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Chapter

Treatment of Advanced Hepatocellular Carcinoma

Mahmoud Aryan, Ellery Altshuler, Xia Qian and Wei Zhang

Abstract

Hepatocellular Carcinoma (HCC) is the fifth most common cancer and represents the fourth most common cause of cancer related death worldwide. Treatment of HCC is dictated based upon cancer stage, with the most universally accepted staging system being the Barcelona Clinic Liver Cancer (BCLC) staging system. This system takes into account tumor burden, active liver function, and patient performance status. BCLC stage C HCC is deemed advanced disease, which is often characterized by preserved liver function (Child-Pugh A or B) with potential portal invasion, extrahepatic spread, cancer related symptoms, or decreased performance status. Sorafenib has been the standard treatment for advanced HCC over the past decade; however, its use is limited by low response rates, decreased tolerance, and limited survival benefit. Researchers and clinicians have been investigating effective treatment modalities for HCC over the past several years with a focus on systemic regimens, locoregional therapy, and invasive approaches. In this systemic review, we discuss the management of advanced HCC as well as the ongoing research on various treatment opportunities for these patients.

Keywords: hepatocellular carcinoma, advanced stage, systemic therapy, locoregional therapy

1. Introduction

Primary liver cancer represents an enduring global threat as the fifth most common cancer worldwide and the second highest global cause of cancer-related mortality [1]. The most common form of liver cancer is hepatocellular carcinoma (HCC), which makes up over 90% of primary hepatic malignancies and independently represents the fourth most common cause of cancer-related death worldwide [2, 3]. Hepatotropic viruses such as hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis D virus (HDV) are the most common causes of HCC, accounting for at least 80% of cases. HCC is also prevalent in individuals with underlying cirrhosis with other risk factors being alcohol use, non-alcoholic fatty liver disease (NAFLD), diabetes mellitus, obesity, aflatoxin exposure, hereditary hemochromatosis, tobacco use, oral contraceptive use, and other inherited metabolic disorders including tyrosinemia and glycogen storage disease type 1 (Von Gierke disease) [4–7].

The American Association for the Study of Liver Disease (AASLD) recommends that adults with cirrhosis undergo screening for HCC given the overall observed mortality benefit. Surveillance consists of abdominal ultrasonography every six

months either with or without alpha fetoprotein (AFP) measurement. Patients who have a lesion ≥ 1 cm or AFP measurement ≥ 20 ng/mL are recommended to undergo further diagnostic evaluation with multiphasic computed tomography (CT) scan or magnetic resonance imaging (MRI) of the abdomen [8, 9]. In some instances, HCC can be diagnosed radiographically via LI-RADS criteria (LR-5 is diagnostic), which consists of imaging findings of washout, enhancing capsule, and threshold growth in addition to overall size diameter increase over the course of months [10]. In instances in which lesions are indeterminate or cannot be diagnosed radiographically, patients typically undergo either biopsy or close interval repeat imaging [8].

Solid tumor oncological staging is usually based on the tumor (T), node (N), and metastasis (M) classification system. This system does not take into account the degree of liver dysfunction or patient performance status and is less useful for predicting the course of HCC [9]. The Barcelona Clinic Liver Cancer (BCLC) staging system is the most universally accepted staging system for HCC as it takes into account tumor burden, liver functional status, and patient performance status. In the BCLC system, patients are classified into different stages, including very early (BCLC stage 0), early (BCLC stage A), intermediate (BCLC stage B), advanced (BCLC stage C), and terminal (BCLC stage D). Very early to early-stage HCC (BCLC stage 0 or A) cancers are treated with curative intent through resection, ablation, or even liver transplant (LT); overall survival is as high as 75% at 5 years. The standard of care for patients with intermediate stage HCC (BCLC stage B) is transarterial chemoembolization (TACE) or transarterial radioembolization (TARE). Patients with advanced HCC (BCLC stage C) often present with cancer-related symptoms but usually have moderately preserved liver function (Child-Pugh A or B). These patients receive systemic therapy, though other treatment modalities are under investigation. BCLC stage D HCC is considered terminal and is usually managed with best supportive care [11, 12].

Unfortunately, over 80% of HCC are diagnosed at the advanced stage (BCLC stage C or D). Therapy options such as TACE and tumor resection are often not appropriate in these patients, and 5-year survival is as low as 18% [13, 14]. Researchers and physicians have been investigating potential effective treatment options in these patients in the past decade and have made great advances. In this systemic review, we summarize the latest strategies and upcoming methods of managing advanced (BCLC stage C) HCC.

2. First line systemic therapy

HCC has been historically considered a chemotherapy-resistant tumor. Most chemotherapy agents require hepatic metabolism and cannot be used in the setting of severely impaired liver function [15]. Overall survival is often dictated by underlying hepatic function rather than extensive tumor burden. Despite these challenges, researchers have applied targeted immunotherapy for advanced HCC treatment and, at least in certain clinical scenarios, have found benefit [16].

2.1 Atezolizumab + Bevacizumab combination therapy

Multi-agent combination therapy with atezolizumab and bevacizumab has recently replaced sorafenib as first line treatment for advanced HCC. Atezolizumab and bevacizumab are monoclonal antibodies that target program death ligand 1 (PD-L1) and vascular endothelial growth factor (VEGF), respectively [17, 18]. When used together, these medications inhibit both T cell apoptosis and angiogenesis. The combination of these medications was compared to sorafenib in patients

with treatment naïve advanced HCC in the IMbrave150 trial. The trial showed that patients treated with atezolizumab and bevacizumab had significantly improved overall survival (OS) and progression free survival (PFS) when compared to those treated with sorafenib [17]. Adverse events occurred at similar rates among the two groups, with the most common adverse effects in patients given atezolizumab with bevacizumab being hypertension and proteinuria. Following systemic review of nine randomized control trials, the American Society of Clinical Oncology (ASCO) has deemed combined atezolizumab/bevacizumab as the first line treatment for advanced HCC applicable to those with Child-Pugh A liver disease, Eastern Cooperative Oncology Group Performance Status (ECOG PS) no higher than one and treated esophageal varices (EV) [18]. Recent updates from Finn and colleagues on the IMbrave150 trial reported that median OS was 19.2 months in those taking atezolizumab and bevacizumab vs. 13.4 months in those taking sorafenib (HR, 0.66 [95% CI, 0.52, 0.85]; P=0.0009). At 18 months, those treated with atezolizumab and bevacizumab had an OS of 52% while patients on sorafenib has an OS of 40%. Atezolizumab and bevacizumab combination therapy has demonstrated the longest OS in a front-line phase III clinical study for advanced HCC to date and remains the standard of care for treatment-naïve, advanced HCC [19].

2.2 Sorafenib

Tyrosine protein kinase inhibitors (TKIs) had been at the forefront of advanced HCC treatment for quite some time. The first TKI approved by the Food and Drug Administration (FDA) for treatment of advanced HCC was sorafenib, which was first approved for treatment of unresectable HCC in 2007 (**Table 1**). This TKI targets VEGF, platelet derived growth factor (PDGF), and others molecular pathways to inhibit angiogenesis [20]. The Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) study was the first multi-center, placebo-controlled, phase III clinical trial in untreated, Child-Pugh A advanced HCC patients, and demonstrated a 2.8-month overall survival (OS) in those treated with sorafenib versus placebo (10.7 vs. 2.9 months) [21]. Further clinical trials and subset analysis showed that sorafenib provides survival benefit in patients with HCC not amendable to loco-regional therapy, though the benefit appears to be greater for patients

Regimen	ASCO recommendations	Criteria for use
Atezolizumab + Bevacizumab	First-line	ECOG PS ≤ 1, Child-Pugh A, following EV treatment
Sorafenib	First-line	When there are contraindications to Atezolizumab – Bevacizumab therapy
Lenvatinib	First-line	
Nivolumab	First-line or Second-line	
Cabozantinib	Second-line or Third-line	
Regorafenib	Second-line	Those who failed Sorafenib
Ramucirumab	Second-line	AFP ≥ 400
Pembrolizumab	Second-line	
Nivolumab + Ipilimumab	No recommendations	

Table 1.
American Society of Clinical Oncology (ASCO) recommendations for systemic therapy in advanced (BCLC stage C) HCC [18].

with Child Pugh A cirrhosis than Child Pugh B cirrhosis [22]. Cheng et al. performed a randomized, double-blind, placebo control trial of sorafenib in the Asian Pacific region in patients with advanced HCC. Following six weeks of therapy, patients treated with sorafenib had significantly higher median OS (6.5 months vs. 4.2 months; [HR] 0.68 [95% CI 0.50–0.93]; p=0.014) and time to progression (2.8 months vs. 1.4 months; HR 0.57 [0.42–0.79]; p=0.0005) [23]. Despite the clinical benefits of sorafenib, many patients are unable to tolerate the significant side-effects, which include diarrhea, hand and feet skin irritation, weight-loss, and electrolyte derangements [21, 24, 25]. With its OS benefits and effects on disease progression, sorafenib remains a first-line option for advanced HCC [18].

2.3 Lenvatinib

Following the success of Sorafenib, several other TKIs were developed as potential treatment options in advanced HCC patients. Lenvatinib is a TKI that targets multiple pathways within angiogenesis including VEGF receptors, fibroblast growth factor (FGF) receptors, platelet derived growth factor (PDGF) alpha as well as RET and KIT [26]. An open-label, multicenter, phase III clinical trial known as the REFLECT trial showed lenvatinib to be non-inferior to sorafenib in advanced HCC patients with respect to OS. In the same trial, patients treated with lenvatinib had a higher incidence of hypertension, decreased appetite, and weight loss, while those treated with sorafenib had a higher incidence of hand-foot skin reaction (HFSR) and diarrhea. Patients treated with lenvatinib had significantly better progression-free survival (PFS) (7.4 months vs. 3.7 months, $p < 0.001$), time to progression (8.9 months vs. 3.7 months, $p < 0.001$), and objective response rate (24.1% vs. 9.2%, $p < 0.001$) [25, 27]. Vogel et al. analyzed prognostic factors of the REFLECT trial and reported that baseline liver function tests such as albumin-bilirubin grade and Child-Pugh score were predictive of OS. These markers may be used to monitor overall safety and efficacy of lenvatinib treatment. Regardless of baseline liver function, lenvatinib led to longer OS than sorafenib [28]. Given this data, the ASCO now considers lenvatinib a reasonable first-line treatment option for advanced HCC [18].

Ongoing studies are being conducted on the use of lenvatinib alongside nivolumab, an anti-PD-1 monoclonal antibody often used as second line therapy for HCC, in patients with unresectable, advanced HCC. Early results from the phase 1b trial of this open label study show that lenvatinib combined with nivolumab is well tolerated in BCLC stage C HCC with multiple patients demonstrating partial or complete response [29].

3. Second line systemic therapy

3.1 Cabozantinib

Other agents have been investigated for advanced HCC for patients with disease resistant to first-line therapy. Cabozantinib is a TKI that targets mesenchymal-epithelial transition (MET) factor to disrupt hepatocyte growth factor pathway, a pathway that is often important for HCC oncogenesis [30]. A phase III clinical study known as the CELESTIAL trial showed that for patients who had suffered disease progression while on sorafenib, cabozantinib led to longer OS and PFS than placebo [31–33]. Although adverse effects such as diarrhea, HFSR, hypertension, nausea, and decreased appetite, were found to be twice as high in the cabozantinib group

than in the placebo group, the effects were generally mild and considered manageable [31–33]. Given its clinical benefit, the ASCO has classified cabozantinib as a second-line therapy for advanced HCC [18].

3.2 Regorafenib

Regorafenib is another TKI that has been utilized as a second-line agent in advanced HCC [18, 34, 35]. The RESORCE trial along with other studies support the use of regorafenib in treatment-resistant advanced HCC with active investigations focusing on applying the use of regorafenib in combination with other medications against advanced HCC [36]. When comparing cabozantinib and regorafenib as second line therapy in patients who had failed sorafenib therapy, the side effect profile of these medications was similar (with only increased incidence of diarrhea in patients taking Regorafenib), and both therapies provided similar benefits in regard to OS and PFS [37].

3.3 Apatinib

The latest TKI to show efficacy in advanced HCC is a VEGF receptor inhibitor called apatinib. This medication had been implemented in patients with hepatitis B infection in the past. Li et al. performed a multi-center, double blind, randomized phase III control trial in China in patients with advanced HCC refractory to at least one systemic agent [38]. The median OS was significantly higher in those treated with apatinib compared to placebo (8.7 months vs. 6.8 months, $p < 0.05$). The most common adverse effects of apatinib were hypertension, thrombocytopenia, and HFSR [38].

3.4 Nivolumab

Clinicians have also applied the use immunomodulatory checkpoint inhibitors as treatment for advanced HCC. Nivolumab is an immunoglobulin (IgG) 4 antibody that targets program death 1 (PD-1) on the surface of T cells to promote the anti-tumor properties of T cells [39]. Clinical trials have shown nivolumab to be a safe treatment option for advanced HCC with non-comparison studies showing durable and effective clinical response to treatment [40]. Multicenter phase III clinical trials comparing nivolumab to sorafenib are currently underway [41, 42]. Interim results of the CheckMate 459 trial, a randomized, multicenter phase III study, have shown no significant difference in median OS between nivolumab and sorafenib; however, the objective response rate was as high as 15% in those taking nivolumab vs. 7% in those taking sorafenib [41, 42]. Additionally, nivolumab was associated with superior health-related quality of life with patients reporting fewer side effects [43].

3.5 Pembrolizumab

Pembrolizumab is another monoclonal antibody directed against PD-1 that has been used as therapy for patients with advanced HCC [44]. The KEYNOTE trials were conducted to evaluate the efficacy of pembrolizumab and were expanded to compare the use of pembrolizumab following disease progression while on sorafenib to best supportive care. Despite pembrolizumab reducing the risk of death by 22%, there was no significant difference in OS between the two groups [44, 45]. Continued research is ongoing regarding the use of this anti-PD-1 agent for advanced HCC treatment.

3.6 Ramucirumab

Ramucirumab is a monoclonal antibody directed against vascular endothelial growth factor receptor 2 (VEGFR-2) that is approved for advanced HCC therapy in patients with alpha-fetoprotein (AFP) levels ≥400 ng/mL. Ramucirumab was initially compared versus placebo in a double-blind, multicenter, randomized control phase III trial known as REACH-1; unfortunately, there was no statistically significant difference in OS for those given ramucirumab or placebo in those who had failed first line sorafenib therapy [46]. Following subgroup analysis of the REACH-1 trial, the REACH-2 trial showed that ramucirumab had a statistically significant survival benefit compared to placebo in patients with AFP ≥400 ng/mL [47, 48]. The side-effect profile of ramucirumab is mild, with only reported increased frequency of hypertension and proteinuria, making it a second-line therapy for advanced HCC by the ASCO for patients with AFP ≥400 ng/mL [18, 46, 47]. Given its specific target population, ramucirumab is not routinely used in HCC patients with AFP <400 ng/mL.

3.7 Ipilimumab

Ipilimumab is a monoclonal antibody that targets cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) to downregulate immune function. The Checkmate 040 trial assessed the use of ipilimumab alongside nivolumab for advanced HCC patients and demonstrated combination therapy to have an object response rate twice as high as nivolumab monotherapy (31% vs. 14%) This combination therapy was also well tolerated with an acceptable side effect profile when compared to similar systemic therapy [49, 50].

The Checkmate 040 trial was expanded to investigate triple combination therapy consisting of nivolumab, ipilimumab, and cabozantinib altogether [51]. When compared to the combination of just nivolumab and ipilimumab, those on triple therapy had a longer period of progression-free survival (6.8 months vs. 5.5 months). Treatment related adverse events were higher in those taking triple therapy with a discontinuation rate of 20% in the triple therapy group and 3% in the double therapy group [51].

4. Locoregional therapy

Therapies in the form of embolization fall under the category of locoregional therapy and are typically contraindicated in patients with advanced HCC with underlying vascular invasion, extrahepatic spread, or poor performance status. However, some patients with advanced HCC classified as BCLC stage C have benefited from locoregional therapies [52].

4.1 TACE

Advanced HCC patients with tumor invasion off a branch of the portal vein or limited extrahepatic disease involvement have been trialed with TACE therapy [53]. TACE consists of injecting an emulsified chemotherapeutic agent into the hepatic artery flowing towards the underlying tumor, followed by embolization of the vessel to contain the drug and localize cell death within the malignancy [52, 53]. TACE has historically been more successful in localized disease without extrahepatic or diffuse vascular involvement and serves as the first-line treatment for intermediate (BCLC stage B) HCC. Consensus regarding the overall clinical utility of TACE

in advanced HCC when compared to systemic therapy remains under discussion [54]. Certain studies have shown TACE to be clinically safe and feasible in select advanced HCC patients with good collateral blood flow, and a meta-analysis reported TACE to be associated with higher treatment responses in advanced HCC when compared to other more conservative treatment approaches [54]. However, a retrospective analysis by Pinter and colleagues demonstrated no significant difference in OS between patients treated with TACE versus sorafenib, with Child-Pugh class predicting OS in these patients [55]. Meanwhile, Choi et al., reported through retrospective analysis that TACE in addition to sorafenib is associated with significantly increased time to progression when compared to sorafenib therapy alone, though no difference was seen with regard to OS [56]. Other retrospective studies including the TACTICS trial also found that combining TACE with sorafenib in advanced HCC improved progression-free survival when compared to sorafenib therapy alone [57–61].

4.2 Y-90 trans-arterial radio-embolization

Y-90 trans-arterial radio-embolization (TARE) is a therapy modality by which the isotope yttrium90 is delivered in in small vector beads to malignancy areas through branches of the hepatic artery [62]. TARE has been applied to treatment of advanced HCC in tumors that invade discrete segmental areas of the liver. Additionally, TARE has been shown to decrease overall portal vein tumor thrombus load [62]. Recent data indicates that when comparing the efficacy of TARE vs. sorafenib in advanced HCC patients, those who underwent TARE had a significantly higher tumor response rate, though there was no significant difference in OS [63]. Studies have also been conducted on combining TARE with systemic therapy in advanced HCC. No clear benefit was seen when combining TARE with sorafenib [64]; however, there have been case reports or series of positive outcomes in combining TARE with different systemic modalities [65, 66].

Most recently, a multicenter, single-arm, retrospective study conducted at three separate medical centers called the LEGACY study assessed the clinical efficacy of TARE therapy in unrespectable HCC [67]. Chemoembolization served as a primary treatment for 72.2% of the cohort with advanced disease. The three-year OS rate for the entire cohort was 86.6% with 62.2% of patients experiencing a duration of response of greater than six months [67]. This study led to the FDA approval of TheraSphere Y-90 Glass Microsphere for treatment of advanced HCC [68].

Garin et al. conducted research on the dosimetry of TARE therapy through a randomized, multicenter, open-label phase II trial known as DOSISPHERE-01 [69]. Patients received either a standard dose of Y-90 to the perfused lobe or a personalized dose of Y-90 targeted to the index lesion. Results showed that personalized dosimetry significantly improved response rates when compared to standard dosimetry in cases of locally advanced HCC (71% vs. 35%, $p < 0.01$) [69].

4.3 Hepatic artery infusion chemotherapy

Hepatic artery infusion chemotherapy (HAIC) has been used in the treatment of advanced HCC to directly delivery high concentrations of chemotherapeutic agents [70]. Studies on advanced HCC lesions that were unresectable, refractory to TACE, or associated with portal vein thrombus (PVT) have demonstrated positive responses to HAIC within patient cohorts. Groups in Korea and Japan have implemented HAIC with agents including cisplatin, 5-fluororuacil (5-FU), and pegylated interferon α-2b [70]. A randomized trial comparing interferon therapy coupled with 5-FU HAIC to sole interferon therapy in advanced HCC patients

showed a significantly higher response rate (45.6% vs. 24.6%, $p < 0.05$) and longer median progression free survival (6.5 months vs. 3.3 months, $p=0.0048$) in the patients who received HAIC [71]. In their study comparing HAIC and sorafenib in advanced HCC patients, Song and colleagues reported that the median overall survival was significantly longer in the patients who received HAIC (OS: 7.1 months vs. 5.5 months, $p < 0.05$) [72].

5. Surgery

As medical and surgical expertise continue to improve, surgery is no longer contraindicated in some advanced HCC patients [73]. Surgical resection of advanced HCC, either in the form of hepatectomy or en-bloc resection, has been revisited as a potentially efficacious way of increasing OS. Data has shown that the overall median survival time in advanced HCC patients with PVT who undergo surgical resection to be between 8 and 22 months, with OS between 21.7% to 69.6% at one year [74]. Given the high incidence of post-operative recurrence, multi-disciplinary approach to surgical planning on a case-by-case basis is needed [74, 75]. Liang and colleagues performed a meta-analysis and found that patients who underwent surgical resection of advanced HCC with PVT had longer OS than those who were treated with TACE therapy [76].

The combination of systemic therapy with surgical resection has also been applied to advanced HCC patients. Takeyama et al. studied the use of sorafenib as a potential neo-adjuvant therapy prior to surgical resection. Patients who underwent surgical resection following treatment with sorafenib had a significantly increased three-year survival than patients who underwent therapy with sorafenib alone [77]. Incorporating surgical resection with other treatment modalities including TACE and radiofrequency ablation have also promoted positive prognostic outcomes in select patients [74, 75]. Overall, the indication for surgical therapy in advanced HCC patients with or without PVT requires a multi-disciplinary approach and may entail utilizing systemic or locoregional therapy during treatment planning.

6. Future directions

Several systemic agents have been trialed for treatment of advanced HCC over the past decade. As newer agents are approved for use in advanced HCC, combined treatment options remain intriguing topics for investigation. Gosain et al. have hypothesized that sorafenib and pembrolizumab may have synergistic effects and are currently conducting a trial to evaluate the efficacy of these drugs when used in combination [78]. Given the favorable response rates of nivolumab that were seen in the Checkmate 040 trial, Welling et al. are conducting a phase II, randomized control of nivolumab combined with HuMax-IL8 and cabiralizumab (an anti-CSF1R antibody) in advanced HCC patients. HuMax-IL8 (now known as BMS-986253) is a novel, fully human monoclonal antibody that inhibits interleukin-8 (IL-8) [79]. Combining locoregional with systemic therapy is also under investigation [80]. Among multiple studies being conducted, the EMERALD-1 trial is a randomized, double-blind, placebo-controlled phase III study assessing anti-PD-1 agent durvalumab alongside TACE therapy with or without bevacizumab [81].

Alternative molecular targets are also being evaluated. El-Khouiery et al. are currently working on an advanced HCC phase I trial of humanized agonist IgG2 monoclonal antibodies to a specific tumor necrosis factor receptor known as OX40. Underlying safety and pharmacodynamic dose-dependent response are now being

investigated [82]. Another phase I trial currently underway involves a small activating RNA (saRNA) known as MTL-CEBPA that targets transcription factor C/EBP-α, which is involved in hepatic homeostasis and cell-cycle control. The preliminary results showed that it is relatively safety and can have potential synergistic efficacy with tyrosine kinase inhibitors in HCC [83]. Like new combinations of locoregional-systemic combinations and new uses of systemic agents, novel molecular-targeting agents offer hope for improved outcomes in advanced HCC.

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