Review

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Systemic treatment of HCC in special populations

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Summary

Recent years have seen significant progress in the systemic treatment of hepatocellular carcinoma (HCC), including the advent of immunotherapy. While several large phase III trials have provided the evidence for a multi-line treatment paradigm, they have focused on a highly selected group of patients by excluding potentially confounding comorbidities. As a result, high quality evidence for the systemic treatment of HCC in patients with various comorbidities is missing. This review summarises current knowledge on the use of approved medicines in patients with HIV, autoimmune disease, cardiovascular disease, diabetes, fibrolamellar HCC, mixed HCC-cholangiocarcinoma, decompensated cirrhosis (Child-Pugh B and C), a significant bleeding history, vascular invasion or portal vein thrombosis, as well as the elderly, those on haemodialysis, and those after solid organ transplantation. The article highlights relevant knowledge gaps and current clinical challenges. To improve the safety and efficacy of HCC treatment in these subgroups, future trials should be designed to specifically include patients with comorbidities.

Keywords: Hepatocellular carcinoma; Transplant; HIV; Autoimmune diseases; Diabetes; Metabolic syndrome; Fibrolamellar; Mixed HCC/CCC; Child-Pugh B; Elderly; Haemodialysis; Vascular invasion.

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Introduction

Since 2007, the multikinase inhibitor (MKI) sorafenib has been the global standard of care for patients with hepatocellular carcinoma (HCC), preserved liver function and advanced or intermediate stage disease not suitable for locoregional treatments.[1]

After a decade of unsatisfactory results, additional agents with prevalent antiangiogenic properties have been approved either as first-line alternatives to sorafenib,[2] or in a second-line setting, after sorafenib.[3–5] Also, immune checkpoint inhibitors (ICIs) targeting the programmed cell death 1 (PD-1) receptor have recently been granted accelerated approval.[6,7]

Although trials testing ICIs alone have failed to meet their respective primary endpoints,[8,9] novel combinations of ICIs plus agents that target angiogenesis have shown promise in treatment-naïve patients.[10] Moreover, strategies combining a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody plus an anti-PD-1 antibody have been approved in patients previously treated with sorafenib.[11]

Despite the unprecedented wealth of systemic treatment options now available,[12] there exist special populations for whom, paradoxically, no treatment can be recommended because of a lack of clinical information for their specific conditions. Historically, these patients represent an unmet medical need.

HCC clinical trials usually exclude individuals with HIV, a history of solid organ transplantation, decompensated cirrhosis, or fibrolamellar HCC (FLHCC). Similarly, active autoimmune diseases are typical exclusion criteria for virtually all clinical trials involving ICIs. In contrast, evidence on the treatment of patients with portal vein thrombosis (PVT) is more heterogeneous, since some trials considered it an exclusion criterion, while others did not (Table 1). Despite the lack of an upper age limit, elderly patients are often underrepresented in clinical trials[13] and, therefore, more data are required to properly inform treatment decisions. Due to the lack of applicable, high-quality evidence from prospective clinical trials, there exist some medical conditions, such as bleeding, metabolic syndrome and concurrent haemodialysis, that pose concrete challenges in daily practice (Table 2).

As there is a clear need to adhere to real-world scenarios, our review paper summarises current knowledge regarding approved treatments in these special populations, highlighting challenges and potential future directions.

Patients after solid organ transplantation

Solid organ transplant recipients carry a higher risk of *de novo* malignancies, which affect long-term survival.[14] In western cohorts, the incidence of HCC in non-liver graft recipients was similar to that in the general population, while it was elevated among liver graft recipients.[15,16] Despite well-established selection criteria for orthotopic liver transplantation (OLT), HCC recurrence occurs in 10–16% of patients.[17–19] While neoadjuvant locoregional therapies prior to transplantation (bridging) are considered to be standard of care, adjuvant

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Key point

Phase III trials of systemic agents for HCC excluded patients with relevant and frequent comorbidities.

Table 1. Inclusion and exclusion of special populations of HCC patients in phase III trials.

Special population	SHARP[1]	REFLECT[2]	IMbrave150[10]	RESORCE[3]	CELESTIAL[4]	REACH-2[5]	CheckMate 459[9]	KEYNOTE-240[8]
Solid organ transplantation	NO	NO	NO	NO	NO	NO	NO	NO
HIV	NO	NO	NO	NO	NO	NO	NO	NO
Prior or active autoimmune diseases	YES	YES	NO	YES	YES	YES	NO	NO
Significant cardiovascular disease	NO	NO	NO	NO	NO	NO	NO	YES
Diabetes/metabolic syndrome	YES	YES	YES	YES	YES	YES	YES	YES
Fibrolamellar, mixed HCC/CCC, other histological subtypes	NO	NO	NO	NO	NO	NO	NO	NO
Decompensated cirrhosis (Child-Pugh B and C)	YES*	NO	NO	NO	NO	NO	NO	NO
Elderly patients	YES	YES	YES	YES	YES	YES	YES	YES
Significant bleeding history	NO	NO	NO	NO	NO	NO	NO	NO
Haemodialysis	NO	NO	NO	NO	NO	NO	NO	NO
Vascular invasion/portal vein thrombosis	YES	YES**	YES	YES	YES	YES	YES	YES**

NO means patients are excluded; YES means patients are included.
HCC/CCC, mixed hepatocellular/cholangiocellular carcinoma.
*Child-Pugh C excluded.
**Vp4 excluded.

therapies post OLT have not demonstrated a significant benefit on HCC recurrence.[20,21] Furthermore, immunosuppressive regimens, especially mammalian target of rapamycin (mTOR) inhibitors, have been evaluated for their potential anticancer properties and use in post-OLT management. Small-centre retrospective studies and meta-analyses have reported beneficial effects of mTOR inhibitors, including reduced HCC recurrence rates. However, the largest multicentre randomised controlled trial to date (SILVER study) could not confirm that sirolimus significantly improved recurrence-free survival beyond 5 years.[22–24]

Several studies have demonstrated that surgical treatment in well-selected patients with HCC recurrence and limited disease is an independent predictor of long-term survival.[25,26] In case of unresectable HCC recurrence, locoregional and systemic approaches can be applied, but data are limited and restricted to small case series and studies. Data on the safety and efficacy of systemic therapies are mainly based on the use of sorafenib with or without mTOR inhibitors. The safety of sorafenib has been confirmed in the post-transplant setting, wherein it was associated with a median survival of 12 months (1.45–20.1).[27,28] Combinations with mTOR inhibitors can lead to increased toxicity, resulting in dose reduction or discontinuation of treatment.[29,30] Therefore, close monitoring is important, especially during the first weeks of treatment. A multicentre retrospective study further showed the safety of regorafenib in the second-line setting in sorafenib-tolerant patients with HCC recurrence after OLT and provided the rationale for sequential therapy.[31] Experience with ICIs in solid organ transplant recipients is limited because of the increased risk of allograft rejection and graft lost. A retrospective pilot evaluation reported on the safety and efficacy of PD-1 inhibitors in 7 patients with recurrent HCC (n = 5) and melanoma (n = 2) after OLT. Graft rejection was observed in 2 patients with HCC. Only 4 patients were restaged. While 3 patients with HCC recurrence progressed under ICI, 1 patient with metastatic melanoma had a complete response (CR) without graft rejection in this study.[32] Further case reports on patients with recurrent HCCs after OLT reported rapid irreversible liver dysfunction under ICI.[33,34] Therefore, published data highlight the severe risks of graft loss under immunotherapy, which should not therefore be recommended in the setting of solid organ transplantation (Table 2).

Patients with HIV

In people living with HIV (PLWH), due to the high prevalence of coinfection with HBV and HCV, HCC is frequently diagnosed at a young age and at an advanced stage, representing an increasing cause of morbidity and mortality, and accounting for over 40% of liver-related deaths.[35–38]

It is still unclear if HIV may negatively influence the clinical course of HCC or whether PLWH may be safely treated with systemic treatments for HCC.[39] In fact, HIV-positive patients are less likely to receive treatment at recurrence (61% *vs.* 86.2%, p <0.001)[40] and more likely to receive best supportive care for advanced disease (60% *vs.* 38%, p = 0.02).[41]

For PLWH with advanced HCC, one concern relates to the potential synergistic toxicity of using systemic treatments alongside combined antiretroviral therapy (cART) (Table 2).[42] Available data are limited and a Spanish real-world study of sorafenib showed a significantly worse outcome compared to historical data on non-HIV-infected patients. However, there were no modifications of cART, and CD4+ T-cell counts, and HIV viral load remained stable.[43] In contrast, a retrospective Italian study reported similar efficacy and safety data for sorafenib in PLWHs as in non-HIV patients, with a median OS of 12.8 (range 1.1–23.5) months in PLWHs. Most drug-related adverse events (AEs) were manageable with grade 3–4 diarrhoea, and hand-foot skin reaction (HFSR) in 15% of patients, and hypertension in 11%.[44] The first publication on

Table 2. Factors and open issues to consider in the management of special populations of HCC patients.

Special population	Impact on prognosis	Contraindicated treatments	Clinical challenges	Open issues
Solid organ transplantation	Positive	Checkpoint inhibitors	Infections	How to safely apply immunotherapy without increasing the risk of graft rejection
HIV	Negative	No data available*	Drug-drug interaction (cART)	Elucidate biological underpinnings of aggressive disease, Multidisciplinary and worldwide collaboration to characterise biology, treatment, and survivorship, Increase clinical trial accrual, Clarify optimal treatment strategies
Prior or active autoimmune diseases	None	Checkpoint inhibitors to be used with caution	Flare management	Safe use of checkpoint inhibitors
Significant cardiovascular disease	Potentially negative	Antiangiogenics	Cardiovascular events, thromboembolic events	Anticipate life expectancy, Clarify optimal treatment strategies
Diabetes/metabolic syndrome	Potentially negative	Bevacizumab, ramucirumab and lenvatinib to be used with caution in case of proteinuria	Obesity, diabetic/metabolic complications	Explore the potential of anti-inflammatory/-fibrotic treatments to reduce the risk of HCC, Validate the potentially protective effect of metformin
Fibrolamellar, mixed HCC/CCC, other histological subtypes	Negative	None	Lack of trial data to support clinical decision-making	Discover targeted treatments (e.g., using basket or umbrella trials), Explore benefit of immuno- and combination therapies
Decompensated cirrhosis (Child- Pugh B and C)	Negative	Any systemic treatment in Child-Pugh C	Ascites, HRS, ACLF, wasting	Identify patients who benefit from systemic therapy despite impaired liver function, Define safe and effective treatment protocols
Elderly patients	None	None	Comorbidities, drug-drug interactions, compliance	Increase clinical trial accrual, Geriatric assessment of frailty, Predict, prevent, and mitigate toxicity
Significant bleeding history	Negative	Antiangiogenics (based on current risk)	Repeated bleeding events despite screening/treatment of varices	Multidisciplinary collaboration to define optimal management of varices, Anticipate life expectancy
Haemodialysis	Potentially negative	No data available**	Impaired drug metabolism and risk of higher plasma concentration	Address dosing, toxicity, and life expectancy, Multidisciplinary and worldwide collaboration
Vascular Invasion/ portal vein thrombosis	Negative	None	Portal hypertension, oesophageal varices	Define most effective treatment strategies

ACLF, acute-on-chronic liver failure; cART, combined antiretroviral therapy; HCC/CCC, mixed hepatocellular/cholangiocellular carcinoma; HRS, hepatorenal syndrome.
*Available data for sorafenib and regorafenib confirm the safety profile of the two drugs; no data available for other agents.
**Available data for sorafenib confirm the safety profile of the drug; no data available for other agents.

regorafenib in an HIV-positive patient with advanced HCC reported stable disease, good tolerability, and no impact on the underlying HIV infection.[45]

The possibility of treating PLWH with advanced HCC with ICIs has been tested in case series and a small phase II study in patients with different cancer types (with a single HCC patient); this study reported similar efficacy and safety data to those achieved in HIV-negative patients, without an impact on HIV viral load or CD4+ T-cell counts.[46–48] Given the life expectancy benefits shown by cART and the negative prognostic impact of HCC, there is a compelling need for safe and effective treatments for HCC in PLWH.[49] Of note, the ongoing phase IIIb AMETHISTA study of atezolizumab plus bevacizumab as front-line treatment for patients with unresectable HCC (NCT04487067) includes HIV-positive patients provided they are stable on cART, have a CD4+ T-cell count ≥200/μl, and an undetectable viral load. Although this trial is ongoing and no data are yet available, it represents the approach needed to evaluate novel therapies for HCC among PLWH, along with a close collaboration between HCC and HIV specialists (Table 2) since the number of HCC in PLWH is expected to rise.[42,49]

Patients with prior or active autoimmune diseases

Autoimmune liver diseases

It is well established that autoimmune liver disease is a risk factor for HCC.[50] Regarding autoimmune hepatitis (AIH), a meta-analysis calculated a pooled incidence rate for HCC of 3.06 per 1,000 patient-years.[51] In AIH with cirrhosis at diagnosis, the rate was even higher at 10.07 per 1,000 patient-years. However, the overall risk of HCC seemed to be lower in patients with AIH and cirrhosis compared to patients with cirrhosis related to HBV/HCV

Key point

High-quality data on the safety and efficacy of currently approved drugs in these patients are missing.

infection or primary biliary cholangitis (PBC). A meta-analysis in PBC revealed a significantly higher HCC risk than for the general population, with a pooled risk rate of 18.8.[52]

With only limited data available on the treatment of HCC in the context of autoimmune liver disease there are no apparent restrictions on the use of MKIs and ramucirumab in such patients (Table 2). Yet the safety of ICIs in this group is unclear, since patients with AIH have been excluded from clinical trials with ICI (Table 1). Although ICI-related hepatotoxicity is poorly understood, a pathophysiology similar to AIH has been assumed. However, differences in clinical and pathological features have emerged.[53] Although some authors have suggested that ICIs carry only a small risk of exacerbating preexisting autoimmune disorders and may therefore be used in such patients,[54,55] there are insufficient data to expand this view to AIH, which warrants evaluation in future clinical trials (Table 2).

Other autoimmune diseases

Data regarding the incidence of HCC in patients with non-liver autoimmune disease are missing. Equally, it is unknown which systemic treatments can be used safely and effectively in these patients (Table 1). This is complicated by the large number of different conditions ranging from hypothyroidism with very good prognosis to systemic lupus erythematodes with potentially life-threatening complications. In the absence of contraindications, MKIs and ramucirumab can be employed in these patients (Table 2). However, the situation is less clear for ICIs: some authors have propagated their use in patients with preexisting autoimmune disorders.[54,55] However, a prospective study of the REISAMIC registry found a significantly increased risk of immune-related AEs (irAEs) in such patients.[56] A systematic review of 49 studies with a total of 123 patients reported an exacerbation and/or irAE rate of 75%.[57] Therefore, ICIs should be used with caution in patients with preexisting autoimmune disease and HCC (Table 2).

Patients with significant cardiovascular disease

Due to partly overlapping risk factors, the prevalence of cardiovascular disease (CVD) in the general population, and the incidence in similar age groups, arterial hypertension, coronary heart disease, cerebrovascular disease, and thromboembolic events are frequent comorbidities in patients with HCC.[58] Patients with uncontrolled CVD or recent acute events, such as myocardial infarction, pulmonary embolism or stroke, are excluded from clinical trials assessing systemic treatments for HCC (Table 1). A large cross-sectional Chinese study (n = 22,500) showed that of 2,574 patients with advanced HCC, 25.1% had concomitant hypertension, 4.7% had coronary heart disease, 3% atrial fibrillation, and 2% heart failure. Of note, most patients with HCC had high grade hypertension (76.7%) associated with a higher prevalence of other concomitant CVDs.[59] Based on these data, although they cannot be extrapolated to other populations, a large number of patients with HCC present with contraindications to antiangiogenic treatment. Moreover, arterial hypertension is a frequently observed treatment-related AE, with an incidence of grade ≥3 arterial hypertension of 15–23%.[60] Conversely, hypertension has been shown to correlate with better outcomes with sorafenib, lenvatinib, and cabozantinib.[60–62] Therefore, blood pressure should be controlled before treatment initiation, should then be monitored regularly, and treated in a timely fashion.[60] Of note, based on their safety profile, ICIs could be considered a potential treatment option for patients with CVD unsuitable for antiangiogenics, but specific data in this patient population are lacking (Table 2).

Patients with diabetes/metabolic syndrome

Diabetes and non-alcoholic fatty liver disease (NAFLD) associated with metabolic syndrome have been linked to an increased HCC risk.[63] The underlying pathophysiology probably involves increased hepatic/peripheral insulin resistance, increased pro-inflammatory mediators, oxidative stress, JNK-1 activation, increased insulin-like growth factor-1 (IGF-1) activity, and an altered gut microbiome.[64]

Patients with diabetes or metabolic syndrome were not excluded in the registrational trials of the currently approved systemic treatments for HCC (Table 1). Therefore, they can generally be used in patients with these comorbidities without restriction. However, in case of active proteinuria, a frequent diabetic complication, a treatment with bevacizumab, ramucirumab or lenvatinib should be initiated with caution, monitored closely, and discontinued in case of worsening of proteinuria (Table 2).

There has been some debate regarding whether diabetes treatment affects hepatocarcinogenesis. Recently, a meta-analysis on 8 studies reported a combined odds ratio of 0.468 for the association between HCC and metformin treatment, signalling a potentially protective effect.[65] In the HCC treatment setting, mixed signals have been reported: In a meta-analysis of 6 retrospective cohort studies, the use of metformin in patients with type 2 diabetes was associated with a significantly prolonged OS after curative treatment of HCC (p <0.00001).[66] In contrast, a negative effect of metformin in addition to sorafenib has been suggested.[67]

Future studies on treatments for NAFLD and non-alcoholic steatohepatitis will need to show whether their anti-fibrotic/anti-inflammatory properties translate into protection against HCC (Table 2).

Patients with fibrolamellar and mixed hepato-cholangiocellular carcinomas

Despite conventional HCC representing the most common histological type of primary liver cancer, a small subset of patients develop primary hepatic tumours with distinct pathological features, including FLHCC, scirrhous, spindle cell, clear, pleomorphic as well as mixed hepato-cholangiocellular carcinomas (HCC/CCC). Rare subtypes are generally excluded from prospective trials (Table 1) and clinical outcome and treatment approaches are not clearly defined. FLHCC and mixed HCC/CCC represent the most common rare pathological subtypes and will be further discussed.[68]

FLHCC occurs more frequently in younger patients (<40 years) without a clear gender preponderance.[69] However, 2 peak incidences have been described: one in a younger age group (10–30 years) and one in an elderly age group (70–79 years).[70,71] Clinically, histologically and molecularly FLHCC is a distinct subtype of HCC. In contrast to conventional HCC, FLHCC has not been associated with risk factors such as viral hepatitis, alcohol or other underlying inflammatory liver diseases.[72] Besides typical diagnostic features of FLHCC on imaging and histological examinations,[73] a recent study showed *DNAJB1-PRKACA* fusion mutations to be 100% specific for FLHCC.[74]

Clinico-pathological data and survival outcomes are mostly collected from case reports, single-institutional case series and/or registry-based studies.[68,75–78] The treatment of choice is a complete primary resection resulting in 5-year OS rates of 70%. However, recurrence rates are high and (neo)adjuvant therapeutic approaches have not been shown to improve survival.[68,78] In case of advanced stages of disease, prognosis is poor with a median survival of less than 12 months. Given the rarity of the disease and its limited incidence, no randomised controlled trials have been performed to investigate the most efficacious treatment strategy. Systemic therapies include classical chemotherapies (mainly based on 5-fluorouracil combinations), but FLHCC tends to be chemoresistant.[78] Targeted approaches include sorafenib but have shown limited effectiveness.[76,78] Case-reports on the use of ICIs are limited and response varies from progression to CR.[79] Notably CR was achieved in a patient with PD-L1 expression of 10%.[78] Therefore, further research is required to define the role of ICIs in the treatment of FLHCC (Table 2).

HCC/CCC is another rare subtype of primary liver tumour characterised by the presence of both hepatocellular and cholangiocellular components in biopsies or surgical specimens.[80] Aetiologically, HCC/CCC share common risk factors with conventional HCC and are mainly based on chronic inflammatory liver diseases. Currently, treatment allocations are based on tumour stage, liver function and the patient's performance status. Patients are mainly treated according to guidelines of either HCC or CCC depending on the dominant type in diagnosed tumour and/or metastases. While integrative approaches and characterisation of genetic alterations identified druggable targets such as fibroblast growth factor receptor 2 (*FGFR2*) gene fusions and isocitrate dehydrogenase (*IDH*) mutations in intrahepatic CCC, molecular alterations of HCC/CCC remain poorly characterised.[81] One of the largest molecular characterisation studies to date included 133 Asian HCC/CCC cases and revealed distinct subtypes with different clinical and molecular features.[82] However, further comprehensive molecular analyses are necessary to better understand the complexity of distinct subgroups and to pave the way for new and effective targeted treatment approaches (Table 2).

Key point

Available evidence stems from low-quality sources, such as case reports, retrospective series and small clinical trials.

Patients with decompensated cirrhosis (Child-Pugh B and C)

HCC typically occurs on the background of cirrhosis, whose natural course leads to hepatic decompensation and organ failure. Being a strong confounder, patients with impaired liver function are usually excluded from clinical trials (see Table 1). In fact, the only successful registrational phase III trial which was not limited to Child-Pugh class A was the SHARP trial which tested sorafenib (Table 1). In addition, hepatotoxicity is a risk with currently approved systemic treatments, particularly MKIs, which should therefore be used with caution in clinical practice (Table 2). Data on their safety and efficacy are limited in patients with Child-Pugh B and even more so in those with Child-Pugh C.

A meta-analysis of 30 studies evaluating sorafenib as first-line treatment in a total of 8,678 patients with advanced HCC revealed that Child-Pugh B liver function is associated with worse OS (p = 0.001).[83] The GIDEON study, which was included in the aforementioned meta-analysis, quantified median OS in the intention-to-treat population (n = 3,213) as 13.6 *vs.* 5.2 *vs.* 2.6 months in Child-Pugh A, B and C patients, respectively.[84] With regard to lenvatinib, a retrospective single-centre study including Child-Pugh A, B and C patients reported a median OS of 8.5 months, with Child-Pugh B and C being associated with poor survival.[85] In the second-line setting, ramucirumab showed no trend towards a response in Child-Pugh B patients in the initial, negative REACH trial,[86] while being associated with a higher rate of grade ≥3 AEs.[87] As a consequence, the following REACH-2 trial, which tested ramucirumab in patients with baseline alpha-fetoprotein levels of ≥400 ng/ml, excluded patients with a Child-Pugh score >6.(5) While only patients with Child-Pugh A liver function were included in the CELESTIAL trial, a retrospective analysis of patients whose liver function deteriorated to Child-Pugh B by week

Key point

Clinical trials including patients with comorbidities are needed to provide robust evidence for their systemic treatment.

8 demonstrated the manageable safety profile and efficacy of cabozantinib in this subgroup.[88] The first ICI to be tested in Child-Pugh B patients was nivolumab as part of the CheckMate 040-trial (cohort 5). The disease control rate was 55.1% and the median OS 7.6 months.[89]

In conclusion, MKIs and ICIs can be used with a reasonable degree of caution in patients with Child-Pugh B liver function. However, local availability and labelling issues may restrict the discussed treatment options. Due to the lack of a demonstrated therapeutic benefit, patients with Child-Pugh C cirrhosis should not receive targeted therapy but best supportive care.

Elderly patients

The incidence of HCC is age dependent, although age at diagnosis varies according to the aetiology of the underlying liver disease. Most diagnoses of HCC occur in patients ≥60 years in Japan, North America and European countries while in Asia (excluding Japan), and in most African countries, where chronic HBV infection is prevalent, HCC is diagnosed at ages ranging between 30 and 60 years.[90]

While there is no agreement on the age cut-off that defines an elderly population, the median age of patients enrolled in most trials testing systemic agents for HCC is roughly 65 years.[1–7,10]

Considering age as a prognostic factor, current evidence does not suggest significant differences in OS, as long as 65 years is the selected cut-off (Table 3).[1–10] While the SHARP trial did not report subgroup analyses by age,[1] the subsequent Asia-Pacific trial did not establish a survival benefit from sorafenib over placebo in older patients[91] although only 32 patients were in fact aged >65 years. Nonetheless, a pooled analysis that involved both trials did not detect prognostic differences between patients aged <75 years and those aged ≥75 years, confirming the benefit of sorafenib regardless of age.[92] Other studies demonstrated that age was not prognostic but was independently related to treatment discontinuation due to intolerance.[93] A global trend towards earlier discontinuations emerges in elderly patients,[94,95] even though more tailored approaches with closer follow-up consultations are felt to improve long-term compliance.[96,97] In contrast, no significant differences were reported in terms of AEs in patients treated with lenvatinib who were analysed according to a cut-off age of 75 years.[96] Also, in the IMbrave150 trial, similar safety profiles and patient-reported outcomes (PROs) were observed in patients aged <65 year and ≥65 years, who received the atezolizumab-bevacizumab combination.[97]

For second-line treatments, subgroup analyses by age indicate slight differences in hazard ratio that were consistent with the OS benefit provided by the investigational agent. In the CELESTIAL study, the proportions of patients aged <65 year and older who received anticancer therapy after cabozantinib were comparable, suggesting that access to additional treatments is independent of age.[98] In patients with alpha-fetoprotein levels ≥400 ng/ml, no differences were observed in terms of efficacy, safety and PROs for ramucirumab, according to 3 different age ranges: <65 years, ≥65 to <75, ≥75.[99]

Whilst progressive shifts in recruitment age[4,8,9] indicate easier handling of targeted and immuno-oncology therapies, the inter-quartile ranges of baseline ages reported in major trials suggest that patients aged >70 years are underrepresented.[3,10]

Given the growing need to appraise patients' functioning besides routine performance measures, frailty may provide more accurate metrics.[100] The use of frailty metrics to guide treatment modifications is gaining tremendous interest in elderly cancer patients.[101,102] With respect to sorafenib, reduced doses were indeed shown to increase survival,[93] lower the incidence of severe AEs,[103] and reduce treatment discontinuation.[104]

In conclusion, current evidence supports reduced starting doses of sorafenib and timely clinical follow-up for the early management of AEs, particularly in patients aged >75 years (Table 2). That said, most available information in elderly patients comes from studies exploring sorafenib, while less is known regarding other agents.

Patients with a significant bleeding history

In patients with cirrhosis, the actuarial risk of variceal bleeding is up to 15% after variceal ligation[105] and is largely dependent on clinical parameters pertaining to liver function, but not coagulation disorders.[106] In this context, antiangiogenic agents may confer an increased risk, which has long been acknowledged,[107] given the interplay with concomitant cirrhosis (Table 1).

Besides variceal bleeding, bleeding events that occur relatively frequently with antiangiogenics include epistaxis and gingival bleeding, which have been reported in patients with HCC[108] as well as in non-HCC contexts.[109,110] Such minor bleeding events do not require medical attention and their impact can be minimised with adequate patient education.

A pooled analysis including randomised trials of sorafenib in HCC confirmed that a significant risk of any-grade bleeding events exists, but did not substantially differ from renal cancer trials: 6.65% with sorafenib *vs.* 3.37% in control arms (p = 0.04).[111]

The rate of bleeding events (grade 3–5) related to ramucirumab was similar (1%) in the experimental and placebo arms of the REACH-2 trial,[5] whereas the KEYNOTE-240 trial reported 3 such grade 5 events (1%) with pembrolizumab and none with placebo.[8]

Following 3 episodes of gastrointestinal haemorrhage (including a fatal one), 2 earlier trials testing bevacizumab were amended to provide an upper endoscopy in patients with oesophageal

Table 3. Survival outcomes in phase III pivotal trials in patients <65 years and patients ≥65 years.

Trial	Treatment arms Number of patients (N)	Median age, years (range)	Patients ≥65 years	HR OS (<65 years)	HR OS (≥65 years)
SHARP[1]	Sorafenib (299) Placebo (303)	65 (53–76) 66 (56–76)	n.a.	n.a.	n.a.
REFLECT[2]	Lenvatinib (478) Sorafenib (476)	63 (20–88) 62 (22–88)	44% 41%	0.94 (95% CI 0.77–1.15)	0.84 (95% CI 0.66–1.07)
RESORCE[3]	Regorafenib (379) Placebo (194)	64 (54–71) 62 (55–68)	45%*	0.65 (95% CI 0.49–0.87)	0.74 (95% CI 0.54–1.02)
CELESTIAL[4]	Cabozantinib (470) Placebo (237)	64 (22–86) 64 (24–86)	49% 48%	0.81 (95% CI 0.62–1.05)	0.74 (95% CI 0.56–0.97)
REACH-2[5]	Ramucirumab (197) Placebo (95)	64 (58–73) 64 (56–71)	48% 48%	0.64 (95% CI 0.42–0.95)	0.84 (95% CI 0.42–0.95)
CheckMate 459[9]	Nivolumab (371) Sorafenib (372)	65 (19–89) 65 (20–87)	50% 53%	0.80 (95% CI 0.63–1.02)	0.88 (95% CI 0.68–1.12)
Keynote 240[8]	Pembrolizumab (278) Placebo (135)	67 (18–91) 65 (23–89)	58%*	0.75 (95% CI 0.52–1.09)	0.92 (95% CI 0.65–1.30)
IMbrave150[10]	Atezolizumab + bevacizumab (336) Sorafenib (165)	64 (26–88) 66 (33–87)	47% 55%	0.59 (95% CI 0.38–0.91)	0.58 (95% CI 0.36–0.92)

HR, hazard ratio; n.a., not available; OS, overall survival.
*Refers to the overall cohort.

varices during screening procedures.[112,113] Despite the enrolment of patients with Child-Pugh B liver function, no further gastrointestinal haemorrhages were reported once screening measures were implemented.[113]

Policies mandating the exclusion of patients at risk of variceal bleeding might explain, at least in part, the absence of any high-grade bleeding events in further trials of MKI.[3,4,114]

More recently, in the IMbrave150 trial, bleeding events (any grade) were experienced by 25.2% of patients in the atezolizumab plus bevacizumab arm, and 17.3% of patients in the sorafenib arm. Grade 3–4 bleeding was reported in 6.4% of the patients under bevacizumab plus atezolizumab, but did not differ from the sorafenib arm (5.8%).[10] Although upper endoscopy and primary prophylaxis were requested within 6 months prior to treatment start, fatal bleeding events or perforated ulcers occurred in 6 patients (1.8%) assigned to combination, and in 1 patient (<1%) assigned to sorafenib. Since patients with deteriorating liver function are more likely to have portal hypertension and higher risks of bleeding, data from the IMbrave150 trial cannot be extrapolated to these patients (Table 2). Despite a rate of severe bleeding events similar to that reported in prior studies investigating bevacizumab, real-world studies of atezolizumab plus bevacizumab are necessary to better assess the generalisability of the IMbrave150 trial.

Most importantly, screening for varices has led to a significant decline in variceal bleeding and related mortality over the last decades.[115] In patients newly diagnosed with cirrhosis, the benefit of such screening measures is currently endorsed by several consensus guidelines.[116,117]

Patients undergoing haemodialysis

The overall incidence of HCC among patients with chronic kidney disease (CKD) was estimated to be approximately 2.03 per 1,000 person years.[118] Patients undergoing haemodialysis are often diagnosed with more advanced HCC compared to non-dialysis patients, resulting in a worse prognosis. In fact, patients on haemodialysis are frequently not screened for HCC, even if a considerable percentage of them, especially those who are HCV positive, are at risk of HCC.[119] Therefore, a collaborative effort among HCC and CKD specialists is crucial to improve patient outcomes (Table 2).

Owing to their exclusion from clinical trials, there is very limited data available on patients with HCC and CKD under haemodialysis (Table 1). A phase I and pharmacokinetic study evaluated sorafenib in patients with hepatic or renal dysfunction.[120] This study consisted of multiple cohorts including 17 patients with HCC and 17 patients on haemodialysis. However, no details regarding the cancer type and liver function status of patients on haemodialysis were provided. Therefore, no specific conclusions can be drawn for patients with HCC undergoing haemodialysis. However, for patients under haemodialysis, a starting dose of sorafenib of 200 mg daily was suggested, considering dose escalation if the drug was well tolerated.[120] A large European and Latin American retrospective multicentre real-world study reported data on 6,156 patients with HCC treated with sorafenib, of whom 22 (0.36%) had CKD and required haemodialysis.[121] Seventeen patients (77.3%) required at least 1 dose reduction, mostly due to clinical deterioration or diarrhoea. Further AEs included HFSR and liver decompensation. Treatment was discontinued in 18 (77.8%) patients because of disease progression and in 22.2% of patients because of AEs, half of them deemed sorafenib-related (1 diarrhoea and 1 arterial thrombosis). Seven patients (31.8%) had a grade ≥3 serious AE. Although none of the patients received second-line treatment, median OS was 17.5 months (95% CI 7.2–24.5).[121] Based on these results sorafenib use seems feasible in patients under haemodialysis, with outcomes similar to those in patients without

Key point

Clinicians must pay extra attention to these special populations and apply currently approved treatments with caution.

haemodialysis. However, the lack of randomised clinical trial data urges caution and an overall clinical evaluation is warranted before administering sorafenib to these patients (Table 2). Furthermore, these results cannot be extrapolated to other systemic treatments such as other MKIs, antiangiogenics, and ICIs. However, a recently published review on targeted and immune therapies for patients with metastatic renal carcinoma undergoing haemodialysis, including 55 patients treated with sorafenib, 18 patients treated with nivolumab, and 6 patients treated with bevacizumab, concluded that haemodialysis did not seem to modify the expected efficacy and safety of these drugs.[122] Therefore, it seems that these agents can be safely used in patients undergoing haemodialysis, although careful monitoring is recommended in this special population because of frailty and comorbidities associated with CKD.

Patients with vascular invasion or portal vein thrombosis

It is well known that patients with HCC are at a high risk of pathological thrombosis. PVT is the most common thrombotic complication in patients with HCC and cirrhosis.[123,124] Compared to cirrhotic patients without malignancy, the incidence of PVT in patients with HCC has been reported to be more than doubled (24.4% *vs.* 11.4%; $p = 0.05$).[123] Non-malignant thromboses have to be distinguished from malignant thromboses, since macrovascular tumour invasion (MVI) has important therapeutic consequences. MVI, being most commonly a portal vein tumour thrombosis (PVTT), is an exclusion criterion for curative therapies such as OLT (Table 1).[125] Interestingly, the presence of either MVI/PVTT or PVT is associated with poor survival in patients with HCC.[126] Studies have shown that for patients with PVTT, prognosis depends on grade, with median survivals of just 2–5 months reported in patients with PVTT of the main trunk.[126,127]

Patients with HCC and diagnosed PVTT have advanced disease (BCLC stage C). Several guidelines recommend systemic therapies for patients with HCC and PVTT.[128,129] Most data are based on sorafenib treatment. Median survival time was slightly longer in the sorafenib group (8.1 months) than in the placebo group (4.9 months) in a subgroup analysis of the phase III SHARP trial of patients with HCC and PVTT.[130] Recent randomised studies stratified or excluded patients with pronounced PVTT. Lenvatinib has shown to be non-inferior to sorafenib in the first-line setting, but patients with main portal trunk invasion were excluded from the phase III study (Table 1).[131] A recent retrospective analysis observed favourable outcomes for patients with advanced HCC and pronounced PVTT (grade 3/4) treated with lenvatinib in comparison to sorafenib.[132] Thus, current data suggest that lenvatinib is a viable option in this setting as well.

Especially in Eastern countries, different treatment approaches including liver resection (144), transarterial chemoembolisation,[133] radiotherapy,[134] radioembolisation with yttrium-90,[135] hepatic arterial infusion chemotherapy as well as combination therapies with sorafenib for patients with HCC and PVTT have been investigated and have provided promising results for specific conditions.[136] However, comparing the efficacy of different treatment modalities in these studies is difficult due to patient heterogeneity. Thus, the treatment of patients with HCC and PVTT remains challenging. Future recommendations need to be based on clear evidence from prospective randomised trials in larger patient cohorts (Table 2).

Conclusion

As outlined, there are various groups of patients with HCC and specific comorbidities or disease features who require extra clinical attention. These groups reflect the heterogeneity of patients encountered in real-world practice who are not adequately represented in clinical trials, because they do not meet the criteria of the “standard” patient with HCC. The main reason for excluding patients with certain comorbidities, such as vascular invasion or decompensated cirrhosis, is the well-known negative impact of these comorbidities on prognosis, which potentially confounds trial data. This practice has resulted in a general lack of data on treatment safety and efficacy in the described patient groups, which poses a significant and unmet medical need. The challenge of treating HCC in these special populations should be an incentive to design management algorithms tailored to patients’ needs and to conduct clinical trials that address open questions (Fig. 1), which could help to define best practice and identify novel treatments. Both the heterogeneity of HCC and the heterogeneity of affected patients make research and clinical management challenging. Yet it is essential that future research and clinical management reflect this heterogeneity.

Abbreviations

AE, adverse events; AIH, autoimmune hepatitis; cART, combined antiretroviral therapy; CKD, chronic kidney disease; CR, complete response; CVD, cardiovascular disease; FLHCC, fibrolamellar HCC; HCC, hepatocellular carcinoma; HCC/CCC, mixed hepatocellular/cholangiocellular carcinoma; HFSR, hand-foot skin reaction; ICI, immune checkpoint inhibitor; irAE, immune-related AE; mTOR, mammalian target of rapamycin; MVI, macrovascular tumour invasion; NAFLD, non-

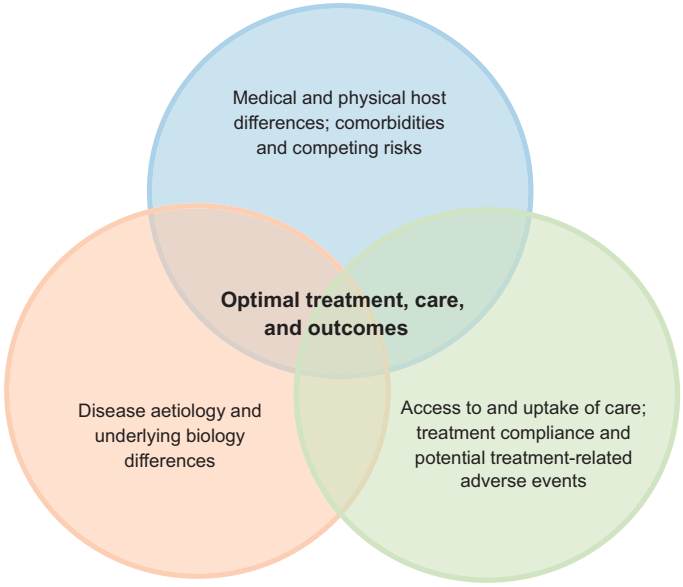

Fig. 1. Considerations to optimise treatment, care, and outcomes in special HCC populations. HCC, hepatocellular carcinoma.

alcoholic fatty liver disease; OLT, orthotopic liver transplantation; OS, overall survival; PBC, primary biliary cholangitis; PD-1, programmed cell death 1; PLWH, people living with HIV; PROs, patient-reported outcomes; PVT, portal vein thrombosis; PVTT, portal vein tumour thrombosis.

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Conflict of interest

LR reports receiving consulting fees from Amgen, ArQule, AstraZeneca, Basilea, Bayer, BMS, Celgene, Eisai, Exelixis, Genenta, Hengrui, Incyte, Ipsen, Lilly, MSD, Nerviano Medical Sciences, Roche, Sanofi; lectures fees from AbbVie, Amgen, Eisai, Gilead, Incyte, Ipsen, Lilly, Roche, Sanofi; travel fees from Ipsen; and institutional research funding from Agios, ARMO BioSciences, AstraZeneca, BeiGene, Eisai, Exelixis, Fibrogen, Incyte, Ipsen, Lilly, MSD, Nerviano Medical Sciences, Roche, Zymeworks. NP reports receiving consulting fees from Amgen, Merck Serono, Servier; lectures fees from AbbVie, Gilead, Lilly; travel fees from Amgen, ArQule; and institutional research funding from Basilea, Merck Serono, Servier. CC reports receiving consulting fees from MSD and lectures fees from EISAI. FF reports receiving consulting fees from Roche; lectures fees from Lilly and Pfizer. PRG reports receiving consulting and lectures fees from Adaptimmune, AstraZeneca, Bayer, BMS, Eisai, Ipsen, Lilly, MSD, Roche, Sirtex.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

All of the authors performed the research, writing, and review of all of the drafts of this paper and approved the final version.

Supplementary data

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