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Mini Review

Navigating the Landscape of Advanced Hepatocellular Carcinoma Treatment: Old and New Systemic Approaches

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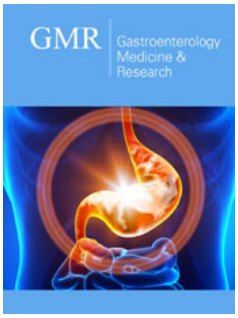

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Introduction

Hepatocellular Carcinoma (HCC) is often an evolutive event of chronic liver disease, particularly associated with cirrhosis. Different etiology factors such as viral infections, excessive alcohol consumption or nonalcoholic fatty liver disease start the cascade of molecular events that can culminate in the development of HCC. HCC staging and treatment decision are made in conformity with Barcelona Clinic Liver Cancer staging (BCLC), which accordingly systemic approaches are reserved to those with advanced and unresectable tumors and for whom surgery, liver transplantation and directed therapies are not appropriate [1]. Also, therapeutic options are frequently limited by the patient's hepatic reserve as indicated by the Child-Pugh classification. However, with a revival of interest for HCC treatment, its therapeutic approaches have continued to evolve rapidly, and a critical review of both old and new systemic treatments is essential for guiding clinical practice.

Advanced hepatocellular carcinoma treatment: integration of new targeted therapies and immunotherapy

First-line therapy: The emergence of Tyrosine Kinase Inhibitors (TKI), such as sorafenib, changed the paradigm of advanced HCC treatment, given that these were the first drugs demonstrating survival benefits in these patients. Sorafenib, a multitargeted TKI was the first systemic therapy to show an Overall Survival (OS) benefit for advanced HCC as demonstrated in SHARP trial [2]. This was a multicentric European trial including patients with advanced HCC and Child-Pugh A liver disease, that compared sorafenib versus placebo, revealing a superior OS within the Sorafenib arm with 10.7 months vs 7.9 months in the placebo group. It also proved a benefit of time to radiologic progression (5.5 months in Sorafenib group vs 2.8 months in placebo). Toxicity profile included hand-foot skin reaction, diarrhea, fatigue being the most common grade 3-4 side effects. This trial established sorafenib as the reference standard treatment for advanced treatment at the time. About ten years later, lenvatinib, also a multitargeted TKI, demonstrated non-inferiority to sorafenib through the REFLECT trial [3]. This study included patients with unresectable HCC, Child-Pugh A disease and excluded patients with involvement of more than 50% of the liver, bile duct or portal invasion. It compared lenvatinib against sorafenib and reached its goal of proving non-inferiority of lenvatinib for median OS (13.6 months in the lenvatinib group versus 12.3 months in the sorafenib group) and demonstrating a longer median progression free survival (PFS) (7.4 versus 3.7 months). The most frequent adverse events were hypertension, diarrhea, anorexia, and weight loss. Moreover, real-life clinical data has proven significant advantage in OS of lenvatinib compared to sorafenib (with a 48% reduction of death risk) [4]. Most recently, immunotherapy changed the paradigm of advanced HCC treatment.

Combined therapy with atezolizumab (an antibody inhibitor to programmed cell death ligand 1 (PD-L1)) plus bevacizumab (an antibody targeting Vascular Endothelial Growth Factor (VEGF)) was compared to sorafenib in the IMbrave 150 trial which included patients with advanced HCC and no worse than Child-Pugh A cirrhosis [5]. This study revealed a significantly better median OS with combined therapy (19.2 vs 13.4 months), improved PFS (6.9 vs 4.3%) and an objective response rate three times higher with atezolizumab plus bevacizumab (30 vs 11%). Toxicities included hypertension, transaminase elevation and proteinuria, but in a similar percentage in both groups (43 vs 46%). Therefore, treatment with atezolizumab plus bevacizumab provides the longest overall survival seen in a trial for advanced HCC, setting this combination as the standard of care for first-line therapy of unresectable HCC.

Later, HIMALAYA trial studied the association of durvalumab (an anti-PD-L1 antibody) with a priming dose of tremelimumab (anti Cytotoxic T-Lymphocyte-Associated protein 4 (CTLA-4) antibody) versus sorafenib [6]. This combined therapy provided a longer median OS (16.4 vs 13.8 months) and a higher objective response rate (20 vs 5%). The most frequent grade 3-4 toxicities were diarrhea, nausea, skin rashes and pruritus. It was also evaluated durvalumab monotherapy versus sorafenib, which proved to be noninferior with a trend towards better median OS for durvalumab (16.6 vs 13.8 months). Thus, tremelimumab plus durvalumab is a viable alternative to those with contraindication to bevacizumab. Also, camrelizumab (a PD-1 inhibitor) plus rivoceranib (a TKI targeted VEGF receptor 2 (VEGFR2)) was compared to sorafenib as first-line therapy for unresectable HCC in CARES-310 trial, improving PFS (5.6 vs 3.7 months) and OS (22 vs 15 months) [7]. Finally, RATIONALE-301 trial evaluated tislelizumab (a PD-1 inhibitor) versus sorafenib, excluding patients with tumor involvement of portal vein or inferior vena cava, which resulted in a higher objective response rate (14.3 vs 5.4%) and more durable responses and noninferiority to sorafenib (median OS of 15.9 vs 14.1 months and median PFS 2.1 vs 3.4 months) [8].

Second-line therapy: The choice of second-line treatment depends in part of what regimen was administered first. Most data available are for treatment after progression under sorafenib or unable to tolerate it. RESORCE trial showed a benefit with regorafenib (a multi-target TKI) after sorafenib with longer median OS (10.6 vs 7.8 months) and higher objective response rate (11 vs 4%) [9].

CELESTIAL trial presented cabozantinib (another multi-target TKI) as a possible second-line therapy option after sorafenib with longer median OS (11.3 vs 7.2 months) [10]. Both treatments appeared to be well tolerated with most frequent grade 3 or 4 adverse events like other TKIs (hypertension, palmar-plantar erythrodysesthesia, fatigue, and diarrhea). Ramucirumab, an antibody against VEGFR2, is other second-line option after sorafenib as proven by REACH trial which showed better median OS (9.2 vs 7.6 months) with a higher benefit for those with high level of alpha-fetoprotein (≥400ng/mL) [11]. Then there are immune checkpoint inhibitors, which have demonstrated the best OS in second-line treatment after sorafenib. These include nivolumab plus ipilimumab (anti-PD-1 plus CTLA-4 inhibitor) or pembrolizumab (anti-PD-1) monotherapy. The benefit of nivolumab and ipilimumab combination therapy was proved in Checkmate 040 trial with median OS achieving 22.2 months [12]. Side effects included rash, adrenal insufficiency, hypothyroidism, colitis, and pneumonitis. On the other hand, pembrolizumab benefit was demonstrated in KEYNOTE-240 and KEYNOTE-394 trials achieving median OS of 14 and 15 months respectively (vs 11 and 14 months for placebo groups), also improving objective response rates (18 vs 4% for KEYNOTE-240 and 13 vs 1% in KEYNOTE-394) [13,14]. However, both OS and PFS differences were not statistically significant in the KEYNOTE-240 study [13].

Other agents include nivolumab monotherapy (median OS of 15.6 months) and tremelimumab and durvalumab combination (median OS of 18.7 months), requiring more evidence for use in this setting. 6,12

There is a shortness of data for second-line therapy after progression or intolerance with lenvatinib, as there is only available real-world data for second-line therapy with sorafenib and regorafenib, although it appears that sorafenib may not be as effective as regorafenib in this setting [15]. There is no data and no approved drugs yet for treatment of advanced HCC after first-line combination therapy with atezolizumab plus bevacizumab, but there are several ongoing clinical trials namely with atezolizumab plus lenvatinib/sorafenib, camrelizumab plus rivoceranib, pembrolizumab plus regorafenib, and cabozantinib.

Conclusion

In these former years, smorec treatment for unresectable HCC went from one to two lines with multiple therapy choices, adding more complexity to sequencing treatment. A major question about first-line therapy is that every study was made in comparison with sorafenib, arising a deficit for existing knowledge due to the absence of comparative studies between each of these referred treatments. The same happens for patients initially treated with sorafenib, the choice of any of TKIs or immunotherapy as second-line therapy is empiric, as there are no comparator trials in this setting. The data shortage is even more evident in the second line setting after immunotherapy use as first-line. Despite these questions, there is no doubt that recent advancements in HCC treatment switched the paradigm in the management of advanced disease, but also creating a challenge in integrating these new agents in an orientating algorithm.

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