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REVIEW ARTICLE

Piotr Potemski

Medical University of Lodz, Copernicus Memorial Multidisciplinary Centre for Oncology and Traumatology, Lodz, Poland

Systemic treatment of patients with advanced hepatocellular carcinoma

Address for correspondence:
Prof. dr hab. n. med. Piotr Potemski
Medical University of Lodz, Copernicus Memorial Multidisciplinary Centre for Oncology and Traumatology, Lodz, Poland
e-mail: piotr.potemski@umed.lodz.pl

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ABSTRACT

Hepatocellular carcinoma is the most common histologic type among primary liver neoplasms, which are the second cause of cancer-related deaths worldwide. Resection, ablation, liver transplantation or transarterial chemoembolization can be used in some patients but majority of patients receive systemic treatment provided their performance status is good and liver function is preserved. Overall, 5-year survival remains low and in Europe is 12%. Since 2008 sorafenib was the only drug with proven survival improvement in the first-line treatment. Regorafenib and cabozantinib showed efficacy in second-line treatment. Recently published the results of IMbrave150 trial showed that combination of atezolizumab with bevacizumab is much more effective than sorafenib in the first-line treatment. These results of IMbrave150 study will most probably change a daily-practice entirely.

Key words: hepatocellular carcinoma, systemic treatment, sorafenib, atezolizumab, bevacizumab

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver. Primary liver cancers are the second most common cause of cancer-related deaths in the world [1]. There are app. 800,000 new cases of primary liver cancer diagnosed every year, and about 750,000 people die. HCC is almost 3-fold more prevalent among men than women, and the highest incidence occurs in the countries of Eastern and South-Eastern Asia. The incidence of liver cancer is also increasing in Western countries, e.g. according to the SEER (The Surveillance, Epidemiology, and End Results) registry data, in the United States the incidence of HCC increased from 1.51/100,000 in 1973 to 6.20/100,000 in 2011 [2].

In Poland — according to the National Cancer Registry data — in 2017 almost 1,500 new HCC cases were diagnosed, and more than 2,000 patients died of this disease [3].

The prognosis of patients with HCC is poor — the 5-year survival rate in Europe is 12% [4].

Radical treatment methods include resection of the liver parenchyma, radiofrequency ablation (RFA) and organ transplantation. A valuable method that can be used in selected patients is transarterial chemoembolization (TACE). In the case of inability to use or ineffectiveness of the above-mentioned methods a palliative systemic treatment is indicated.

The choice of treatment method depends primarily on the disease stage and liver function. Many scoring systems assessing liver function have been developed — the oldest is the Child-Pugh scale, originally intended for risk assessment in patients undergoing surgical treatment (Tab. 1). The Child-Pugh scoring system was widely used during qualification of patients for prospective clinical trials, where in majority class A was the prerequisite. A useful scale that combines the assessment of liver function, general patient's performance status and the disease stage is the so-called Barcelona scale (BCLC, Barcelona-Clinic Liver Cancer staging system). In addition to prognostic information, the BCLC scale has therapeutic implications (Tab. 2).

Table 1. The Child-Pugh scoring system [5]

Measure	Number of points		
	1	2	3
Encephalopathy (grade)	0	1–2	3–4
Ascites	None	Mild	Severe
Serum albumin [g/dL]	> 3.5	2.8–3.5	< 2.8
INR	< 1.7	1.7–2.3	> 2.3
Total bilirubin [mg/dL]	< 2	2–3	> 3
Total	5–6	7–9	10–15
Liver functional class	A	B	C
Operational risk	Low	Moderate	High

INR — international normalized ratio

Table 2. Barcelona-Clinic Liver Cancer (BCLC) staging system [6]

Stage	0	A	B	C	D
Features	Single tumor < 2 cm and Child-Pugh A and PS 0	1–3 tumors < 3 cm and Child-Pugh A and PS 0	Many unresectable tumors and Child-Pugh A and PS 0	Portal vein invasion (PVI) and extrahepatic spread (ES) and Child-Pugh A and PS 0–2	Liver transplantation not possible and Child-Pugh B-C or PS 3–4
Treatment	RFA, resection	RFA, resection, liver transplantation	TACE	Systemic treatment	Only palliative treatment

TACE — transarterial chemoembolization; RFA — radiofrequency ablation; PS — performance status

Chemotherapy

The value of classical cytotoxic drugs in patients with advanced HCC is unconfirmed. The results of a prospective, controlled study in a small group of patients were published many years ago, indicating that doxorubicin may slightly (median 10.6 *vs.* 7.5 weeks) prolong overall survival (OS) compared to symptomatic treatment; however, at the expense of significant toxicity [7]. The value of doxorubicin in systemic palliative treatment has not been confirmed in subsequent studies.

Antiangiogenic drugs

The era of therapeutic nihilism in patients with advanced HCC ended in 2008, when the results of the Phase III SHARP (Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol) were published [8]. The study included 602 previously systemically untreated patients with overall performance status according to ECOG from 0 to 2 and liver efficiency class A according to the Child-Pugh classification. Patients were randomly assigned to experimental arm receiving sorafenib or control arm with placebo. Sorafenib is an inhibitor of RAF-1 and BRAF serine/threonine kinases, as well as VEGFR1-3 and PDGFR-β tyrosine kinases. The primary endpoint of the SHARP study was OS and time to symptomatic progression defined as a deterioration in quality of life of at least 4 points on the FHSI-8 (FACT Hepatobiliary Symptom Index) questionnaire for at least 3 weeks or worsening of performance status to 4 or death. The study turned out to be positive only for the first endpoint — sorafenib increased the median OS by 2.8 months (10.7 *vs.* 7.9 months), with the hazard ratio (HR) of 0.69 (95% CI: 0.55–0.87; $p < 0.001$). The median symptomatic progression-free survival (sPFS) was 4.1 *vs.* 4.9 months ($p = 0.77$).

The value of sorafenib was also confirmed in a study with no formal endpoints conducted among China, South Korea and Taiwan residents [9].

Sunitinib is multitargeted inhibitor of receptor tyrosine kinases, including VEGFR1-3, PDGFRα, PDGFRβ, KIT, FLT3, CSF-1R and RET. Therefore, a phase III study SUN1170 HCC was conducted comparing sunitinib to sorafenib in the first-line palliative treatment of HCC patients [10]. The study enrolled over 1,000 patients, the primary endpoint was OS, and it was assumed that sunitinib would be more effective, or at least not inferior as compared to sorafenib. The study was terminated prematurely due to the futility analysis results and for safety reasons — the OS of patients receiving sunitinib was shorter and the toxicity of the drug was higher.

The phase III CALGB 80802 study showed no improvement of prognosis after addition of doxorubicin in patients treated with sorafenib [11].

Lenvatinib is a multi-kinase inhibitor that inhibits VEGFR1-3, FGFR1-4, PDGFRα, RET and KIT. A non-inferiority study comparing lenvatinib to sorafenib was planned and performed [12]. The primary endpoint was OS, non-inferiority hypothesis was scheduled first, and if proven, testing the superiority hypothesis was assumed. It was also assumed that lenvatinib would retain at least 60% of the effect of sorafenib in prolonging OS compared to placebo. The delta value was thus defined as the upper limit of the 95% CI for a HR OS less than 1.08. In total 954 patients were enrolled to the study, and the HR OS in the intent-to-treat population was 0.92 (95% CI: 0.79–1.06), which allowed to reject the null hypothesis. It was also confirmed in per-protocol population, involving 929 patients. However, lenvatinib did not improve the quality of life and reduce the toxicity of the treatment. Obviously, lenvatinib was not more effective than sorafenib.

Regorafenib is a multi-kinase inhibitor of VEGFR1-3, TIE2, KIT, RET, RAF-1, BRAF, PDGFR, FGFR and CSF1R. The phase III RESORCE study involved 843 patients with progression during sorafenib therapy, provided that the drug is well tolerated (daily dose of at least 400 mg for at least 20 days during the last 4 weeks of sorafenib use) [13]. Patients were randomized in a 2:1 ratio to regorafenib or placebo. The primary endpoint of the RESORCE study was OS. The study was positive, median OS was 10.6 months *vs.* 7.8 months, HR OS 0.63 (95% CI: 0.50–0.79). Grade 3 or 4 treatment-related adverse events occurred in 67% of patients receiving regorafenib recipients compared to 39% in the placebo group.

Another drug that has shown an improvement in prognosis in the next line of systemic treatment in patients previously receiving sorafenib was cabozantinib, which is an inhibitor of VEGFR1-3, MET and AXL tyrosine kinases. The CELESTIAL study included 707 patients after no more than 2 lines of previous systemic treatment including sorafenib (approximately 30% of patients) [14]. Patients were randomized in 2:1 ratio to cabozantinib or placebo. The primary endpoint was OS. During the second of three pre-planned interim analyzes the observed difference met the assumptions of statistical significance. The median OS in the experimental arm was 10.2 months compared to 8.0 months in patients receiving placebo (HR 0.76; 95% CI: 0.63–0.92; $p = 0.005$). Grade 3 or 4 side effects occurred in 68% of patients in the experimental arm and in 36% of patients in the control group.

Immunotherapy

Patients with advanced HCC previously treated with sorafenib were enrolled to various cohorts of the CheckMate 040 uncontrolled study with objective response rate as the primary endpoint. Monotherapy with nivolumab (anti-PD-1 antibody) resulted in 20% of objective responses, and in the case of combined use of nivolumab and ipilimumab (anti-CTLA-4 antibody), the objective response rates ranged between 27% and 32%, depending on the doses and administration schedule [15, 16].

A phase III CheckMate 459 study was also conducted, comparing nivolumab with sorafenib in a group of 743 previously systemically untreated patients with advanced HCC. The primary endpoint of the study was OS. The outcome was negative – it was not possible to demonstrate a statistically significant difference in favor of nivolumab [17].

Pembrolizumab (anti-PD-1 antibody) was used in patients previously treated with sorafenib in a phase II uncontrolled KEYNOTE-224 study [18]. In the group of 104 patients, 17% of objective responses were achieved. However, the results of the phase III KEYNOTE-240 study, including 413 patients previously treated with sorafenib, were very disappointing [19]. Patients were randomized to pembrolizumab or placebo, and the co-primary endpoints were OS and PFS. There were no differences meeting the specified criteria of statistical significance for OS and PFS. Adopting a more conventional study design with a single endpoint of OS would likely be considered formally positive as the median OS of patients receiving pembrolizumab was 13.9 months compared to 10.6 months in the placebo group (HR 0.78; 95% CI: 0.61–1.00; nominal $p = 0.02$).

When it seemed that sorafenib would remain the standard of first-line palliative treatment, and immunotherapy would only be used in selected patients in subsequent treatment lines, the results of the IMbrave150 study were presented for the first time at the 2019 ESMO-Asia congress [20]. The study enrolled 501 previously untreated patients with advanced HCC who were randomized in 2:1 ratio to atezolizumab (anti-PD-L1 antibody) with bevacizumab (anti-VEGF antibody) or sorafenib arm. One of the exclusion criteria was the presence of an active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Randomization was stratified by geographic region (Asia without Japan *vs.* other countries), presence of large vessel infiltration or extrahepatic dissemination (yes *vs.* no), baseline AFP level (400 *vs.* ≥ 400 ng/mL), and ECOG performance status (0 *vs.* 1). The primary endpoints of the study were OS and PFS. After a median follow-up of almost 9 months, a significant increase in OS was achieved (HR 0.58; 95% CI: 0.42–0.79; $p < 0.001$; median not reached *vs.* 13.2 months; estimated 1-year survival rate was 67% *vs.* 55%). Median PFS was 6.8 months *vs.* 4.3 months (HR 0.59; 95% CI: 0.47–0.76; $p < 0.001$). Grade 3 or 4 adverse events occurred in 57% of patients in the experimental group and 55% of patients in the control group. The incidence of serious adverse events was 38% *vs.* 31%. Importantly, the quality of life of patients in the experimental group was maintained longer. The median

Table 3. The most important phase III studies, the results of which shaped the strategy of systemic treatment in patients with advanced hepatocellular carcinoma

Author, year and reference	Sample size, N	Treatment line	Experimental arm	Control arm	Primary endpoint	Outcomes
Llovet 2008 [8]	602	1.	Sorafenib	Placebo	OS Time to symptomatic progression	Median OS 10.7 *vs.* 7.9 months (SS) Time to symptomatic progression (NS)
Kudo 2018 [12]	954	1.	Lenvatinib	Sorafenib	OS	The hypothesis that lenvatinib is inferior to sorafenib has been rejected
Bruix 2017 [13]	846	2.	Regorafenib	Placebo	OS	Median OS 10.6 *vs.* 7.8 months (SS)
Abou-Alfa 2018 [14]	707	2. or 3.	Cabozantinib	Placebo	OS	Median OS 10.2 *vs.* 8.0 months (SS)
Finn 2020 [20]	501	1.	Atezolizumab with bevacizumab	Sorafenib	OS and PFS	HR OS 0.58; 95% CI: 0.42–0.79 (SS). Median PFS 6.8 *vs.* 4.3 months (SS)

CI — confidence interval; HR — hazard risk; NS — statistically non-significant; OS — overall survival; PFS — progression-free survival; SS — statistically significant

time to a significant deterioration in the quality of life was 11.2 months *vs.* 3.6 month, respectively [21].

At the end of May 2020, the US Food and Drug Administration (FDA) approved atezolizumab with bevacizumab in the first-line treatment of patients with advanced HCC.

Table 3 summarizes the results of the most important phase III studies.

Summary

Since the publication of the SHARP study results, several clinical trials have been conducted to improve the effectiveness of systemic treatment in patients with advanced HCC. Most of them failed. It has been shown that regorafenib and cabozantinib improve prognosis in patients previously treated with sorafenib, and modern immunotherapy in some patients allows obtaining an objective response with moderate toxicity, but without a proven effect on the improvement of OS. In this context, the results of the IMbrave150 study should be considered a very significant advance defining a new first-line treatment strategy.

Conflict of interest

Advisory and lecture fees from Roche and Ipsen; travel grants from Roche.

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