child Pugh A cirrhosis and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, potentially not representing many patients with HCC seen in clinical practice. Within this patient population, for those naïve to systemic therapy, sorafenib prolongs OS compared to placebo (1), atezo-bev prolongs OS compared to sorafenib (5), lenvatinib provides non-inferior OS compared

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to sorafenib (2), and nivolumab has shown a trend towards improved OS compared to sorafenib (8). In the second-line setting, regorafenib (4), cabozantinib (3), and ramucirumab (9) all prolong OS compared to placebo. ICI therapies have been approved as second-line treatments based on single-arm trials, including pembrolizumab (10), and combination of ipilimumab with nivolumab (11).

While atezo-bev has been the preferred first-line systemic therapy, the benefit is unknown in patients with hepatitis B virus (HBV)-hepatitis C virus (HCV) coinfection, human immunodeficiency virus (HIV) infection, ECOG performance status >1, liver transplant, Child Pugh Class B or C cirrhosis, uncommon histology and presence of brain metastases. Nivolumab monotherapy in CheckMate040 has been shown to be safe in patients with Child Pugh B cirrhosis, and has also been supported by real-world analysis (12), but such evidence is lacking for atezo-bev. Therefore, treatment decisions should be individualized. Dedicated clinical trials are required to address management of HCC in patient populations with concurrent co-morbidities and impaired liver function.

Recent and ongoing clinical trials in advanced HCC

There are several updates on recent and ongoing clinical trials evaluating combination systemic therapies in advanced HCC since the time of this Bruix *et al.*'s publication. For example, a randomized phase III trial compared the combination of tremelimumab plus durvalumab, durvalumab, or sorafenib in patients with advanced or unresectable HCC. Durva-tremi significantly prolonged OS compared to sorafenib [median OS 16.4 *vs.* 13.7 months; hazard ratio (HR) =0.78, 96.02% confidence interval (CI): 0.65-0.93; P=0.0035] with similar rates of grade 3 or 4 toxicities in the combination group as compared to sorafenib (50.5% *vs.* 52.4%). Further, durvalumab monotherapy was non-inferior to sorafenib (6). The combination of durva-tremi recently received Food and Drug Administration (FDA) approval for the treatment of patients with unresectable or advanced HCC, and may represent a regimen for patients who are not candidates for atezo-bev, i.e., patients who cannot receive anti-vascular endothelial growth factor (VEGF) therapy due to uncontrolled hypertension, uncontrolled esophageal varices, or high bleeding risk. The appropriate sequencing of therapies in the frontline setting (i.e., atezo-bev *vs.* durva-tremi) is not yet known. ICIs are also being studied in combination with TKIs. In a randomized, double-blind phase III study, lenvatinib plus pembrolizumab was compared to lenvatinib alone in advanced HCC in the first-line setting, where the primary endpoints of OS at final analysis and progression-free survival (PFS) at interim-analysis did not meet pre-specified statistical significance (median OS 21.2 *vs.* 19.0 months; HR =0.84, P=0.02; median PFS 8.2 *vs.* 8.0 months; HR =0.867, P=0.05) (13). Similarly, another study evaluating the combination of cabozantinib plus atezolizumab compared to sorafenib in the first-line setting for patients with unresectable or advanced HCC was negative, where the median PFS was 6.8 *vs.* 4.2 months (HR =0.63, P=0.0012) and median OS was 15.4 *vs.* 15.5 months (HR =0.9, P=0.44) (14). These studies raise concerns regarding the efficacy of TKI in combination with ICI in the management of advanced HCC.

Bruix *et al.* also identify significant challenges in designing clinical trials for HCC (7). This is in part due to HCC being a heterogenous tumor which occurs in patients with underlying chronic disease with variable liver function. The usual endpoint of OS is often impacted by the competitive risk of the natural history of cirrhosis in patients with HCC. Response rate measurements using traditional Response Evaluation Criteria in Solid Tumors (RECIST) criteria may also be altered by prior locoregional therapies.

Future directions

The treatment landscape for advanced HCC has changed dramatically over the last decade, and the incorporation of ICI has significantly improved outcomes for patients with HCC. However, several areas of unmet need exist including identifying biomarkers to select patients who will and will not respond to ICI therapy. Understanding immune resistance is a major area of ongoing research. With increasing number of therapies approved in the first-line setting, biomarker identification is especially important. Further, another area of unmet need is to identify effective and safe therapies for patients with impaired liver function who often make up the majority of clinical practice in the real-world setting. The future of HCC will likely involve the greater use of systemic therapies either in combination (VEGF/ICI, ICI/ICI), or combined with locoregional therapy (ICI/locoregional). Equally important will be the focus on developing data-driven guidelines to treat patients

with impaired liver function and in the use of biomarkers to guide treatment options.

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