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Editorial

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Current landscape and future directions for systemic treatments of hepatocellular carcinoma

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Systemic treatment is the optimal approach for patients with advanced or intermediate-stage hepatocellular carcinoma (HCC) with contraindications or refractoriness to locoregional treatments[1]. The aim of systemic treatment is to prolong survival and delay clinical deterioration. Until 2008, no systemic therapy provided meaningful clinical benefit. In the past, studies that evaluated the role of conventional chemotherapy, mainly doxorubicin or combinations of platinum agents, resulted in significant toxicities, without a clear demonstration of efficacy[2].

In the early 2000s, there were advances in the knowledge of the molecular mechanisms that drive hepatocarcinogenesis, such as the hyperactivation of intracellular signaling pathways of protein kinases and angiogenesis[3]. This knowledge has boosted the development of molecular target drugs that inhibit receptors and mediators of these signaling pathways, which have been translated into clinical studies that included patients with advanced HCC.

Sorafenib, a multikinase inhibitor, was the first systemic agent to demonstrate a survival benefit in patients with unresectable HCC based on two placebo-controlled trials[4,5]. It is important to highlight that this drug increased survival without causing a significant reduction in tumor burden. The radiological response rate,

however, remains low, ranging from only 2% to 3%. In addition, some adverse events such as fatigue, hand-foot reaction, diarrhea and arterial hypertension indicate the need for strict follow-up during treatment with this drug[4,5].

In 2016, regorafenib (a tyrosine kinase inhibitor against VEGFR1-3, PDGFR, KIT RET, and RAF) showed a significant increase in survival after progression with sorafenib, with a median survival of 10.6 months in the regorafenib arm versus 7.8 months for placebo[6]. An exploratory analysis showed that the sorafenib-regorafenib sequence reached a median survival of 26 months, which reflects a significant advance in the treatment of patients with advanced HCC[7].

Between 2016 and 2019, other drugs were introduced for the management of HCC after the results of prospective randomized studies. Lenvatinib, another tyrosine kinase inhibitor, demonstrated non-inferiority to sorafenib in the first-line setting and was incorporated as an option in this scenario[8]. Cabozantinib, a tyrosine kinase inhibitor against VEGFR, MET and AXL, increased the survival of patients with advanced HCC after progression to sorafenib and became a second-line option[9]. Finally, ramucirumab, a monoclonal antibody against VEGFR-2, was associated with better survival in patients with AFP ≥ 400 ng/mL[10]. Besides the imaginary targets, there may be a general mechanism of action of tyrosine-kinase inhibitors aimed at blocking a wide spectrum of pathways, which remain underexplored but can be addressed in the setting of a personalized approach[11].

As of 2020, immunotherapeutic agents have also been incorporated into the management of advanced HCC. The phase III study IMBRAVE150 included patients with advanced HCC to receive the combination of atezolizumab (a PD-L1 inhibitor) with bevacizumab (a VEGF inhibitor) or sorafenib. The study demonstrated a significant increase in overall survival, with a median survival of 19.2 months for the experimental arm and 13.4 months for the control arm[12]. In 2022, another combination of immunotherapeutic agents demonstrated a benefit in overall survival in a phase III study with patients with advanced HCC. In this study, patients who received the combination of durvalumab (a PD-L1 inhibitor) and tremelimumab (a CTLA-4 inhibitor) had better median survival (16.4 months) compared to patients who received sorafenib (13.8 months)[13]. Therefore, combinations of immunotherapeutic agents have become the standard choice in the first line of patients with advanced HCC.

The alternatives of systemic therapies for HCC are rapidly evolving and clinical decisions are challenging. In order to offer guidance on the selection of first-line and subsequent second-line systemic therapies, the American Association for the Study of Liver Diseases (AASLD) recently released recommendations, which are summarized in Table 1[14].

Several questions remain open in regard to the applicability of systemic treatment for HCC, most notably the use in earlier stages aimed at preventing recurrence and the safety in populations underrepresented in pivotal trials, such as patients with liver dysfunction or prior transplantation.

The pivotal trials restricted the inclusion of Child-Pugh A patients, while there is limited available data on the use of systemic treatment in patients with liver dysfunction. A recent real-world study with 202 patients, including 48 patients with Child-Pugh B treated with atezolizumab and bevacizumab, showed that these patients had comparable rates of treatment-related adverse events to Child-Pugh A, and a median overall survival of 6.7 months versus 16.8 months for Child-Pugh A patients[15]. A meta-analysis evaluated different studies of immunotherapy in patients with liver dysfunction and observed a median survival of 6.05 months, but concluded that the high heterogeneity across studies reflects the incapacity of the current

Table 1. Summary of american association for the study of liver diseases guidelines

First line	Level	Recommendation
Indication: patients with preserved liver function (Child-Turcotte-Pugh A or well-selected Child-Turcotte-Pugh B cirrhosis), ECOG PS 0-1, who have BCLC Stage C HCC, or BCLC Stage B HCC not amenable to or progressing after locoregional therapy	1	Strong
Atezolizumab plus bevacizumab or durvalumab plus tremelimumab are preferred first-line therapy options	2	Strong
Patients considered for atezolizumab plus bevacizumab should undergo an EGD to assess for risk of variceal or other gastrointestinal bleeding	5	Strong
The optimal treatment of large varices prior to atezolizumab plus bevacizumab initiation is unknown, although AASLD recommends at least one session of banding. Carvedilol may be considered as an alternative prior to atezolizumab and bevacizumab	5	Weak
Patients with recent bleeding within 6 months and those with high-risk stigmata for bleeding on EGD should have varices adequately treated prior to atezolizumab plus bevacizumab initiation, or these patients may be considered for durvalumab and tremelimumab	5	Strong
First-line sorafenib or lenvatinib should be offered to patients with contraindications to atezolizumab plus bevacizumab or durvalumab plus tremelimumab	1	Strong
Second-line		
Indication: patients with preserved liver function (Child-Turcotte-Pugh A or well-selected Child-Turcotte-Pugh B cirrhosis), ECOG PS 0-1, who develop HCC progression or intolerance with first-line systemic therapy	1	Strong
Sorafenib or lenvatinib as preferred agents after first-line if patients are not eligible for clinical trials	5	Weak
Cabozantinib, regorafenib, or ipilimumab plus nivolumab may be alternatives after immunotherapy-based regimens	5	Weak
AASLD advises cabozantinib or regorafenib (or ramucirumab in patients with AFP ≥ 400 ng/ml) as preferred agents after sorafenib or lenvatinib if patients are not eligible for clinical trials	1	Strong
AASLD advises against the use of immunotherapy after liver transplantation	4	Strong

HCC: Hepatocellular carcinoma; ECOG-PS: eastern cooperative oncology group performance status; BCLC: barcelona clinic liver cancer; EGD: esophagogastroduodenoscopy; AFP: alpha-fetoprotein; AASLD: American Association for the study of liver diseases

evidence to support the indication of immunotherapy in HCC patients with relevant liver dysfunction[16].

Global real-world data reported that sorafenib is safe in Child-Pugh B patients, but survival outcomes are worse compared to Child-Pugh A[17]. Additionally, an Italian multicentric randomized trial was designed to explore the benefit of sorafenib in Child-B7-9 patients. The trial was planned to include 320 patients, but only 35 patients were enrolled. Although not statistically powered, a median overall survival of 3.5 months was observed[18].

Solid organ transplantation is a formal contraindication to immunotherapy because of its potential risk of inducing allograft rejection, and therefore this subgroup was also excluded from the pivotal trials. Although small series have reported cases of transplanted patients safely treated with immune checkpoint inhibitors, the standard systemic therapy for these patients is still based on tyrosine kinase inhibitors[19].

The use of systemic treatment in early stages is currently under active research. Adjuvant treatment with atezolizumab plus bevacizumab has been shown to delay recurrence after surgery or ablation in patients at high risk of recurrence, but no positive impact on survival has been demonstrated[20]. In intermediate stage (BCLC-B) HCC, systemic treatment is preferable for patients with high tumor burden. In a propensity-matched study, lenvatinib was shown to provide better survival and lower liver alteration compared to transarterial chemoembolization, in patients with BCLC-B and beyond up-to-seven criteria[21]. In addition, several trials are testing combinations of immune checkpoint inhibitors plus transarterial treatments such as transarterial chemoembolization or radioembolization. The rationale for this approach is to harness the immune boost provided by tumor cell death with local treatments and to optimize systemic antitumor activity with immune checkpoint inhibitors.

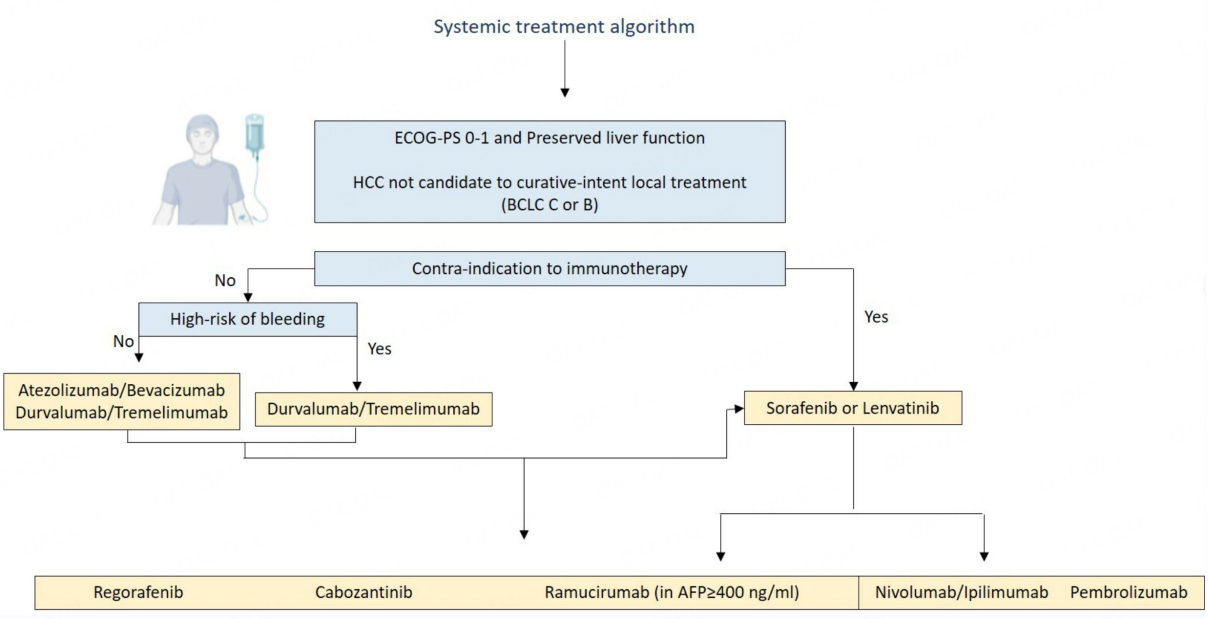

Figure 1. Treatment strategy for HCC with systemic therapies. BCLC: Barcelona clinic liver cancer; ECOG: eastern cooperative oncology group; HCC: hepatocellular carcinoma; AFP: alpha-fetoprotein.

Finally, the achievements in the management of advanced HCC in recent years were remarkable. A clear survival benefit has been seen with the incorporation of immunotherapy and novel targeted therapies. Optimal sequences remain to be defined, while clinical practice should be tailored by the risk of adverse events and the use of drugs that proved survival benefits in prospective trials [Figure 1]. Future directions will explore how to broaden new strategies in orphan conditions and how to integrate different modalities into HCC treatment algorithms.

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Authors' contributions

Conception, design, writting and critically reviewed the manuscript: Fonseca LG
Conception and critically reviewed the manuscript: Carrilho FJ

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Not applicable.

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Conflicts of interest

Leonardo G Fonseca: lecture fees from Bayer, BMS, AstraZeneca, Roche. Advisory Board: Bayer, AstraZeneca and Roche. Carrilho FJ: no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. *J Hepatol* 2022;76:681-93. DOI PubMed PMC
2. da Fonseca LG, Marta GN, Braghiroli MIFM, et al. Safety and efficacy of cytotoxic chemotherapy in hepatocellular carcinoma after first-line treatment with sorafenib. *BMC Cancer* 2018;18:1250. DOI PubMed PMC
3. Nault JC, Martin Y, Caruso S, et al. Clinical impact of genomic diversity from early to advanced hepatocellular carcinoma. *Hepatology* 2020;71:164-82. DOI
4. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009;10:25-34. DOI
5. Llovet JM, Ricci S, Mazzaferro V, et al; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359:378-90. DOI
6. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017;389:56-66. DOI
7. Finn RS, Merle P, Granito A, et al. Outcomes of sequential treatment with sorafenib followed by regorafenib for HCC: additional analyses from the phase III RESORCE trial. *J Hepatol* 2018;69:353-8. DOI
8. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018;391:1163-73. DOI
9. Abou-Alfa GK, Meyer T, Cheng A-L, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *N Engl J Med* 2018;379:54-63. DOI PubMed PMC
10. Zhu AX, Kang YK, Yen CJ, et al; REACH-2 study investigators. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2019;20:282-96. DOI
11. Ramadori G, Füzesi L, Grabbe E, Pieler T, Armbrust T. Successful treatment of hepatocellular carcinoma with the tyrosine kinase inhibitor imatinib in a patient with liver cirrhosis. *Anticancer Drugs* 2004;15:405-9. DOI
12. Cheng AL, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. *J Hepatol* 2022;76:862-73. DOI PubMed PMC
13. Abou-alfa GK, Lau G, Kudo M, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. *NEJM Evidence* 2022:1. DOI
14. Singal AG, Llovet JM, Yarchoan M, et al. AASLD practice guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. *Hepatology* 2023. DOI
15. D'Alessio A, Fulgenzi CAM, Nishida N, et al. Preliminary evidence of safety and tolerability of atezolizumab plus bevacizumab in patients with hepatocellular carcinoma and Child-Pugh A and B cirrhosis: a real-world study. *Hepatology* 2022;76:1000-12. DOI
16. El Hajra I, Sanduzzi-Zamparelli M, Sapena V, et al. Outcome of patients with HCC and liver dysfunction under immunotherapy: a systematic review and meta-analysis. *Hepatology* 2023;77:1139-49. DOI
17. Marrero JA, Kudo M, Venook AP, et al. Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: the GIDEON study. *J Hepatol* 2016;65:1140-7. DOI
18. Daniele G, Schettino C, Arenare L, et al. BOOST: a phase 3 trial of sorafenib *vs.* best supportive care in first line treatment of hepatocellular carcinoma in patients with deteriorated liver function. *Hepatoma Res* 2021;7:61. DOI
19. Anugwom CM, Leventhal TM, Debes JD. Understanding immune perspectives and options for the use of checkpoint immunotherapy in HCC post liver transplant. *Hepatoma Res* 2022;8:7. DOI PubMed PMC
20. Hack SP, Spahn J, Chen M, et al. IMbrave 050: a Phase III trial of atezolizumab plus bevacizumab in high-risk hepatocellular carcinoma after curative resection or ablation. *Future Oncol* 2020;16:975-89. DOI PubMed
21. Kudo M, Ueshima K, Chan S, et al. Lenvatinib as an initial treatment in patients with intermediate-stage hepatocellular carcinoma beyond up-to-seven criteria and child-pugh a liver function: a proof-of-concept study. *Cancers* 2019;11:1084. DOI PubMed PMC