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Evolving Systemic Therapy in Hepatocellular Carcinoma: Current Management and Opportunities for Integration With Radiotherapy

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The majority of patients with hepatocellular carcinoma (HCC) present with advanced disease. While first-line therapy with sorafenib is considered standard of care for patients with advancedHCC, outcomes remain poor. Despite early evidence of antitumor activity from Phase II trials of multiple other tyrosine kinase inhibitors, Phase III trials have largely failed to show an improvement insurvival outcomes over sorafenib. Given the encouraging early results with liver-directed radiotherapy for patients with advanced HCC, there is an increased interest in combination of these therapies tooptimize patient outcomes and improve survival by maximizing both local and distant disease control. Phase II trials of checkpoint inhibitors in HCC have also reported encouraging results, and Phase IIItrials are ongoing. Trials of combining radiotherapy with immunotherapy in solid tumors have shown intriguing results, potentially reflecting the opportunity for synergistic effects with the use of both modalities.

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Hepatocellular carcinoma (HCC) represents the second leading cause of cancer deaths worldwide, with approximately 745,000 deaths each year.[1] The incidence of HCC continues to rise in some parts of the world, including in the United States, where the age-adjusted incidence of HCC tripled between 1975 and 2005.[2] In the year 2017, there were approximately 40,710 new diagnoses and 28,920 deaths from primary liver cancer in the United States.[3] While HCC screening guidelines exist for patients with cirrhosis, most patients with HCC have advanced disease at the time of diagnosis and therefore are not candidates for definitive-intent therapies such as resection, transplantation, or ablation. Comorbidities, including underlying cirrhosis, also limit both systemic and liver-directed treatment options.

Moreover, while multiple pathways have been implicated in hepatocarcinogenesis, inhibitors of these pathways have thus far produced limited improvements in patient outcomes. In this review, we will discuss the role of targeted agents in HCC, and the emerging role of immunotherapy. We will also discuss the potential for integration of these agents with targeted local radiotherapy to improve patient outcomes.

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The Current Landscape of Systemic Therapy in Advanced HCC

First Line Therapy

For patients with advanced disease, sorafenib is considered first-line systemic therapy. Sorafenib is a small molecule tyrosine kinase inhibitor targeting Raf kinase and multiple receptor tyrosine kinases including VEGFR and PDGFR. Randomized controlled trials of sorafenib vs placebo have demonstrated modest but significant improvements in overall survival with sorafenib. The Sorafenib HCC Assessment Randomized Protocol (SHARP) Trial[4] randomized 602 patients with advanced HCC and Child-Pugh class A cirrhosis to sorafenib vs placebo. Of note, while 28% of patients had hepatis C virus (HCV)-related cirrhosis and 26% of patients had alcohol-related cirrhosis, only 12% of patients

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had HBV-related cirrhosis. After a second planned interim analysis, the trial was stopped early due to a significant improvement in overall survival (OS) with the use of sorafenib (10.7 months vs 7.9 months, HR 0.69, 95% CI 0.55 to 0.87, $P < 0.001$). The response rate was low in both arms, 2% with sorafenib vs 1% with placebo ($P = 0.05$), and there were no complete responses. An unplanned subgroup analysis of the SHARP Trial showed that there was no improvement in progression-free survival in patients with HBV-related cirrhosis treated with sorafenib. While sorafenib was associated with improvement in OS in patients with both HCV-related and HBV-related cirrhosis,[5] the magnitude of the survival benefit differed by etiology. The largest improvement in OS was seen in patients with HCV-related cirrhosis (14 vs 7.4 months) as compared with HBV-related cirrhosis (9.7 vs 6.1 months) and alcohol-related cirrhosis (10.3 vs 8 months).

Similarly to the SHARP Trial, the Asia-Pacific Trial[6] was a randomized trial of sorafenib in patients with advanced HCC and Child-Pugh class A cirrhosis. Reflecting the different patient population enrolled in the Asia-Pacific Trial as compared with the SHARP Trial, the majority of patients (73%) had HBV-related cirrhosis, while only 8.4% had HCV-related cirrhosis. While sorafenib was again associated with an improvement in OS over placebo (HR 0.68, 95% CI 0.5 to 0.93, $P = 0.014$), survival was substantially reduced compared with the SHARP trial (6.5 months with sorafenib vs 4.2 months with placebo). There were no complete responses; partial response rate 3.3% with sorafenib vs 1.3% with placebo. In addition to the difference in cirrhosis etiology, the reduced survival in the Asia-Pacific Trial has been attributed to the increased enrollment of patients with advanced disease, with an increased proportion of patients with poor performance status, higher number of intrahepatic tumors, and increased extrahepatic disease burden.

As noted above, a subgroup analysis of the SHARP trial showed that the magnitude of benefit with sorafenib varied by etiology, with the largest benefit seen in patients with underlying HCV. Further assessment of the impact of cirrhosis etiology on sorafenib response has been limited by the lack of stratification by cirrhosis etiology in randomized trials. To attempt to answer this question, a meta-analysis[7] was performed of three randomized trials of sorafenib vs alternative small molecule tyrosine kinase inhibitors. This meta-analysis included a total of 3,256 patients treated with sorafenib. While there was an improvement in OS with sorafenib in patients who were HCV positive and HBV negative, there was no improvement of OS in patients who were HCV negative and HBV positive. This analysis provides further support for the potential varying impact of sorafenib in different patient populations.

The majority of patients enrolled on trials of sorafenib had Child-Pugh A cirrhosis, raising questions as to the utility and safety of sorafenib in patients with Child-Pugh B and C cirrhosis. The Global Investigation of therapeutic Decisions in HCC and of its treatment with sorafenib trial[8,9] was an international prospective registry study which enrolled 3,202 patients with unresectable HCC treated with sorafenib. A total of 666 patients (21%) had Child-Pugh B cirrhosis. There was no significant increase in the type or incidence of adverse events in patients with Child-Pugh B cirrhosis. There were also similar rates of sorafenib discontinuation due to drug-related adverse events. Patients with Child-Pugh C cirrhosis are at significant risk for death from underlying hepatic disease, in addition to HCC. There are no prospective data available on the safety or efficacy of sorafenib with HCC with underlying Child-Pugh C cirrhosis, but a retrospective series[10] including 10 patients with Child-Pugh C disease treated with sorafenib reported median survival of only 1.5 months. Given their high competing risk of death from underlying hepatic disease, these patients should not be treated with sorafenib.

Since the initially reported phase III results with sorafenib, multiple subsequent randomized trials have compared sorafenib to alternative tyrosine kinase inhibitors[11–13], as well as combinations of sorafenib with other agents. However, while preclinical data and Phase II trial data have provided the rationale and preliminary efficacy signal, randomized phase 3 trials largely failed to show an improvement in median survival compared with sorafenib (Table 1). For example, the EGFR pathway has been one of many pathways implicated in hepatocarcinogenesis,[14,15] and Phase II trials of single-agent erlotinib in advanced HCC[16,17] and a phase I trial[18] of first-line sorafenib with concurrent erlotinib in solid tumors showed preliminary antitumor results. However, there was no improvement in survival with the addition of erlotinib to sorafenib in the randomized phase 3 SEARCH trial.[19] In this trial, 720 patients with newly-diagnosed advanced HCC and Child-Pugh A cirrhosis were randomized to sorafenib with erlotinib vs sorafenib with placebo. While there was a trend toward an improved overall response rate with sorafenib with erlotinib, there was a reduction in the disease control rate and no significant improvement in time to progression or overall survival.

Similarly, a randomized phase II trial[20] of doxorubicin with or without sorafenib showed an improvement in overall survival, progression-free survival, and median time to progression with sorafenib and doxorubicin as compared to doxorubicin alone. However, a subsequent Phase III trial, CALGB 80,802,[21] of sorafenib with or without doxorubicin was stopped early at an interim analysis when the futility boundary was crossed. Median overall survival was 9.3 months with doxorubicin and sorafenib vs 10.5 months with sorafenib alone (HR 1.06, 95% CI 0.8 to 1.4). There was also no improvement in progression-free survival with combination therapy. In addition, doxorubicin with sorafenib was associated with increased grade 3 and 4 adverse events.

Recently, lenvatinib has emerged as a new first-line treatment option for patients with newly-diagnosed advanced HCC. In the randomized open label phase III REFLECT trial,[22] lenvatinib, a multikinase inhibitor of VEGFR, FGFR, PDGFR, RET, and KIT, demonstrated a comparable overall survival and improved time to progression over sorafenib. A total of 954 patients with advanced HCC and Child-Pugh A cirrhosis were randomized to lenvatinib vs sorafenib. Lenvatinib was noninferior to sorafenib, with a median OS of 13.6 vs 12.3 months (HR 0.92, 95% CI 0.79-1.06). There was also an improvement