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Systemic Therapy for Advanced Hepatocellular Carcinoma: Targeted Therapy and Immunotherapy

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Systemic therapy for hepatocellular carcinoma (HCC) has markedly changed since 2007, with the approval of sorafenib. Sorafenib improved the overall survival of patients with advanced HCC; however, the modest efficacy and toxicity of this therapy present unmet needs. Subsequently, a variety of molecular targeted agents have been tested as first-line or second-line therapies but have failed, and sorafenib has remained the only approved systemic agent for almost 10 years. Recently, regorafenib significantly improved overall survival and was approved for patients with HCC who have been previously treated with sorafenib. Nivolumab, a programmed death protein-1 inhibitor, was also approved as second-line therapy, based on remarkable response rates. ([J Liver Cancer 2018;18:17-22](#))

Keywords: Hepatocellular carcinoma; Molecular targeted therapy; Immunotherapy

INTRODUCTION

Systemic therapy for hepatocellular carcinoma (HCC) has changed markedly since 2007, with the approval of sorafenib. Subsequently, a variety of molecular targeted agents (e.g., sunitinib, erlotinib, brivanib, everolimus, and linifanib) have been tested as first-line or second-line therapies but failed, and sorafenib has been the only approved systemic agent for almost 10 years.¹⁻⁶ Recently, the Food and Drug Administration (FDA) approved regorafenib and nivolumab for the treat-

ment of HCC in patients who have been previously treated with sorafenib in the United States. In this article, the current status and future perspectives of new agents for advanced HCC will be reviewed.

MOLECULAR TARGETED THERAPY

1. Sorafenib

Sorafenib is an oral, multiple kinase inhibitor that blocks the platelet derived growth factor receptor (PDGFR), Raf kinase, and vascular endothelial growth receptor (VEGFR). Two multicenter randomized placebo-controlled phase III trials were conducted for patients with advanced HCC who had not received any prior systemic therapy in Europe and America

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(SHARP trial) and in the Asia-Pacific region.^{7,8} The SHARP trial demonstrated a significantly longer median overall survival (OS) duration of 10.7 months in patients receiving sorafenib, compared to an OS of 7.9 months for patients who received placebos (hazard ratio [HR], 0.69; 95% confidence interval [CI], 0.55–0.87; $P<0.001$).⁷ The disease control rate, defined as the percentage of patients who achieved complete response, partial response, and stable disease based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria, was 43% in the sorafenib group compared with 32% in the placebo group ($P=0.002$). The partial response rate was only 2% in the sorafenib group, and no patients showed complete response. The Asia-Pacific trial also showed a significantly superior median OS of 6.5 months in patients receiving sorafenib, compared with 4.2 months in patients receiving placebos (HR, 0.57; 95% CI, 0.42–0.79; $P=0.014$).⁸ The most common adverse events were hand-foot syndrome, diarrhea, hair loss and fatigue.^{7,8} Sorafenib became the standard 1st-line therapy for advanced HCC through these two trials. Since then, substantial studies have attempted to predict patient responses to sorafenib; however, a clear conclusion has yet to be achieved.^{9–11}

2. Regorafenib

Regorafenib inhibits multiple protein kinases, including VEGFR and tyrosine kinase with immunoglobulin and epidermal growth factor homology domain (TIE). A randomized, double-blind, placebo-controlled phase 3 trial (RESORCE) enrolled 573 patients who progressed on sorafenib.¹² Patients who had not tolerated sorafenib were excluded, because regorafenib and sorafenib have similar toxicity profiles. Enrolled patients were randomized, in a 2:1 ratio, to receive either regorafenib (160 mg) or placebo once daily, during weeks 1–3 of each 4-week cycle. The study met the primary endpoint of OS with a HR of 0.63 (95% CI, 0.50–0.79; one-sided $P<0.001$). The median patient survival durations were 10.6 months with regorafenib and 7.8 months with placebo.¹² The disease control rate was 65% (complete response in 1% and partial response in 10%).¹² The most common clinically-relevant grade 3 or 4 adverse events were hypertension (15%), hand-foot skin reaction (13%), fatigue (9%), and diarrhea (3%).¹²

Based on these results, regorafenib became the first approved second-line agent for advanced HCC. However, whether patients who were intolerant to sorafenib can tolerate and respond well to regorafenib remains unclear, because such patients were excluded from the RESORCE trial.

3. Lenvatinib

Lenvatinib is an oral, multi-kinase inhibitor that targets VEGFR, fibroblast growth factor receptor (FGFR), PDGFR alpha, rearranged during transfection gene (RET), and KIT. Lenvatinib is approved for the treatment of radioactive iodine-refractory differentiated thyroid cancer and advanced renal cell carcinoma. A total of 954 patients with advanced HCC who had not received systemic chemotherapy were randomized to receive either lenvatinib (body weight ≥ 60 kg: 12 mg/day; <60 kg: 8 mg/day) or sorafenib (400 mg twice daily) in a 1:1 ratio.¹³ This noninferiority phase III trial (REFLECT) indicated that lenvatinib was noninferior to sorafenib in OS (13.6 months for lenvatinib vs. 12.3 months for sorafenib; HR, 0.92; 95% CI, 0.79–1.06).¹³ Furthermore, the median time to progression was significantly longer in patients receiving lenvatinib (7.4 months for lenvatinib vs. 3.7 months for sorafenib; HR, 0.63; 95% CI, 0.53–0.73; $P<0.001$).¹³ Objective response rates were also significantly higher (24% for lenvatinib vs. 9% for sorafenib; $P<0.001$), and the most common treatment-related adverse events of lenvatinib were hypertension, diarrhea, decreased appetite, and decreased weight. The approval of lenvatinib as a first-line agent for advanced HCC is anticipated.

4. Cabozantinib

Cabozantinib is an oral, multi-tyrosine kinase inhibitor that targets VEGFR, mesenchymal-epithelial transition (MET), growth arrest-specific 6 gene receptor (AXL), RET, KIT and FMS-like tyrosine kinase 3 (FLT3); however, cabozantinib has most potent activity against VEGFR and MET. A phase II trial was conducted for 41 patients with advanced HCC, all of whom had received up to one prior systemic anticancer therapy for more than four weeks before receiving an initial 12-week lead-in cabozantinib treatment.¹⁴ Patients with a partial

response could continue open-label cabozantinib, while patients with stable disease were randomized into either cabozantinib or placebo cohorts, and patients with progressive disease discontinued therapy at or before week 12. At week 12, two of the 41 patients achieved partial responses (5%), the disease control rate was 66%, and no patients showed complete response.¹⁴

A randomized, double-blind, placebo-controlled phase III trial (CELESTIAL) enrolled 707 patients with advanced HCC who had received up to two lines of prior systemic therapies (including sorafenib) and progressed on at least one.¹⁵ Patients were randomized 2:1 to receive cabozantinib (60 mg) or placebo once daily. At the second planned interim analysis, the primary endpoint was met with longer OS in the cabozantinib-treated group (10.2 months for cabozantinib vs. 8.0 months for placebo; HR, 0.76; 95% CI, 0.63–0.92; $P=0.0049$).¹⁵ The objective response rate was also significantly better in the cabozantinib cohort (4% for cabozantinib vs. 0.4% for placebo, $P=0.0086$).¹⁵ The most common grade 3/4 adverse events were hand-foot skin reaction (17%) and hypertension (16%).¹⁵ The response rate of 4% seems slightly lower compared to other potential drugs; however, approval awaits.

5. Other agents

Tivantinib is an oral c-MET inhibitor. A randomized, placebo-controlled phase II study demonstrated that the median time-to-progression was longer with tivantinib as second-line therapy in patients with advanced HCC (1.6 months vs. 1.4 months; HR, 0.64; 95% CI, 0.43–0.94; $P=0.04$).¹⁶ For patients with high MET expression, the magnitude of the time-to-progression benefit when taking tivantinib was more significant than in patients without high MET expression (2.7 months vs. 1.4 months; HR, 0.43; 95% CI, 0.19–0.97; $P=0.03$).¹⁶ Therefore, a randomized, placebo-controlled phase III trial was conducted for MET-high patients who had shown progression or intolerance while taking sorafenib; however, in this trial, tivantinib failed to improve OS or progression-free-survival over placebo.¹⁷

Ramucirumab is a recombinant immunoglobulin G 1 (IgG1) monoclonal antibody that binds to VEGFR-2 and is approved for colorectal cancer, non-small cell lung cancer,

and gastric or gastroesophageal junction adenocarcinoma. A randomized, placebo-controlled, phase III trial (REACH) for patients with HCC who had previously received sorafenib demonstrated that ramucirumab did not significantly improve OS (9.2 months vs. 7.6 months; HR, 0.87; 95% CI, 0.72–1.05; $P=0.14$).¹⁸ However, subgroup analysis suggested that ramucirumab improved OS of patients with baseline alpha-fetoprotein levels ≥ 400 ng/mL (7.8 months vs. 4.2 months; HR, 0.67; 95% CI 0.51–0.90). Currently, the REACH-2 study of ramucirumab in patients with advanced HCC with baseline alpha-fetoprotein levels of 400 ng/mL or more is underway (NCT02435433).¹⁹

IMMUNOTHERAPY

Immune checkpoints are co-inhibitory proteins that prevent T cells from attacking other cells in the body. Immune checkpoint inhibitors can release the brakes on the immune system and restore the immune response against cancer cells. Targets of immune checkpoint inhibitors include cytotoxic T-lymphocyte protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed cell death ligand 1 (PD-L1).

1. Nivolumab

Nivolumab is a humanized monoclonal IgG4 antibody to human PD-1. A phase I/II, open-label dose escalation and expansion trial (CHECKMATE-040) was conducted for patients with advanced HCC and included patients who experienced disease progression while on at least one prior systemic therapy or who were intolerant of or refused sorafenib.²⁰ The dose escalation phase confirmed the manageable safety profile and acceptable tolerability of nivolumab. At the dose expansion phase, 214 patients with advanced HCC received intravenous nivolumab at 3 mg/kg every 2 weeks.²⁰ The objective response and disease control rates were 20% and 64%, respectively (3 complete responses, 39 partial responses, and 96 stable diseases).²⁰ The 9-month overall survival rate was 74%,²⁰ and grade 3 or 4 treatment-related adverse events were observed in 25% (increased lipase in 13% and increased aspartate aminotransferase in 10%) of the patients.²⁰ In 2017, the CHECKMATE-040

study enabled nivolumab to achieve accelerated approval for the treatment of HCC in patients who have been previously treated with sorafenib. This approval was based on the outstanding overall response (14.3%; 3 complete response and 19 partial response) and duration of response of a 154-patient subgroup who progressed on or were intolerant to sorafenib.²¹ Among the 22 responders, 91% had responses of six months or longer, and 55% had responses of 12 months or longer. A phase III trial of nivolumab versus sorafenib as first-line treatment is ongoing (CHECKMATE-459, NCT02576509).²²

2. Other immune checkpoint inhibitors

Pembrolizumab is an anti-PD-1 antibody that has been approved for melanoma, non-small cell lung cancer, head and neck squamous cell carcinoma, Hodgkin lymphoma, urothelial carcinoma, gastric cancer, and any solid tumor with high microsatellite instability or deficient mismatch repair. Pembrolizumab was the first approval based on a certain genetic feature, without regard to original tumor location. Recently, a phase II study of pembrolizumab (KEYNOTE-224) reported the efficacy and safety of this drug in patients with advanced HCC who were previously treated with sorafenib.²³ Out of the 104 treated patients, one patient (1.0%), 16 (15.4%), and 47 (45.2%) showed complete response, partial response, and stable disease, respectively. The disease control rate was 61.5%,²³ and the 6-month progression-free survival and overall survival rates were 43.1% and 77.9%, respectively.²³ Of the responders, 94% had durable responses of six months or longer.²³

Common adverse events included fatigue (21.2%) and increased aspartate aminotransferase levels (12.5%).²³ Hepatitis B or hepatitis C virus flares were not observed when immune-mediated hepatitis occurred in 2.9% of the patients.²³ A randomized, placebo-controlled phase III study of pembrolizumab as a second-line therapy for advanced HCC (KEYNOTE-240) is currently ongoing (NCT02702401), and promising results are anticipated.²⁴

Durvalumab is a human IgG1 monoclonal antibody that blocks the interactions of PD-L1 with PD-1 and CD80 and has been approved for urothelial carcinoma. Tremelimumab is a human monoclonal antibody against CTLA-4 that has been approved for malignant mesothelioma. Tremelimumab has shown a partial response rate of 17.6% and a disease control rate of 76.4% in patients with HCC and chronic hepatitis C virus infection.²⁵ PD-1 and CTLA-4 have been suggested as non-redundant pathways for the regulation of T cell responses; and therefore, simultaneous inhibition of PD-1 and CTLA-4 pathways may have the potential for synergism.²⁶ According to the results of a phase I part of a phase I/II, open-label, randomized study of durvalumab and tremelimumab for unresectable HCC, the response rate was 20% and the disease control rate at week 16 was 57.5% across 40 enrolled patients.²⁷ A phase III trial of durvalumab and tremelimumab as first-line therapy is currently ongoing (NCT03298451).

ONGOING CLINICAL TRIALS

Agents other than those mentioned above are also under

Table 1. Ongoing phase III clinical trials for patients with advanced HCC

Experimental	Comparator	Identifier
Nivolumab	Sorafenib	NCT02576509
Durvalumab ± tremelimumab	Sorafenib	NCT03298451
Vaccinia virus-based immunotherapy + sorafenib	Sorafenib	NCT02562755
Icaritin	Sorafenib	NCT03236649
BGB-A317	Sorafenib	NCT03412773
Pembrolizumab	Placebo	NCT02702401 NCT03062358
Ramucirumab	Placebo	NCT02435433
Apatinib	Placebo	NCT02329860

HCC, hepatocellular carcinoma.

investigation. Phase III clinical trials of apatinib, a VEGFR-2 inhibitor, and vaccinia, a virus-based immunotherapy, are ongoing for patients with advanced HCC, as shown in Table 1.

CONCLUSIONS

In 2007, there was a breakthrough with sorafenib as a treatment for advanced HCC. These have been hard times, with many failures that may be attributable to heterogeneity of patient populations, deficits in trial designs, marginal antitumor activity of investigational drugs, or absence of biomarkers.^{28,29} Currently, we have two additional approved drugs (regorafenib and nivolumab) and another two with positive results in phase III trials (lenvatinib and cabozantinib), although none of these therapeutics have clear biomarkers. Molecular targeted agents have shown improved OS, with limited response rates. On the contrary, immune checkpoint inhibitors are drawing attention due to remarkable response rates and durable responses. Results based on conventional RECIST criteria alone may underestimate the efficacy of immune checkpoint inhibitors since pseudoprogression and immune-related patterns of mixed response have been reported.³⁰ Immune checkpoint inhibitors might lead the way for future HCC therapies, and warrant further studies.

AUTHOR CONTRIBUTIONS

BH Kim and JW Park were responsible for the acquisition and interpretation of the data, and the drafting of the manuscript.

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Conflicts of Interest

The authors have no conflicts to disclose.

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