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Systemic therapy for intermediate and advanced hepatocellular carcinoma: Sorafenib and beyond

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ABSTRACT

The hepatocellular carcinoma (HCC) treatment landscape changed a decade ago, with sorafenib demonstrating survival benefit in the first-line setting and becoming the first systemic therapy to be approved for HCC. More recently, regorafenib and nivolumab have received approval in the second-line setting after sorafenib, with further positive phase 3 studies emerging in the first line (lenvatinib non-inferior to sorafenib) and second line versus placebo (cabozantinib and ramucirumab). A key recommendation in the management of patients receiving sorafenib is to promote close communication between the patient and the physician so that adverse events (AEs) are detected early and severe AEs can be prevented. Sorafenib-related AEs have been identified as clinical biomarkers for sorafenib efficacy. Healthcare professionals have become more efficient in managing AEs, identifying patients who are likely to benefit from treatment, and assessing response to treatment, resulting in a trend towards increased overall survival in the sorafenib arms of clinical studies. The rapidly changing treatment landscape due to the emergence of new treatment options (sorafenib and lenvatinib equally effective in first line; regorafenib, cabozantinib, and ramucirumab showing OS benefit in second line with nivolumab approved by the FDA based on response rate) underscores the importance of re-assessing the role of the first approved systemic agent in HCC, sorafenib.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and the second leading cause of cancer-related mortality worldwide [1,2]. Cirrhosis due to chronic hepatitis B, alcoholism, or hepatitis C infection is the main risk factor for HCC, followed by nonalcoholic steatohepatitis [2]. The incidence of HCC is highest in regions where hepatitis B virus (HBV) is endemic, including Southeast Asia and sub-Saharan Africa, whereas in Japan, the United States, and parts of Europe, hepatitis C virus (HCV) is the predominant risk factor for HCC [2–4].

Several treatment options are currently available to patients with HCC. Treatment allocation depends on various factors known to impact prognosis, including tumor burden, liver function, and the performance status of the patient [5,6]. The most widely used HCC staging system, the Barcelona Clinic Liver Cancer (BCLC) model, takes these variables into account and is currently the only staging system that uses evidence-based medicine to link prognosis with treatment options [7–9]. The BCLC system differentiates patients with very early-/early-stage disease (BCLC stage 0 or A) who are candidates for potentially curative treatment options (resection, transplantation, ablation), and three subgroups of patients with unresectable HCC: intermediate- (BCLC stage B), advanced- (BCLC stage C), and end-stage disease (BCLC stage D). For intermediate- and advanced-stage disease, standard of care includes transarterial chemoembolization (TACE) or systemic therapy while patients with end-stage disease generally receive palliative care only [5,6,10,11].

Sorafenib was the first systemic therapy to be approved for the treatment of HCC after having demonstrated a survival benefit in patients with advanced HCC in the first-line setting [12,13]. Since the

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results with sorafenib were published, multiple phase 3 trials have failed to demonstrate improved outcomes over sorafenib in this setting [14–18]. Only recently, a phase 3 trial of lenvatinib showed non-inferiority to sorafenib [19]. Similarly, a number of trials have failed in the second-line setting [20–23], with two agents recently approved in patients who have received prior sorafenib: regorafenib, which has demonstrated a survival benefit after progression on sorafenib in sorafenib-tolerant patients [24–26]; and nivolumab, which received an accelerated FDA approval based on tumor response rate and durability of response in an uncontrolled, single-arm study [27]. More recently, results from two phase 3 trials reported improved survival with cabozantinib versus placebo and ramucirumab versus placebo in the second line following sorafenib [28,29]. With the advent of new agents, it appears timely to reflect on the role of sorafenib as the gold standard in the first-line setting, its efficacy, and on the progress achieved in managing its side effects as new drugs are emerging in the first line (none of which have demonstrated superiority to sorafenib), and in second line after sorafenib failure. This review will provide an overview of established and novel systemic therapies in development for unresectable HCC and will discuss ways to improve their use to benefit patients.

Sorafenib history: Efficacy and safety

Sorafenib is an oral multikinase inhibitor that inhibits a number of receptor tyrosine kinases (VEGFR1-3, PDGFR, KIT, and RET) and downstream Raf signaling molecules (Raf-1 and B-Raf), affecting multiple tumor-signaling pathways including those involved in angiogenesis, tumor proliferation, and apoptosis [30–34].

Clinical trials

Four phase 1 trials evaluated a range of oral doses of sorafenib in patients with advanced recurrent or refractory solid tumors [35–38]. The optimal regimen was continuous oral administration of 400 mg sorafenib twice daily (bid) [35]. The most common drug-related toxicities were gastrointestinal or dermatologic [39].

A subsequent single-arm, phase 2 trial was carried out in patients with unresectable HCC (N = 137) who had not received prior systemic treatment and had a Child–Pugh score of A (72%) or B (28%) [40]. Treatment with continuous oral sorafenib 400 mg bid was associated with manageable toxicity – grade 3/4 drug-related toxicities included fatigue (9.5%), diarrhea (8.0%), and hand–foot skin reaction (HFSR; 5.1%). Tumor response rate was low, with 2.2% of patients showing a partial response (PR) based on independent assessment. Investigator-assessed median time to progression (TTP) was 4.2 months and median overall survival (OS) was 9.2 months. Independent review reported an interesting median TTP of 5.5 months, which provided the rationale for the continued development of sorafenib as an HCC treatment.

Subsequently, two phase 3 clinical trials were initiated, the results of which led to the approval of sorafenib for the treatment of HCC [41,42] – the Sorafenib HCC Assessment Randomized Protocol (SHARP) trial (N = 602; randomization ratio 1:1 sorafenib 400 mg bid vs placebo) and the sorafenib Asia-Pacific (AP) trial (N = 226; randomization ratio 2:1 sorafenib 400 mg bid vs placebo) [12,13]. These trials, although from geographically different areas, had the same inclusion and exclusion criteria; patients had advanced HCC with a measurable lesion, received no prior systemic therapy, had Child–Pugh class A liver disease, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and adequate hematological, renal, and hepatic function. Sorafenib demonstrated a significant survival benefit of a similar magnitude in both SHARP and AP (Table 1): in SHARP, median OS was 10.7 months with sorafenib versus 7.9 months with placebo (hazard ratio [HR] 0.69, 95% confidence interval [CI] 0.55–0.87, $P < 0.001$); in AP, median OS was 6.5 months with sorafenib and 4.2 months with placebo (HR 0.68, 95% CI 0.50–0.93, $P < 0.014$). Median time to radiologic progression was significantly longer and the disease control rate (DCR) was significantly higher with sorafenib than with placebo in both studies (Table 1) but no difference in median time to symptomatic progression was observed between study arms. The lower absolute survival observed in the AP study compared with the SHARP study, while maintaining similar relative benefit in both studies (HR 0.69 in SHARP vs 0.68 in AP), may reflect the different patient populations, including more advanced disease in the AP study, and therapeutic options before inclusion in the two studies. The tumor response rates in both studies were low, with no complete responses and low PR rates (Table 1).

Overall, the adverse event (AE) profile of sorafenib was generally comparable in the SHARP and AP phase 3 trials, with the most common grade 3/4 drug-related AEs being HFSR, diarrhea, and fatigue [12,13]. Drug-related AEs of any grade occurring at a higher frequency ($P < 0.001$) in patients treated with sorafenib compared with placebo included diarrhea (39% vs 11%), weight loss (9% vs 1%), HFSR (21% vs 3%), anorexia (14% vs 3%), alopecia (14% vs 2%), and voice changes (6% vs 1%). Grade 3 drug-related AEs that were more common with sorafenib compared with placebo included diarrhea and HFSR ($P < 0.001$). Drug-related AEs resulted in permanent discontinuation of sorafenib in 11% of patients, dose interruptions in 44%, and dose reductions in 26%. The most frequent AEs leading to sorafenib dose reductions were diarrhea (8%), HFSR (5%), and rash or desquamation (3%). A generally similar safety profile has been observed in the sorafenib arms of other phase 3 trials in HCC [14–16].

Real-world evidence: GIDEON

Real-world studies have been instrumental in providing additional information on sorafenib efficacy and safety in a broader population of patients [43–46]. The GIDEON study, a large, prospective, open-label, non-interventional study, evaluated sorafenib safety and HCC treatment practices in 3202 patients in real-world practice across 39 countries, and expanded the patient pool to Child–Pugh B patients (n = 666) [44]. The median OS in patients with Child–Pugh A liver disease was 13.6 months (95% CI 12.8–14.7) compared with 5.2 months (95% CI 4.6–6.3) for Child–Pugh B patients (Table 1). The tolerability profile of sorafenib was comparable between Child–Pugh A and B patients and was consistent with the results of the two pivotal phase 3 trials [12,13,44]. Overall, the incidence of AEs was similar between Child–Pugh A and B patients, except for HFSR which was observed more frequently in Child–Pugh A patients. GIDEON also highlighted regional variation in HCC management, including differences in the prior use of TACE and patient outcomes [47,48]. Other studies have expanded these findings to patients who had become refractory or unresponsive to TACE, showing that survival seemed to be improved in these patients who switched early to sorafenib therapy versus those who continued on TACE [49–51].

Guidelines

Currently, AASLD, EASL, and ESMO-ESDO treatment guidelines, which all use the BCLC staging system, place sorafenib as the standard first-line systemic therapy for patients with advanced HCC (BCLC stage C) [5,6,10,11]. The European guidelines also recommend sorafenib for patients with intermediate-stage HCC (BCLC stage B) who do not respond to TACE (at least two cycles of therapy) [52] or progress following TACE [11]. The Japanese guidelines base their treatment recommendations on different factors (extrahepatic spread [EHS], liver function, macroscopic vascular invasion (MVI), tumor number, and tumor size) and recommend sorafenib as the first choice for patients with EHS and/or MVI and for TACE-refractory patients with Child–Pugh A liver function [53].