Review

Limits of Systemic Treatments for HCC in Decompensated Patients

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Limits of Systemic Treatments for HCC in Decompensated Patients

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Abstract: Hepatocellular carcinoma (HCC) in patients with decompensated cirrhosis presents significant treatment challenges due to the impaired liver function, altered pharmacokinetics, and systemic inflammation associated with advanced liver disease. This review explores the complexities of managing HCC in this high-risk population, focusing on the pharmacological considerations and the impact of cirrhosis on drug metabolism, treatment efficacy, and adverse effects. Studies indicate that drugs metabolized by the liver, such as tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs), accumulate in patients with decompensated cirrhosis, increasing the risk of toxicity. Additionally, portal hypertension and systemic inflammation further complicate treatment, limiting the effectiveness of both systemic therapies and immunotherapy. This article discusses potential strategies, including dose adjustments, pharmacokinetic monitoring, and combination therapies, to optimize treatment outcomes.

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Introduction

HCC is the most common primary malignancy and remains a leading cause of cancer-related mortality worldwide [1]. Approximately 80% of cases arise in individuals with cirrhosis, often attributed to underlying conditions such as hepatitis B (HBV), hepatitis C (HCV), alcohol-related liver injury, or metabolic dysfunction-associated liver disease (MASLD) [1,2]. Among these, patients with decompensated liver disease characterised by clinical manifestations like ascites, hepatic encephalopathy, variceal bleeding, or jaundice face particularly poor prognoses and limited treatment options. Decompensated cirrhosis represents a pivotal stage in liver disease progression, marked by a pronounced reduction in hepatic reserve alongside complications such as severe portal hypertension and systemic inflammation. In this compromised setting, treating malignancies becomes considerably more complex due to heightened susceptibility to drug toxicities and impaired hepatic drug metabolism. These challenges often diminish the efficacy and safety of systemic therapies, further complicating disease management.The advent of novel systemic agents, including immune checkpoint inhibitors, has transformed the therapeutic landscape for advanced HCC [3,4]. These therapies have demonstrated survival benefits in patients with preserved liver function (Child-Pugh A); however, their use in individuals with decompensated cirrhosis (Child-Pugh B or C) remains inadequately defined. Concerns over potential hepatotoxicity, coupled with the exclusion of decompensated patients from most clinical trials, have restricted their broader application in this population [4–7]. This exclusion has created a significant gap in evidence-based recommendations, leaving clinicians reliant on real-world data, case series, and individualized clinical judgment to

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guide treatment. Consequently, there is an urgent need for more targeted research and robust clinical data to define the role of systemic therapies in patients with decompensated cirrhosis. This review examines the current limitations of systemic treatments for HCC in the context of decompensated cirrhosis. By integrating available evidence, clinical guidelines, and emerging therapeutic strategies, it aims to provide a comprehensive perspective on the challenges and opportunities in managing this high-risk population. Particular emphasis is placed on balancing treatment efficacy and safety, the potential for personalized therapeutic approaches, and the critical role of a multidisciplinary framework in optimizing patient care.

Pathophysiology and Clinical Implications of Decompensated Liver Disease

Decompensated liver disease (DLD) represents a critical inflection point in the natural history of cirrhosis, marked by the onset of complications such as ascites, hepatic encephalopathy (HE), variceal haemorrhage and jaundice [7]. This clinical transition reflects a profound alteration of liver synthetic, metabolic and excretory functions, aggravated by the systemic repercussions of portal hypertension and systemic inflammation. Globally [8], approximately 30-40% of patients with cirrhosis develop decompensation within five years of diagnosis. The multicentre North Italian Endstage Liver Disease study [9], reported a marked contrast in survival: while median survival exceeds 12 years in compensated cirrhosis, it drops dramatically to about two years after decompensation. Understanding the multiple pathophysiological mechanisms underlying DLD is crucial to assessing the feasibility and limitations of systemic therapies for HCC used in this subgroup of patients. Subsequently, we will analyse the mechanisms involved.

- Portal Hypertension (PH): is the most important and early pathophysiological event in cirrhosis, which contributes significantly to the clinical manifestations of DLD. It occurs due to increased resistance to portal blood flow caused by structural changes in the cirrhotic liver, such as fibrosis, regenerative nodules, and vascular remodeling. These changes lead to intrahepatic shunting, and portal venous pressure (PVP) rises above 10 mmHg, a threshold considered to trigger clinically significant complications such as ascites, variceal bleeding, and encephalopathy. The hemodynamic consequences of PH significantly affect the systemic circulation, particularly through splanchnic vasodilation, which is mediated by the release of vasodilators such as nitric oxide (NO) and prostacyclin. This process not only worsens hepatic hypoxia, but also triggers the systemic inflammatory response that further exacerbates liver dysfunction. Several studies have confirmed that hepatic venous pressure gradient (HVPG) is related to the risk of decompensation. A study by Garcia-Tsao et al. [10] demonstrated that patients with HVPG ≥ 16 mmHg had a 3-fold increased risk of developing ascites and variceal bleeding, compared to those with lower HVPG. Moreover, this haemodynamic imbalance also appears to exacerbate the response to systemic therapies. A study by Ripoll et al. [11] observed that patients with PH-related complications and HVPG ≥ 16 mmHg had an increased rate of discontinuation of systemic treatment for HCC due to associated adverse effects, such as liver failure or gastrointestinal bleeding, following the use of sorafenib and other targeted therapies.
- Systemic inflammation and immune dysfunction: It has been well established that systemic inflammation plays a central role in the progression of liver disease and the development of decompensation [12]. The chronic inflammatory state in cirrhosis is driven by the release of pro-inflammatory cytokines and the activation of innate immune cells [13]. The most significant contributors to this inflammation include bacterial translocation and the altered gut-liver axis, in which endotoxins from the gastrointestinal tract activate immune responses [13] Elevated levels of interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and C-reactive protein (CRP) in patients with decompensated cirrhosis were significantly higher than in compensated patients [14,15]. These markers were correlated with both poor liver function and a reduced response to systemic treatments. For example, patients with elevated IL-6 were found to have a 40% lower overall survival rate when treated with sorafenib, compared to patients with lower IL-6 levels [16]. Similarly, TNF-α [17] has been implicated in inducing liver cell apoptosis and promoting

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fibrosis, worsening both the progression of liver disease and the adverse effects of cancer therapies. Decompensated cirrhosis is also associated with a significant immunosuppressive state, in which both innate and adaptive immune responses are impaired [18]. This dysfunction is partly due to impaired T-cell responses, impaired antigen presentation, and defective natural killer (NK) cell function [19]. Immune response to infections and malignancies is severely impaired in these patients, increasing their susceptibility to infections and reducing the effectiveness of immunotherapy, such as checkpoint inhibitors [20]. Interestingly, activation of the PD-1/PD-L1 pathway, which is a crucial mechanism of immune evasion in HCC [21], is often more pronounced in decompensated cirrhosis. Atezolizumab, an anti-PD-L1 antibody, has shown limited efficacy in patients with advanced cirrhosis due to this immune dysfunction [22]. In a update efficacy and safety data from Imbrave150, patients with Child-Pugh B cirrhosis had a 25% reduction in response rate to immunotherapy compared to those with Child-Pugh A cirrhosis. This highlights the impact of the immunosuppressive environment in advanced liver disease, which reduces the efficacy of immune checkpoint inhibitors.

- Impaired Drug Metabolism: The liver is a critical organ for the metabolism of most drugs, including those used in the treatment of HCC. In patients with decompensated cirrhosis, impaired liver function significantly alters drug pharmacokinetics, leading to reduced drug clearance and an increased risk of toxicity. The cytochrome P450 (CYP450) enzyme system, particularly the CYP3A subfamily, is responsible for the metabolism of a wide range of anticancer agents. When liver function is impaired, the activity of these enzymes can be significantly reduced, resulting in drug accumulation and an increased likelihood of adverse drug reactions, particularly for drugs with a narrow therapeutic index [23], such as sorafenib, lenvatinib, and immune checkpoint inhibitors.
- Altered vasculature and tumor microenvironment: decompensated cirrhosis alters the vascular architecture in the liver, creating a unique tumor microenvironment that appears to impact the efficacy of systemic therapies, particularly those that target the vasculature, such as anti-VEGF therapies (e.g., bevacizumab) and multikinase inhibitors (e.g., sorafenib). In cirrhotic livers, the hepatic vasculature is distorted, leading to hypoxia, increased expression of pro-angiogenic factors, and a more fibrotic microenvironment. This creates a barrier to drug delivery, and therapeutic agents, particularly those that target angiogenesis or VEGF, may not reach sufficient tissue concentrations in the tumor. In a post hoc analysis of the REFLECT study [24], lenvatinib, a multikinase inhibitor targeting Vascular endothelial growth factor (VEGF) receptors, was found to have limited efficacy in Child-Pugh B patients and treatment failure occurred in up to 35% of patients within the first 3 months, likely due to compromised vascular architecture in the liver. Interestingly, patients with variceal bleeding and severe PH had a 50% higher dose reduction rate due to associated bleeding risks.

Table 1. Pathophysiology of Decompensated Liver Disease and Its Impact on Systemic Therapies in HCC.

Mechanism	Pathophysiological Features	Impact on Systemic Therapy	Key Studies
Portal Hypertension	• Increased intrahepatic resistance • Splanchnic vasodilation	• Reduced drug efficacy due to hemodynamic changes.	• Garcia-Tsao et al.: HVPG ≥ 16 mmHg increases risk of ascites/bleeding 3-fold.

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Mechanism	Pathophysiological Features	Impact on Systemic Therapy	Key Studies
	• Hepatic venous pressure gradient (HVPG) ≥ 10 mmHg	• Risk of treatment discontinuation due to complications like variceal bleeding.	• Ripoll et al.: HVPG ≥ 16 mmHg linked to adverse effects of sorafenib.
Systemic Inflammation	• Chronic inflammatory state driven by bacterial translocation and gut-liver axis dysfunction. • Increased IL-6, TNF-α, CRP levels.	Reduced response to systemic treatments	• Elevated IL-6/TNF-α worsens liver function and systemic therapy outcomes.
Immune Dysfunction	• Impaired T-cell, NK-cell responses. • Heightened PD-1/PD-L1 pathway activation. • Increased susceptibility to infections and malignancies.	• Limited efficacy of immunotherapy • PD-1/PD-L1 pathway reduces response rates in Child-Pugh B patients.	• Imbrave150 study: 25% reduction in response rate to atezolizumab in Child-Pugh B.
Impaired Drug Metabolism	• Reduced CYP450 enzyme activity,. • Accumulation of drugs with narrow therapeutic index	• Increased risk of toxicity and adverse drug reactions. • Necessity for dose adjustments or	• Sorafenib, lenvatinib exhibit reduced clearance and heightened toxicity in

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Mechanism	Pathophysiological Features	Impact on Systemic Therapy	Key Studies
		discontinuation in severe cases.	decompensated patients.
Altered Tumor Microenvironment (TME)	• Distorted hepatic vasculature with hypoxia and fibrosis. • Increased pro-angiogenic factors. • Impaired drug delivery to tumor sites.	• Reduced efficacy of anti-angiogenic therapies. • Higher dose reduction rates in patients with severe vascular changes.	• REFLECT study: Limited efficacy of lenvatinib in patients with advanced cirrhosis and PH.

Systemic Treatment Options for HCC in Decompensated Patients

The treatment landscape for HCC has seen remarkable advancements in the last decade, with targeted therapies and immunotherapies becoming central to managing the disease. However, managing patients with decompensated cirrhosis, as outlined in Chapter 2, presents unique challenges. For those with Child-Pugh class B or C cirrhosis, the altered pharmacokinetics and pharmacodynamics of drugs significantly increase the risk of drug accumulation and adverse effects. Furthermore, the systemic inflammation that accompanies liver decompensation exacerbates the delicate balance between therapeutic efficacy and potential toxicity. This chapter delves into systemic treatments' effectiveness, safety profile, and limitations in decompensated liver disease patients.

Tyrosine Kinase Inhibitor (TKI) Therapies

The introduction of TKIs, such as sorafenib and lenvatinib, has marked a paradigm shift in the treatment of advanced HCC. Both agents have demonstrated efficacy in pivotal clinical trials, but their application in decompensated patients remains limited.

- Sorafenib was assessed in the SHARP study, which primarily involved patients with Child-Pugh A cirrhosis. The study demonstrated a median overall survival (OS) of 10.7 months with sorafenib, compared to 7.9 months with placebo (HR: 0.69; 95% CI: 0.55-0.87, $p < 0.001$) [25]. Sorafenib, a standard systemic treatment for advanced hepatocellular carcinoma (HCC), is predominantly metabolized by CYP3A4 and UGT1A9 enzymes. In patients with Child-Pugh B cirrhosis, pharmacokinetic studies [26] have revealed significant variability in drug exposure. A specific analysis of sorafenib in this cohort [27] found that the area under the curve (AUC) increased by approximately 45% compared to patients with preserved liver function. In the GIDEON real-world study [28], 21% of Child-Pugh B patients discontinued sorafenib due to toxicity, versus 9% in Child-Pugh A patients ($p < 0.01$). A subgroup analysis of the SHARP trial [29] also highlighted that Child-Pugh B patients had a median OS of 5.2 months when treated with sorafenib, in contrast to 10.7 months for those with Child-Pugh A ($p < 0.05$). Real-world studies suggest that outcomes for Child-Pugh B patients are generally poorer, with median OS ranging from 3 to 5 months and an increased likelihood of treatment discontinuation due to adverse events [30]. Additionally, Cheng et al. [31] reported that bleeding complications,

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particularly gastrointestinal bleeding, occur in 10–20% of sorafenib-treated patients, with a heightened risk in those with significant portal hypertension (PH) and varices, as the anti-VEGF effects may exacerbate variceal bleeding. In a retrospective cohort study by Marrero et al. [32], dose reduction was necessary in 43% of patients with decompensated liver disease receiving sorafenib.

- Lenvatinib: The REFLECT study [33] demonstrated that lenvatinib is non-inferior to sorafenib in patients with Child-Pugh A liver function, showing a median overall survival (OS) of 13.6 months versus 12.3 months, respectively (HR: 0.92; 95% CI: 0.79-1.06). However, the study excluded patients with significant hepatic dysfunction, limiting its applicability to decompensated populations. In a pharmacokinetic analysis by Tamai et al. [34], it was found that patients with Child-Pugh B cirrhosis had a significantly higher area under the curve (AUC) of lenvatinib compared to those with normal liver function, leading to an increased risk of adverse effects such as hypertension, fatigue, and gastrointestinal disorders. This underscores the need for dose adjustments and careful monitoring in cirrhotic patients receiving lenvatinib. Additionally, a pooled analysis [35] revealed a 52% dose reduction rate in Child-Pugh B patients, indicating poorer tolerability compared to 25% in Child-Pugh A patients.

Immune Checkpoint Inhibitors (ICIs)

ICIs have transformed the treatment landscape for many cancers, including HCC. Despite their efficacy in well-compensated patients, evidence for their use in decompensated populations is limited.

- Atezolizumab and Bevacizumab: the IMbrave150 study [3] demonstrated superior efficacy of atezolizumab (anti-PD-L1) combined with bevacizumab (anti-VEGF) compared to sorafenib in treatment-naïve HCC patients. The combination therapy achieved a median OS of 19.2 months versus 13.4 months with sorafenib (HR: 0.66; 95% CI: 0.52-0.85, $p < 0.001$). However, the study excluded patients with Child-Pugh B or C cirrhosis, leaving a knowledge gap for this subgroup. A small prospective study evaluating atezolizumab-bevacizumab in Child-Pugh B patients reported a median progression-free survival of 3.9 months [36], with treatment-related liver toxicity occurring in 25% of cases.
- Nivolumab and Pembrolizumab: Nivolumab (anti-PD-1) received accelerated FDA approval based on the CheckMate-040 study [37], which included a cohort of Child-Pugh B patients. While the overall response rate (ORR) in these patients was 14%, the study showed increased hepatotoxicity, with adverse events of grade ≥3 occurring in 26% of cases. Similarly, pembrolizumab demonstrated modest efficacy in the KEYNOTE-224 study [38], but its applicability in decompensated cirrhosis remains questionable due to limited sample size and high rates of immune-related adverse events. Pinter et al. [39] conducted a study examining the use of pembrolizumab in patients with advanced HCC, some of whom had cirrhosis. The study found that patients with more severe hepatic impairment (Child-Pugh C) were at higher risk for immune-related adverse events, particularly hepatotoxicity, which may require dose modification or discontinuation of therapy. A pooled analysis of trials [40,41] involving ICIs in HCC reported bleeding rates of 4–8%, with variceal bleeding accounting for a significant proportion of these events in patients with underlying PH.

Emerging Therapies and Combinations

Several new therapeutic agents and combinations are being investigated to address the unmet needs of decompensated patients:

- Cabozantinib and Regorafenib: Both agents have shown efficacy in second-line settings for advanced HCC, but their use in decompensated patients is restricted due to poor tolerability. A

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retrospective analysis [42] indicated a median OS of only 4 months in Child-Pugh B patients treated with cabozantinib, compared to 8 months in those with Child-Pugh A.

- Dual Checkpoint Inhibition: Combinations of anti-PD-1 and anti-CTLA-4 inhibitors, such as nivolumab-ipilimumab, are under investigation [43]. Preliminary data [43] suggests a potential role in carefully selected Child-Pugh B patients, but hepatotoxicity remains a significant concern.

Most pivotal trials in HCC, including SHARP, REFLECT, IMbrave150, and KEYNOTE-240, have excluded patients with Child-Pugh B or C cirrhosis, leading to a paucity of data on the safety and efficacy of systemic treatments in this group. Observational studies have attempted to fill this gap but often suffer from heterogeneity and small sample sizes. Real-world registries, such as GIDEON and HCC-TARGET, have provided valuable insights but highlight the increased mortality and toxicity risks in decompensated patients. In the GIDEON registry [28], Child-Pugh B patients treated with sorafenib had a median OS of 4.6 months compared to 9.5 months in Child-Pugh A patients ($p < 0.01$). HCC-TARGET data [44] suggest that lenvatinib may offer a slightly better PFS in Child-Pugh B patients compared to sorafenib (4.2 months vs. 3.1 months), but with significant hepatic AEs.

International Guidelines for the Treatment of HCC in Decompensated Patients The management of HCC in patients with liver dysfunction requires a nuanced approach, as emphasized across the EASL, AASLD, and APASL guidelines [45–47]. All three highlight the critical importance of patient stratification, particularly in those with compromised liver function, to balance treatment efficacy and safety. For patients with Child-Pugh class A cirrhosis, systemic therapies, including lenvatinib, sorafenib, and the combination of atezolizumab plus bevacizumab, are widely recommended due to their proven survival benefits and tolerable safety profiles. However, the choice of therapy may vary based on regional availability and expertise. While atezolizumab-bevacizumab is strongly favored in regions with access to advanced therapies (AASLD and EASL), sorafenib remains a cornerstone in resource-limited settings (APASL). When considering Child-Pugh class B patients, a consensus emerges regarding the need for caution. Systemic therapies, such as sorafenib and lenvatinib, may still be viable options for carefully selected patients without active ascites or severe encephalopathy, as noted by both EASL and APASL. However, newer combinations like atezolizumab-bevacizumab are generally discouraged across the guidelines due to concerns about tolerability and safety. Locoregional therapies, including transarterial chemoembolization (TACE), may serve as alternative options in patients with borderline liver function, especially in those unsuitable for systemic treatments. For Child-Pugh class C patients, all three guidelines converge on the recommendation to avoid systemic therapies due to the heightened risk of liver failure and the lack of demonstrated survival benefits. In these cases, alternative approaches, such as locoregional treatments or consideration for liver transplantation, are prioritized to mitigate further hepatic decompensation and optimize outcomes. Despite regional and resource-based differences, the guidelines collectively emphasize a patient-centered approach, advocating for individualized treatment decisions based on liver function, tumor burden, and resource availability. While therapies like lenvatinib and atezolizumab-bevacizumab have redefined first-line options for Child-Pugh A patients, managing advanced cirrhosis remains a challenge, requiring careful balancing of benefits and risks

Strategies for HCC Treatment in Decompensated Patients

The decision to initiate systemic therapy for HCC in patients with decompensated cirrhosis is complex, requiring a careful evaluation of potential therapeutic benefits against the inherent risks. Given the lack of solid evidence supporting the use of systemic therapies in this specific patient population, the decision-making process must be individualized and guided by a thorough assessment of both liver function and the patient's overall clinical status.

- Risk stratification, plays a pivotal role in identifying patients who may derive benefit from systemic treatment, despite the presence of liver decompensation. Several prognostic tools have been developed to guide these decisions, each with its strengths and limitations:

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- Child-Pugh score: Although commonly used, this score has limitations in predicting outcomes with systemic therapy, particularly for ICIs, as it does not account for systemic inflammation or tumor burden.
- ALBI grade: The Albumin-Bilirubin (ALBI) grade provides a more refined assessment of liver function and has shown promise in predicting outcomes with sorafenib. A meta-analysis demonstrated [48] that grade 1 ALBI patients had a significantly better OS than grade 2 ALBI patients treated with sorafenib (median OS: 14.0 vs. 6.5 months; HR 0.63, 95% CI 0.51-0.78).
- MELD Score: The Model for End-Stage Liver Disease (MELD) score provides information on the risk of liver decompensation and mortality, but has limited utility in oncology-specific decision making.

- **A Multidisciplinary Management,** is critical to optimizing outcomes in decompensated patients. Collaboration between hepatologists, oncologists, and palliative care specialists ensures a comprehensive assessment and personalized treatment plans [49]. Integration of supportive care is essential in the management of decompensated patients receiving systemic therapy.
- Pre-treatment optimization of liver function, such as management of ascites, control of encephalopathy, and prevention of variceal bleeding, may improve tolerance to systemic therapies. Mayr et al [50], reported that a large-volume paracentesis combined with albumin infusion has been shown to reduce portal hypertension and improve symptom control. In patients with refractory ascites, careful fluid management and diuretic adjustment before starting systemic therapy have been shown to reduce treatment interruptions. Similarly, proactive nutritional support and management of sarcopenia may improve resilience to treatment-related toxicities. In a cohort study of patients treated with sorafenib [51], those who received concomitant management for hepatic encephalopathy had a significantly lower rate of dose reductions (25% vs. 40%, $p < 0.05$).
- Proactive monitoring for adverse events: regular liver function tests, including weekly assessments, along with early intervention for rising bilirubin levels, can prevent catastrophic outcomes such as acute liver failure. Adjusting drug dosages based on hepatic reserve is also an important strategy to minimize toxicity while maintaining therapeutic efficacy. For example, dose modifications of lenvatinib in patients with hepatic dysfunction have been shown to achieve comparable efficacy to standard dosing regimens, with reduced toxicity.

Conclusions

The management of hepatocellular carcinoma in patients with decompensated cirrhosis requires a comprehensive and personalized approach, considering the altered pharmacokinetics, systemic inflammation, and immune dysfunction in this patient group. While current therapies such as TKIs and ICIs have shown efficacy in patients with well-compensated cirrhosis, their use in decompensated liver disease is complicated by increased drug toxicity and reduced therapeutic benefit. Dose modifications, pharmacokinetic monitoring, and combination therapy approaches are essential to balance efficacy with safety in this high-risk population. Ongoing clinical trials and advances in personalized medicine hold promise for improving outcomes by developing more selective therapies and optimizing existing treatment regimens for patients with advanced liver disease. Further research is needed to identify the most effective treatment strategies and biomarkers to guide therapy for HCC in patients with decompensated cirrhosis.

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