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Nowotwory
Journal of Oncology

ISSN: 0029-540X

e-ISSN: 2300-2115

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DOI: 10.5603/NJO.a2023.0019

Article type: Review paper

Submitted: 2023-03-29

How to cite:

Lompart J, Sałek-Zań A, Püsküllüoğlu M, et al. Novel systemic treatment for hepatocellular carcinoma: a step-by-step review of current indications. NOWOTWORY J Oncol 2023; 73 (Ahead of print).

Accepted: 2023-04-07

Published online: 2023-04-27

Novel systemic treatment for hepatocellular carcinoma: a step-by-step review of current indications

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Abstract

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and the main cause of cancer-related death worldwide. The available treatment options for HCC include liver transplant, locoregional therapy (such as ablation, embolization, and radiotherapy), and systemic treatment. The latter encompasses targeted therapy, immunotherapy, and angiogenesis inhibitors, alone or in combination. The introduction of immune checkpoint inhibitors and targeted drug therapy has been one of the most significant advances in HCC treatment. These therapies were shown to prolong overall survival and progression-free survival in clinical trials including patients with advanced HCC. In recent years, the systemic treatment of advanced HCC has vastly improved, with a median survival of 19.2 months in the IMbrave150 trial. However, further research is needed to determine the optimal sequence of treatment.

Key words: hepatocellular carcinoma, targeted therapy, immunotherapy, systemic treatment

Epidemiology and pathogenesis of hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy. It is diagnosed in 75% to 80% of cases of primary liver cancer [1, 2]. In 2020, there were more than 900,000 new cases of HCC worldwide, and more than 800,000 patients died of HCC [3]. It is the fifth most common malignancy and the fourth most common cause of cancer-related death in the world. The highest prevalence of HCC was reported in south-east Asia. It is more common in men than in women and is usually diagnosed at the age of 60 to 75 years [2, 3].

In 90% of cases, HCC is caused by chronic liver disease, most often liver cirrhosis. The risk factors for liver cirrhosis include viral hepatitis (hepatitis B and C virus infection), alcohol use disorder, nonalcoholic fatty liver disease, aflatoxin exposure, and genetic factors (alpha-1-antitrypsin deficiency, autoimmune hepatitis, hemochromatosis, tyrosinemia type 1, glycogen storage disease, porphyria, and Wilson disease) [1, 2, 4].

The stages of liver cirrhosis are similar irrespective of the etiology. Initially, exposure to the risk factor triggers an acute inflammatory response and liver damage. Acute inflammation progresses into a chronic inflammatory state, leading to liver fibrosis and, ultimately, cirrhosis. These cirrhotic changes underlie the development of HCC [1].

Current approach to diagnosis of hepatocellular carcinoma

The histological subtypes of HCC according to the World Health Organization classification are presented in table I [5–7]. At the initial stage, HCC is asymptomatic. Therefore, it is usually an incidental finding. In patients with liver cirrhosis, it is usually diagnosed during routine follow-up tests. Patients with advanced HCC present with progressive cachexia, abdominal pain, ascites, leg swelling, jaundice, and fever [8].

Laboratory workup is based primarily on liver function tests. The previous gold standard in HCC diagnosis was an alpha-fetoprotein (AFP) test. However, in current clinical practice, its role is considered controversial. Increased AFP levels are neither sensitive nor specific for HCC. About 40% of patients with HCC have normal AFP levels, while elevated levels are seen also in other benign or malignant tumors [8–10].

If imaging tests of the liver reveal a lesion that is likely to be HCC, multiphase computed tomography or contrast-enhanced magnetic resonance imaging of the abdomen should be performed. Lesions should be assessed using the Liver Imaging Reporting and Data System (LI-RADS), which includes 5 categories. A lesion that is assigned to category LR-5 is considered as definitely HCC

[8, 10–12]. If HCC cannot be determined on the basis of imaging tests or if other etiology of the lesion is suspected, a tumor biopsy should be considered. However, it is not indicated in patients with a suspicion of HCC who are referred for liver transplant [8, 11].

If the diagnosis of HCC is confirmed, liver function should be assessed using the Child-Pugh score. The score was originally developed by Child in 1964 for patients undergoing portocaval shunt surgery. It was then modified in 1973 by Pugh to replace the criterion of nutritional status with prothrombin time or international normalized ratio. Currently, it is a widely used tool for assessing liver function and predicting mortality in patients with chronic liver disease [8, 13]. The score is presented in table II.

Treatment of hepatocellular carcinoma

The choice of treatment strategy depends on cancer stage, liver function, and the patient's general condition. There are 18 different scoring systems available in HCC (eg, the Okuda system, Cancer of the Liver Italian Program, tumor node metastasis (TNM) system, and Barcelona Clinic Liver Cancer [BCLC]). Each system has its advantages and limitations [1, 8]. Because HCC is a heterogeneous malignancy, in some cases, a molecular classification is additionally used (gene signature-based, metabolic, immune, or chromosome classification of HCC) [1]. In Western countries, a standard approach is to use the BCLC staging system to guide the management of patients with HCC. The BCLC system assesses the performance status, liver function based on the Child-Pugh score, the number and size of tumors in the liver, and the presence and severity of comorbidities (fig. 1) [8, 14, 15].

Locoregional therapy

HCC can be cured completely by liver resection or transplant. However, in clinical practice, this strategy is rarely feasible. Liver resection can be done at early stage provided that enough functioning liver can be spared. On the other hand, liver transplant options are limited because many patients are not eligible for the procedure. Another problem is an insufficient number of donors and a limited availability of liver transplant centers [13]. In patients with locally advanced cancer, so called locoregional therapies are an important part of treatment. Locoregional therapies are minimally invasive procedures for localized disease. They can be applied before systemic therapy to reduce tumor mass or as a palliative treatment option when systemic therapy is not possible [10, 16, 17]. Locoregional therapies for HCC, together with indications, are presented in table III.

Systemic therapy

Systemic therapy is used only as palliative treatment in patients with advanced HCC, corresponding to BCLC stage C (patients with very good or good functional status, with preserved liver function, that is Child-Pugh class A, and tumor invasion of the portal veins or extrahepatic spread) [19]. According to European Association for the Study of the Liver guidelines, which summarize efficacy data for available HCC treatments, there is no evidence to support the efficacy of standard cytostatic drugs in this indication [20].

First-line palliative systemic therapy

Until 2008, there were no medical treatments available with proven efficacy in patients with HCC. However, a breakthrough in the treatment of HCC occurred in 2008, when the results of the phase 3 SHARP trial were published, which compared a multikinase inhibitor, sorafenib, with placebo [21]. The primary outcomes were overall survival (OS) and the time to symptomatic progression. Sorafenib was shown to prolong the median OS by 2.8 months (median OS, 10.7 months *vs.* 7.9 months in the sorafenib and placebo arms, respectively), while it had no effect on the time to symptomatic progression. Thus, sorafenib became the standard first-line treatment for patients with advanced HCC. For the next 10 years, no new therapy had been developed that would offer better outcomes. Around that time, the efficacy of sorafenib was confirmed in a similar study in the Asian population [22]. However, in a meta-analysis by Zhang et al. [23], a subgroup analysis of these two trials showed a limited therapeutic effect of sorafenib in patients with extrahepatic spread. Based on these findings, sorafenib was not reimbursed in Poland in the treatment of patients with extrahepatic spread, even though it was a standard treatment worldwide. However, a modified drug program was introduced in May 2022, and since then sorafenib has been reimbursed for this indication.

After sorafenib efficacy was confirmed in the treatment of advanced HCC, studies were undertaken to investigate its use as adjuvant therapy after radical local therapy (resection or ablation). However, the phase 3 STORM trial showed no difference in recurrence-free survival between the sorafenib and placebo groups (33.3 months *vs.* 33.7 months, respectively; HR, 0.940; 95% CI 0.780–1.134; p = 0.26) [24].

The phase 3 CALGB 80802 trial assessed whether the addition of a cytostatic drug, doxorubicin, enhanced the effect of palliative treatment with sorafenib, but the results were not satisfactory [25]. There was strong evidence that the combination of doxorubicin and sorafenib therapy does not improve survival (median OS, 9.3 months in the combination arm *vs*. 9.4 months in the sorafenib arm; HR 1.05; 95% CI, 0.83–1.31) [25].

In 2018, the results of the noninferiority REFLECT trial comparing lenvatinib with sorafenib as first-line systemic therapy were published, marking a positive shift in the treatment of HCC [26]. It was assumed that lenvatinib should retain at least 60% of the sorafenib effect on OS *vs.* placebo. The median OS was 13.6 months for lenvatinib *vs.* 12.3 months for sorafenib (HR, 0.92; 95% CI, 0.79–1.06). Thus, lenvatinib was proved to be noninferior to the standard first-line treatment with sorafenib. In Poland, lenvatinib is not reimbursed in the treatment of patients with HCC.

Around this time, it was suggested for the first time that immunotherapy may be effective in HCC. However, studies on immunotherapy alone did show promising results. The CheckMate 459 study compared nivolumab vs sorafenib as first-line treatment in systemic therapy-naive patients with advanced HCC [27]. The primary endpoint was OS. The median OS was 16.4 months (95% CI, 13.9–18.4) for nivolumab and 14.7 months (95% CI, 11.9–17.2) for sorafenib (HR, 0.85 [95% CI 0.72–1.02]; p = 0.075; minimum follow-up, 22.8 months). The protocol-defined significance level of p = 0.0419 was not reached [27].

A breakthrough in the treatment of HCC occurred in 2020. Improved efficacy was achieved by combining immunotherapy with angiogenesis inhibitors. The development of HCC is a complex and multiphase process, with tumor growth dependent on pathological vascularization. The proliferation of cancer cells and neoangiogenesis are induced by numerous factors, including the vascular endothelial growth factor (VEGF). Bevacizumab inhibits the mircrovascular growth of tumor blood vessels by increasing T-lymphocyte infiltration, reducing the activity of immunsuppressive cells and acting synergistically with anti-programmed death ligand 1 (PD-L1) inhibitors [28, 29].

The results of the IMbrave150 trial provided the basis for developing a new first-line standard of care in the treatment of HCC. In this study, a combination of the PD-L1 inhibitor atezolizumab, 1200 mg, with the VEGF inhibitor bevacizumab, 15 mg/kg, was compared with the standard of care (sorafenib) [30]. Patients were randomly assigned in a 2:1 ratio to receive either atezolizumab plus bevacizumab or sorafenib. The study included 501 patients from Asia (excluding Japan) and the rest of the world. Patients with extrahepatic spread constituted 60% of the study population. The primary endpoints were OS and progression-free survival (PFS).

The results were promising, with a median OS of 19.2 months in patients who received the combination therapy *vs.* 13.4 months in the sorafenib group. The PFS was 6.8 months and 4.3 months, respectively. Of note, the objective response rate was 30%, including 10% of total remission cases. Combination therapy prolonged the time to symptomatic progression by 7 months. In contrast, while sorafenib improved survival, it had no effect on the time to symptomatic progression. Sorafenib prolonged survival, but it was associated with a shorter time to deterioration of the quality of life

compared with the atezolizumab–bevacizumab group. Atezolizumab plus bevacizumab also showed an acceptable safety profile. Serious toxic effects were reported in 38% of patients receiving the combination therapy *vs.* 31% of those receiving sorafenib [30].

The most recent area of research into the efficacy of treatment for advanced HCC has focused on the use of dual immunotherapy, The phase 3 HIMALAYA trial evaluated the efficacy and safety of tremelimumab (anti-CTLA-4) plus durvalumab (anti-PD-L1) or durvalumab alone vs sorafenib as the first-line treatment in patients with unresectable HCC [31]. The study showed that the STRIDE (single tremelimumab regular interval durvalumab) regimen, that is, a single dose of tremelimumab at 300 mg added to 1500 mg of durvalumab on the same day, followed by durvalumab, 1500 mg, every 4 weeks, is more effective than sorafenib alone. The median OS was 16.4 months for STRIDE *vs*. 13.8 months for sorafenib. Durvalumab alone was noninferior to sorafenib, with a median OS of 16.6 months *vs.* 13.8 months. The results of the HIMALAYA trial were positive, but in the light of findings from the IMbrave150 trial, it seems that dual immunotherapy might be used in patients with contraindications to antiangiogenic therapy. Clinical trials on first-line treatments for patients with HCC are summarized in table IV.

Second-line systemic therapy

Until 2017, there was no second-line therapy with confirmed efficacy available for patients with cancer progression after sorafenib therapy. However, in recent years, there have been significant advances also in this field. Three multikinase inhibitors were shown to be effective in the second-line setting. The first drug to show promising effects in clinical trials was regorafenib. The phase 3 RESORCE trial included 843 patients with HCC who showed disease progression on sorafenib treatment [32]. Patients were randomly assigned in a 2:1 ratio to receive either regorafenib or placebo. The primary endpoint was OS. Regorafenib improved OS: the median OS was 10.6 months for regorafenib *vs.* 7.8 months for placebo (HR, 0.63; 95% CI, 0.50–0.79) [32]. In Poland, regorafenib is not reimbursed for this indication.

In 2018, the CELESTIAL trial was published, which assessed the efficacy and safety of another multikinase inhibitor, cabozantinib, in previously treated patients with advanced HCC [33]. The study included 707 patients after up to 2 previous lines of systemic treatments, one of which had to be sorafenib. Patients were randomly assigned in a 2:1 ratio to receive either cabozantinib or placebo. Patients in the study arm received cabozantinib at a dose of 60 mg/d. To manage adverse events, treatment interruptions and dose reductions to 40 mg/d and then 20 mg/d were used. The primary endpoint was OS, and the secondary endpoints were the objective response rate and PFS. The study

showed promising results, with a significantly higher median OS in the cabozantinib *vs*. placebo arm (10.2 *vs*. 8 months). There were also significant differences in PFS between groups (5.2 months in the cabozantinib arm *vs*. 1.9 months in the placebo arm) [33]. In Poland, cabozantinib is available within the drug program of the Ministry of Health.

The most modest, but still significant, effect on survival was shown for ramucirumab in the second-line setting in patients with HCC and AFP levels higher than 400 ng/ml. Patients were randomized in a 2:1 ratio to receive ramucirumab or placebo. The primary endpoint was OS. The median OS was significantly higher in the ramucirumab group *vs*. placebo (8.5 *vs*. 7.3 months; HR, 0.710; 95% CI, 0.531–0.949; p = 0.0199. Also PFS was higher in patients receiving ramucirumab *vs*. those receiving placebo (2.8 *vs*. 1.6 months; HR, 0.452; 95% CI, 0.339–0.603; p < 0.0001) [34]. Clinical trials on second-line treatments for patients with HCC are summarized in table V.

Conclusions

Over the past 5 years, there have been significant advances in the systemic treatment of advanced HCC. The median OS increased from 10.7 months in the SHARP trial to 19.2 months in the IMbrave150 trial. However, all therapies that were effective in the second-line setting were investigated in patients with disease progression on sorafenib treatment. Therefore, the sequence of treatment lines is an issue that remains to be addressed in future studies.

Conflict of interest: none declared

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Received: 29 Mar 2023

Accepted: 7 Apr 2023

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Table I. Histological subtypes of hepatocellular carcinoma (HCC) [5–7]

Subtype*	**Characteristics**
fibrolamellar HCC	• a rare subtype of HCC, • often occurs in young patients, • less common in patients with liver cirrhosis, • presents as a single large mass, well demarcated, no hepatic infiltration, • tumor composed of large polygonal cells separated into liver cords or sheets of cells by dense bands of collagen; another characteristic feature is dense intratumoral fibrosis, • associated with a better prognosis
scirrhous HCC	• a rare subtype of HCC, • associated with poor prognosis, • dense intratumoral fibrosis that separates small nests of tumor cells, • tumor cells are small and arranged into cords or nests, • occurs in patients with liver cirrhosis
clear cell HCC	• a rare subtype of HCC, • characterized by cytoplasmic clearing that may be a consequence of glycogen or lipid accumulation in tumor cells, • risk factors include liver cirrhosis, hepatitis B or C, alcohol use disorder, and nonalcoholic fatty liver disease
steatohepatitic HCC	• common HCC subtype, • arises in the background of nonalcoholic or alcoholic steatohepatitis, • associated with liver fibrosis and cirrhosis, • may be accompanied by inflammation and liver necrosis, • tumor cells with a large clear cytoplasm and a high degree of nuclear atypia, • associated with poor prognosis
macrotrabecular HCC	• characterized by macrotrabecular structures that are thicker than the three layers of tumor cells arranged into trabeculae or nests and surrounded by intratumoral fibrosis, • associated with poor prognosis and aggressive tumor progression,

	• more common in the background of liver cirrhosis
chromophobe HCC	• a rare subtype of HCC, • considered to be a variant of conventional HCC, • characterized by large, polygonal cells with pale eosinophilic cytoplasm, • tumor cells arranged into trabeculae or nests; intratumoral fibrosis is common, • associated with a better prognosis, • cirrhotic background less common
neutrophil rich HCC	• a rare subtype of HCC, • characterized by large neutrophil infiltrates within the tumor, a high degree of necrosis and inflammation, • associated with a worse prognosis and a higher risk of recurrence and metastases
lymphocyte rich HCC	• characterized by dense lymphoid infiltrate, • usually occurs in young patients, • associated with a better prognosis

* Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) was not included in this list

Table II. Child-Pugh score [8, 13]

Parameter	**1 point**	**2 points**	**3 points**
total bilirubin (μmol/L)	<34	34–50	>50
serum albumin (g/L)	>35	28–35	<28
INR or PT	<1.7 (<4)	1.71–2.30 (4–6)	>2.3 (>6)
ascites	none	mild (or medically suppressed)	moderate to severe (or refractory)
encephalopathy	none	grade I–II (or suppressed with medication)	grade III–IV (or refractory)
	Class A	**Class B**	**Class C**
total points	5–6	7–8	10–15

1-year survival	100%	80%	45%
2-year survival	85%	57%	35%

INR – international normalization ratio; PT – prothrombin ratio

Table III. Locoregional therapies in hepatocellular carcinoma [10, 17, 18]	ineligible for TACE or systemic treatment

RFA – radiofrequency ablation; TACE – transarterial chemoembolization; BCLC – Barcelona Clinic Liver Cancer

Table IV. Summary of clinical trials on first-line palliative systemic treatment [21, 26, 30, 31]

Study	**Therapy**	**Primary endpoints**	**Median OS**
therapies reimbursed in Poland			
SHARP	sorafenib *vs.* placebo	OS, TTSP	longer by 2.8 months
IMbrave150	atezolizumab + bevacizumab *vs.* sorafenib	OS, PFS	longer by 5.8 months
therapies not reimbursed in Poland			
REFLECT	lenvatinib *vs.* sorafenib	OS	NA
HIMALAYA	tremelimumab + durvalumab *vs.* sorafenib	OS	longer by 2.6 months

NA – not available; OS – overall survival; PFS – progression-free survival; TTSP – time to symptomatic progression

Table V. Summary of clinical trials on second-line palliative systemic treatment [32, 33, 34]

Study	**Therapy**	**Primary endpoints**	**Median OS**
therapies reimbursed in Poland			
CELESTIAL	cabozantinib *vs.* placebo	OS	longer by 2.2 months
therapies not reimbursed in Poland			
RESORCE	regorafenib	OS	longer by 2.8 months

	vs. placebo		
REACH-2	ramucirumab *vs.* placebo	OS	longer by 1.2 months

OS – overall survival

Figure 1. Barcelona Clinic Liver Cancer (BCLC) staging system [14, 15]