ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2021 June 28; 27(24): 3429-3692

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents Weekly Volume 27 Number 24 June 28, 2021

World Journal of Gastroenterology

Weekly Volume 27 Number 24 June 28, 2021

Contents

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NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Andrzej S Tarnawski, Subrata Ghosh

EDITORIAL BOARD MEMBERS
http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE
June 28, 2021

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World J Gastroenterol 2021 June 28; 27(24): 3429-3439

DOI: 10.3748/wjg.v27.i24.3429

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

OPINION REVIEW

Trial eligibility in advanced hepatocellular carcinoma: Does it support clinical practice in underrepresented subgroups?

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Author contributions: All authors equally contributed to this paper with conception and design of the study, literature review, drafting, critical revision and editing; they all have approved the final version.

Conflict-of-interest statement: F Piñero has received Advisory Board and speaker honoraria, and he is consultant for RAFFO, BAYER, LKM-Biotoscana and ROCHE; research grants from the Argentinean National Institute of Cancer (INC ID-190), Argentinean National Ministry of Science and Technology Development (PICT 2017, FONCYT) and from the Latin American Liver Research Educational and Awareness Network (LALREAN).

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Abstract

Although hepatocellular carcinoma is considered a highly lethal malignancy, recent therapeutic advances have been achieved during the last 10 years. This scenario resulted in an unprecedented improvement in survival for patients with advanced hepatocellular carcinoma, almost reaching 20-26 mo of overall survival after first-second line sequential treatment. The advent of the combination of atezolizumab with bevacizumab showed, for the first time, superiority over sorafenib with improvement in overall survival. However, first and second-line trials were correctly based on the premise that a strict selection of patients enhances the power to capture the positive effect of treatment by excluding competing risks for mortality such as liver failure, decompensated cirrhosis or other underlying medical conditions. As a result, the inclusion criteria used in clinical trials do not support the use of novel therapies in several real-world scenarios involving underrepresented subgroups, such as patients with unpreserved liver function, other comorbid conditions, a history of solid-organ transplantation, autoimmune disorders and those with a high risk of bleeding. The present text aims at discussing treatment strategies in these subgroups.

Key Words: Eligibility; Systemic therapies; End-stage; Hepatocellular carcinoma

Core Tip: The strict criteria used in clinical trials in advanced hepatocellular carcinoma have led to a scarcity of available data in a considerable proportion of patients in the real-world practice. The daily challenge of treating these underrepresented subgroups

Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Argentina

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 17, 2021
Peer-review started: March 17, 2021
First decision: May 1, 2021
Revised: May 6, 2021
Accepted: May 20, 2021
Article in press: May 20, 2021
Published online: June 28, 2021

P-Reviewer: Chiu KW, Elbaz A, Poggio PD, Wang J
S-Editor: Zhang L
L-Editor: Filipodia
P-Editor: Liu JH

can be overcome by future clinical trials addressing special situations, collaborative studies and real-world data.

Citation: Piñero F, da Fonseca LG. Trial eligibility in advanced hepatocellular carcinoma: Does it support clinical practice in underrepresented subgroups? *World J Gastroenterol* 2021; 27(24): 3429-3439
URL: https://www.wjgnet.com/1007-9327/full/v27/i24/3429.htm
DOI: https://dx.doi.org/10.3748/wjg.v27.i24.3429

INTRODUCTION

Although hepatocellular carcinoma (HCC) is considered a highly lethal malignancy, recent therapeutic advances have been achieved during the last 10 years. These achievements were unthinkable 20 years before. Historically, patients with HCC at advanced stages or refractory to locoregional therapies (such as surgery, ablation or intra-arterial treatments) were associated with a dismal prognosis[1]. This scenario has fortunately changed.

In 2008, the first positive phase III trial (SHARP trial) using a systemic agent for HCC was published, showing that sorafenib improved overall survival over placebo in a selected population[2]. This result was observed in the Asia-Pacific trial, repeating similar observations yet in another population[3]. Sorafenib has succeeded due to its activity against different tumor pathways, particularly angiogenesis and proliferation signaling activation even in the absence of significant tumor shrinkage. It showed a favorable safety profile, particularly in patients with a well-preserved liver function (Child-Pugh A), a performance status of 2 or less and no other organ failure.

Following sorafenib, several drugs with similar or different targets were tested with disappointing results in phase III trials[4]. On the other hand, lenvatinib, shown to be non-inferior to sorafenib in the phase III REFLECT trial in patients without main portal trunk tumor invasion or without more than 50% of liver involvement[5], became an alternative in the first-line setting. Other agents such as regorafenib[6], cabozantinib[7] and ramucirumab[8] were incorporated as second-line options after sorafenib failure. This scenario resulted in an unprecedented improvement in survival for patients with advanced HCC, almost reaching 20-26 mo of overall survival after first-second line sequential treatment[9,10].

The advent of immune checkpoint inhibitors (ICI) with impressive results in solid tumors underpinned trials in advanced HCC. ICIs were rapidly incorporated after encouraging results with nivolumab and pembrolizumab in phase II trials with HCC patients, with durable objective response rates in 15%-20% of the patients[11,12]. In 2020, the combination of atezolizumab (a programmed death ligand 1 inhibitor) with bevacizumab [an anti-vascular endothelial growth factor-vascular endothelial growth factor (VEGF)-antibody] showed for the first time superiority over sorafenib in the phase III IMBRAVE150 trial[13]. This result was followed by approval of this combination as the standard first-line treatment for advanced HCC in different countries.

However, first and second-line trials were correctly based on the premise that a strict selection of patients enhances the power to capture the positive effect of treatment by excluding competing risks of mortality such as liver failure, decompensated cirrhosis or other underlying medical conditions (Figure 1). As a result, the inclusion criteria used in clinical trials do not support novel therapies in several real-world scenarios involving underrepresented subgroups. Moreover, due to the mechanism of action of ICIs and the risk of immune-related adverse events, the IMBRAVE trial did not enroll specific subgroups, such as patients with a history of solid-organ transplantation, auto-immune disorders, and a high risk of bleeding. The present text aims at discussing treatment strategies in these subgroups.

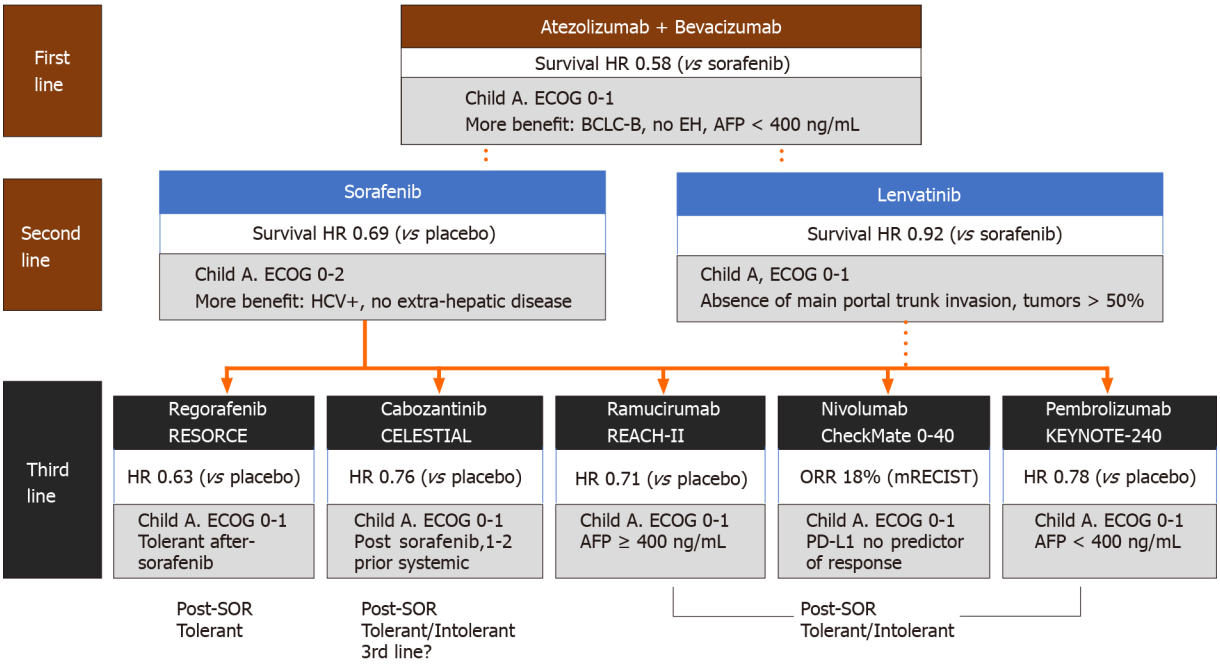

Figure 1 Systemic therapy for advanced hepatocellular carcinoma. Note: First and second-line options may be presented as first-line options in parallel. Exclusion criteria in the REFLECT trial shown for lenvatinib[5]. AFP: Alpha-fetoprotein; BCLC: Barcelona Clinic Liver Cancer; ECOG: Eastern Cooperative Oncology Group; EH: Extrahepatic; HCV: Hepatitis C virus; HR: Hazard ratio; ORR: Overall response rate; PD-L1: Programmed death ligand 1; SOR: Sorafenib.

CHALLENGES IN REAL-WORLD SCENARIOS

Etiology of underlying liver disease: does it really matter for decision making?

In Western countries (mainly Europe and the United States), the leading risk factor for HCC is chronic hepatitis C virus (HCV) infection. In contrast, hepatitis B virus (HBV) chronic infection is predominant in China, Asia and sub-Saharan Africa, where a higher burden of HCC is found compared to the rest of the world[14]. In Latin America, HCV represents the most prevalent risk factor for HCC[15,16], but other etiologies, such as nonalcoholic fatty liver disease, are steadily increasing[17,18].

This geographic heterogeneity directly impacts the recruitment of patients. Trials that restrict enrollment to a specific region are likely to be enriched with the predominant local etiology. Clinical trials that recruit globally tend to have HBV as the most frequent etiology when the Asian population predominates. A noticeable transition in risk factors has been observed in Western countries, with growing evidence that metabolic-associated fatty liver disease is an increasing cause of HCC, often associated with other comorbidities such as obesity, hypertension and diabetes [19].

This geographical eligibility is exemplified by the pivotal trials exploring sorafenib. In the SHARP trial, only 18.4% of the enrolled population had HBV-related HCC[2], while 73% of the patients enrolled in the Asia-Pacific trial had HBV-related HCC[3]. Although both trials showed a benefit in overall survival irrespective from underlying liver disease, a combined analysis of these two trials demonstrated a significant benefit in patients with HCV[20].

Nonviral etiologies represent only 30% to 45% of the included population in recent immunotherapy trials (Table 1). Whether immunotherapy is equally effective across all etiologies is still uncertain[13], shown through subgroup analysis in the IMBRAVE150 study suggesting that atezolizumab plus bevacizumab may have a lower benefit over sorafenib in nonviral etiologies [hazard ratio (HR): 0.91, 95% confidence interval (CI): 0.51-1.60], when compared to HBV (HR: 0.51; 95%CI: 0.32-0.81) or HCV-associated HCC (HR: 0.43; 95%CI: 0.22-0.87). This was also shown in the first-line trial comparing nivolumab *vs* sorafenib (Checkmate-459 trial, NCT02576509), in which nivolumab did not reach superiority over sorafenib in the overall population. Stratified subgroup analysis showed an HR of 0.91 (95%CI: 0.72-1.16) in nonviral etiologies when compared to HBV (HR: 0.79; 95%CI: 0.59-1.07) or HCV-associated HCC (HR: 0.72; 95%CI: 0.51-1.02). More recently, it has been shown that chronic inflammation in nonalcoholic fatty liver leads to liver injury and promotes liver cancer, impairing tumor surveillance. A meta-analysis of three randomized-control trials (IMbrave150,

Table 1 Studies reporting the effect and safety of first-line therapies in advanced hepatocellular carcinoma

	IMbrave: Phase III, open-label		REFLECT: Phase III, open-label		CheckMate-459: Phase III, open-label	
	Atezo + Bev	Sorafenib	Lenvatinib	Sorafenib	Nivolumab	Sorafenib
n	336	165	478	476	371	372
Age, median	64	66	63	62	65	65
≥ 65 yr, %	48	55	44	41	NR	NR
Male, %	82	83	85	84	85	85
Asia, %	56	58	70	68	NR	NR
ECOG 1, %	38	38	36	37	27	30
AFP ≥ 200 ng/mL, %	43	45	46	39	39	43
HBV, %	49	46	53	48	31	31
HCV, %	21	22	19	26	23	23
Nonviral, %	30	32	28	26	45	45
MVI trunk			Excluded		Excluded	
MVI, %	38	43	23	19	NR	NR
EH, %	63	56	61	62	NR	NR

AFP: Alpha-fetoprotein; Atezo + Bev: Atezolizumab + bevacizumab; ECOG: Eastern Cooperative Oncology Group; EH: Extrahepatic tumor disease; HBV: Hepatitis B virus; HCV: Hepatitis C virus; MVI: Macrovascular invasion or neoplastic thrombosis of the main portal trunk; NR: Not reported.

Checkmate-459 and KEYNOTE-240), showed that treatment with ICIs in these patients is associated with reduced survival compared to other etiologies[21].

Although not conclusive, subgroup analysis might offer partial information and generate a hypothesis for future trials. In regard with etiology, there is some molecular background that supports the existence of different molecular activated pathways according to molecular and transcriptomic-based features, which may lead to distinct activation of antitumor immunity or even to ICI resistance[22].

Elderly patients: discrepancy between trials and real-world scenario?

Approximately 70% of patients with cancer are aged 65 or older. The number of patients with cancer in this age group is projected to increase over the next decades significantly[23]. The aging process has been associated with changes in antineoplastic agents' pharmacokinetics due to a number of age-related changes, including modifications in renal and liver function, leading to altered drug absorption, metabolism and distribution.

The mean age of patients with HCC included in clinical trials is around 65-years-old. However, a substantial proportion of HCC patients are older. In HCC and other malignancies, elderly patients are underrepresented in clinical trials. In HCC, exceptionally, the concomitance of advanced age with chronic liver disease raises concerns about toxicity and clinical benefit.

A pooled analysis of both sorafenib pivotal trials (SHARP and Asia-Pacific) did not demonstrate prognostic differences between patients < or ≥ 75 years[20], suggesting that well-selected individuals could derive benefit from systemic treatment irrespective of age.

A concern that elderlies may present a poor tolerance to systemic treatment primes a trend for early discontinuation of sorafenib in field-practice studies[24]. However, in this cohort study (SOFIA Italian study), patients with half dosing sorafenib were associated with improved overall survival and discontinuation with worse outcomes. Consequently, early reduction avoiding definitive treatment discontinuation should be mandatory[24]. On the other hand, other studies did not show significant differences in overall survival and class-specific adverse events with lenvatinib in older patients [25]. A subanalysis of the IMBRAVE150 trial evaluating patients aged < or ≥ 65 years showed a similar toxicity profile, patient-reported outcomes and survival outcomes [26].

Most available data come from retrospective studies and subanalysis of prospective trials, mainly with sorafenib. Most of these data support that age alone should not

restrict treatment in advanced HCC, but a multidisciplinary approach and frailty metrics, apart from Eastern Cooperative Oncology Group grades, can be helpful in managing this group.

The limits of liver function: Is it unquestionable?

Cirrhosis and its complications (ascites among others) are the most significant competing risk for mortality in patients with HCC. In fact, prior evaluation of liver function, liver decompensation (prior history of ascites and its complications) or clinically significant portal hypertension are mandatory before systemic therapy initiation or selection (*e.g.*, presence of gastric or esophageal varices, other abdominal collaterals, enlarged spleen more than 120 mm, low platelet count < 150000 mm^3, among others). Due to this fact, clinical trials specifically selected those populations in which HCC determines the risk of mortality so that the antitumor treatment effect is more likely to be captured without distortion by cirrhosis-imposed threats. The majority of trials strictly included patients with preserved liver function, Child-Pugh A, or without liver decompensation events. It results in the lack of robust data showing how to manage patients with advanced HCC and impaired liver function. On the other hand, liver decompensation during systemic therapy leads to a significant impact on overall survival and an exclusion of sequencing systemic options[27,28].

The GIDEON study[29], the most extensive real-world data including patients treated with sorafenib, demonstrated that the median survival of patients with unpreserved liver function or Child-Pugh B and C was 5.2 mo and 2.6 mo, respectively. On the one hand, this result shows almost futility and discourages systemic agent use in patients with very poor liver function (Child-Pugh C) due to lack of treatment benefit. On the other hand, Child-Pugh B patient data suggests that well-selected patients can be considered for treatment, although more robust data is lacking. It seems that the presence of clinically significant ascites is a mandatory exclusion criterion. For example, in patients treated with sorafenib, those with a Child-Pugh B7 score without ascites presented similar outcomes than Child-Pugh A6[30]. Another retrospective study showed poor survival in patients with Child-Pugh B treated with lenvatinib[31].

Some authors recommend against grading ascites due to its subjective assessment, showing that the albumin-bilirubin score may be an alternative tool to evaluate prognosis in candidates for systemic treatment[32]. However, events of liver decompensation, such as ascites, jaundice or encephalopathy, have been associated with a significant worse prognosis and should always be part of eligibility criteria in trials and in the real-world setting.

Safety and efficacy in patients with liver dysfunction should not be extrapolated to all tyrosine kinase inhibitors (TKIs). The GIDEON cohort study showed an increasing incidence rate of serious adverse events from Child Pugh A to B or C, with a rising rate of sorafenib discontinuation[29]. Moreover, almost 20% of the patients may experience clinical deterioration due to liver impairment with the treatment with TKIs, particularly during the first 4 wk of therapy[6,24,33]. Nevertheless, in the second-line setting, patients allocated to cabozantinib in the CELESTIAL trial who presented worsening in liver function by week 8 had a manageable safety profile and maintained treatment benefit compared to the total cohort[7].

Whether these data could be extrapolated to ICIs is a matter of debate. Nivolumab was tested in a prospective Child-Pugh B cohort (75% of Child-Pugh B7)[11]. The median overall survival was 7.6 mo, with a disease control rate of 55.1%. Although safety profile may be more favorable, there is a paucity of data on other immune-oncology drugs in the setting of liver dysfunction.

The safety of combined therapies, including ICIs and VEGF targeted pathways (TKIs or anti-VEGF), in patients with unpreserved liver function is a matter to be clarified in prospective real-world data. Tyrosine kinase inhibitors and immunotherapy seems to be feasible in patients with a mild liver alteration. A close follow-up and multidisciplinary management are paramount to secure safety and better outcomes.

Recurrent HCC after liver transplant: An orphan situation in clinical trials

Liver transplantation has been an exclusion criterion in all clinical trials enrolling patients with advanced HCC, TKIs or ICIs. Safety concerns and overall survival in immunosuppressed patients has been one of the main explanations of this exclusion criteria.

However, the use of TKIs has been reported in retrospective cohort studies with acceptable results. Sorafenib was shown to be safe and effective, with a median overall survival of 20.1 mo[34]. The toxicity profile and the risk for liver graft deterioration

have been reported to be similar and lower than patients with no history of transplantation, respectively[35]. Favorable outcomes were observed in a multicenter retrospective study exploring the sorafenib-regorafenib sequencing therapy in the post-transplant setting. The median survival was 12.9 mo (95%CI: 6.7-19.1) since regorafenib initiation and 38.4 mo (95%CI: 18.5-58.4) since sorafenib discontinuation [36]. Other studies have already reported outcomes with lenvatinib in the post-transplant setting.

The risk of allograft rejection with ICI therapy precludes these patients from being treated with ICIs, either monotherapy or in combination with TKIs or anti-VEGF[37]. Therefore, sequencing TKIs is the optimal approach for patients with tumor recurrence after liver transplantation not amenable to local treatment.

Risk of bleeding events associated with systemic treatments

Patients with HCC and coexisting cirrhosis have an increased risk of bleeding events due to portal hypertension. However, the risk of spontaneous bleeding in other organs is rare, and these patients are paradoxically at a higher risk of thrombotic events[38, 39]. The risk of bleeding goes in parallel with the presence and severity of portal hypertension. In patients without prior endoscopy, at least during the last 6 mo, the risk of variceal hemorrhage should be assessed before systemic therapy, particularly with bevacizumab. Primary or secondary prophylaxis of variceal hemorrhage should be implemented according to International Consensus guidelines (*e.g.*, BAVENO VI), either with beta-blockers or endoscopic variceal banding or both for secondary prophylaxis. In some patients without any surrogate marker of clinically significant portal hypertension (*e.g.*, presence of enlarged spleen more than 120 mm, low platelet count < 150000 mm^3 or other abdominal collaterals), upper endoscopy may be replaced by transient elastography as a first or additional approach to rule-out gastroesophageal varices.

Bleeding can occur either due to variceal cause or spontaneous tumor rupture, both dramatic events associated with dismal outcome in patients with advanced HCC. In fact, HCC leads to an increase in portal hypertension, and consequently the risk of bleeding should be reassessed in these patients. Drugs with antiangiogenic activity, TKIs or anti-VEGF are associated with an increased risk of bleeding that usually does not require significant interventions. In pivotal trials, sorafenib was associated with a low risk of severe bleeding events (7% any grade, 1% grade 3) as well as ramucirumab (1% of grade 3-4)[2,8].

On the contrary, the IMBRAVE150 trial did not include patients with untreated or incompletely treated esophageal or gastric varices (according to local clinical practice, either beta-blockers or endoscopic procedures)[13]. This concern was based on the risk of tumor-associated hemorrhage with bevacizumab (3%-5%), with reported fatal bleeding cases in earlier trials[40]. Despite the exclusion of high-risk patients and a well-balanced risk of bleeding (26% of each group had varices), there was a 25.2% rate of any grade bleeding events in the atezolizumab-bevacizumab arm, and fatal bleeding events occurred in 6 patients in the IMBRAVE150 trial (1.8%). Specifically, variceal bleeding occurred more frequently in the atezolizumab plus bevacizumab arm *vs* sorafenib (7% *vs* 4.5%)[13].

The risk of bleeding should be extensively assessed in systemic treatment candidates, and a careful follow-up should be carried out in the real-world setting. Particular attention is required for those patients considered for atezolizumab and bevacizumab, patients using anticoagulants and those with a recent history or higher risk of variceal bleeding (*e.g.*, esophageal or gastric varices with red spots).

Common comorbidities and other conditions excluded in HCC trials

The classes of agents used for treating advanced HCC have particular prescribing concerns due to their mechanism of action. TKIs with antiangiogenic properties may increase the risk of cardiovascular disease and ischemic events. Consequently, patients with risk for cardiovascular events, such as diabetes or prior cardiovascular complications, are underrepresented in clinical trials, although they were not entirely excluded from enrollment. The challenge in such situation relies on the proper management of risk factors. ICIs, on the other hand, carried a low risk of cardiovascular events.

Drug interaction is a crucial topic, particularly with antiretroviral therapy for HIV. Patients with HIV are not included in clinical trials, but a real-world study showed that sorafenib does not impact viral load and CD4-T cell count[41]. Data with immunotherapy for HIV-positive patients lack as they were excluded from pivotal trials with ICIs.

Patients under supportive renal care or hemodialysis have been excluded from clinical trials, and more recent real-world data has been reported with sorafenib treatment[42]. Finally, ICIs may exacerbate autoimmune disorders. Some of these disorders are associated with an increased risk of HCC, such as autoimmune hepatitis.

Exacerbation of immune disorders and immune-related adverse events may occur in up to 75% of the cases. In this regard, ICIs should be used with caution in this population[43]. Many of these events can be managed without discontinuing therapy, but further data are required. Also, there is a deep concern with extrapolating the management of these adverse events in patients with cirrhosis. Most clinical guideline recommendations are based on non-cirrhotic patients[43]. Although immune-related events should be promptly recognized and adequately treated, the use of high steroid doses should be cautiously implemented in cirrhosis[44]. It is already known that the use of steroids may accelerate or result in liver decompensation (*e.g.*, ascites development, among other events).

Sequencing therapies beyond clinical trials

In the second-line setting, all effective options were explored after sorafenib, either intolerance or tumor progression. There is no comparative study that evaluated how second-line drugs perform after lenvatinib or atezolizumab plus bevacizumab. Regorafenib was superior to placebo in sorafenib-tolerant patients[6], ramucirumab was effective in patients with high alpha-fetoprotein (AFP) levels[8], and cabozantinib showed better survival in second or third-lines over placebo[7]. In addition, the combination of nivolumab-ipilimumab (a dual ICI combination) was granted approval after sorafenib based on an encouraging phase II trial[45].

Although more recent retrospective studies have compared nivolumab *vs* regorafenib efficacy, all second-line competitors have not been compared face-to-face in clinical trials[46]. Head-to-head comparisons between all these options are unlikely to be addressed in future trials, so sequencing strategies will be an unmet knowledge requiring real-world data outside clinical trials. Some assumptions are reasonable to be considered when choosing the best strategy (Figure 2).

The selection based on the safety profile is crucial. For example, risk of bleeding, cardiovascular events or immune-related adverse events may impact negatively if not correctly assessed. Survival is the primary objective, but patients with tumor-related symptoms may also benefit from therapies with a higher response rate, such as lenvatinib or atezolizumab plus bevacizumab. Special subgroups not included in trials may be more safely managed based on real-world data showing favorable results. For example, this is the case of sorafenib-regorafenib therapy in transplanted patients.

Alternating treatments with different mechanisms of action instead of using sequences of drugs directed to the same target is a reasonable strategy, although not evidenced-based in clinical trials, particularly for third or even fourth-line therapies. For example, after progression on immunotherapy-based therapy, a TKI is more likely to be effective and vice versa. This issue will be a major discussion when novel therapies are incorporated following the results of ongoing clinical trials.

There is still an unmet need in HCC. The use of biomarkers for treatment selection, except high AFP levels for ramucirumab therapy, is lacking. Even the expression of programmed death ligand 1 in tumor tissue has not been associated with a predictive response. While the neutrophil-lymphocyte ratio has already been associated with better response with sorafenib[20] and lenvatinib[47], other biomarkers in other settings have been extensively explored without clinical implication[48,49].

CONCLUSION

The strict criteria used in clinical trials in advanced HCC have led to a scarcity of available data in a considerable proportion of patients in real-world practice. The daily challenge of treating these underrepresented subgroups can be overcome by future clinical trials addressing special situations, collaborative studies and real-world data [50]. A critical view of study design is essential to avoid excessive extrapolation and not limit efforts to provide better care to some subgroups that are not widely included in clinical research.

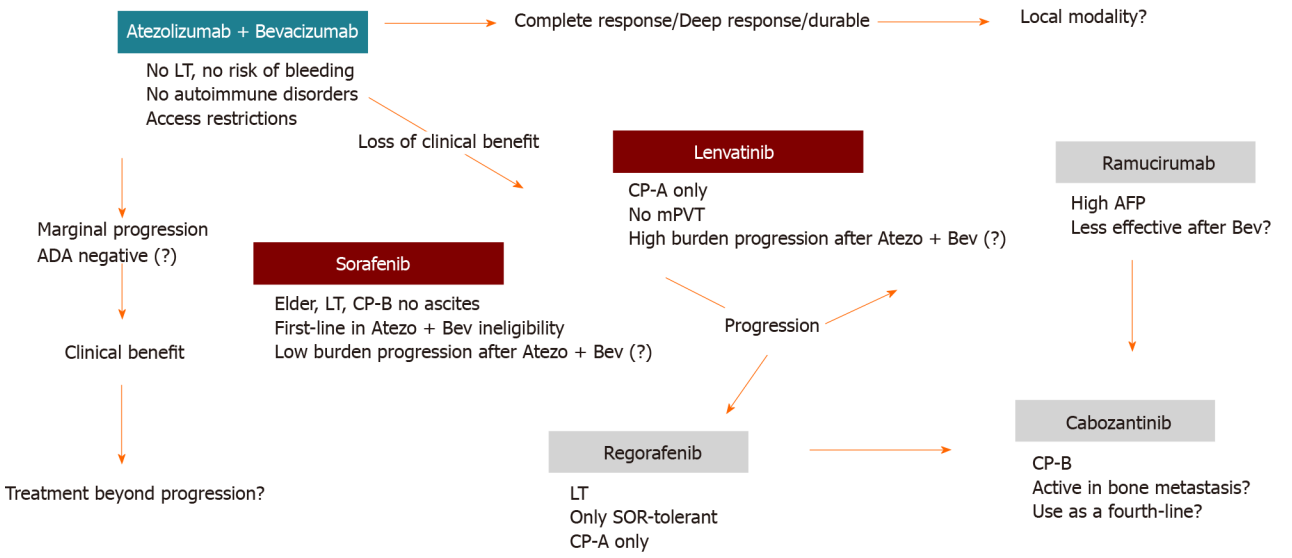

Figure 2 Sequencing systemic therapies in real-world setting. Note: These recommendations should be individualized for each patient. ADA: Anti-drug antibodies; AFP: Alpha-fetoprotein; Atezo + Bev: Atezolizumab + bevacizumab; CP: Child-Pugh; LT: Liver transplantation; mPVT: Main portal vein thrombosis; SOR: Sorafenib.

ACKNOWLEDGEMENTS

On behalf of the Latin American Liver Research, Education and Awareness Network (LALREAN).

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