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Alcohol-Related Hepatocellular Carcinoma In The Era Of Immunotherapy: Clinical Impact Of Atezolizumab Plus Bevacizumab

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Abstract

Alcohol-related liver disease has emerged as a major driver of hepatocellular carcinoma worldwide, reflecting the changing epidemiology of chronic liver disease. Hepatocellular carcinoma arising in the context of chronic alcohol exposure develops within a pro-inflammatory and immunosuppressive microenvironment, raising concerns regarding responsiveness to immune-based therapies. The combination of atezolizumab, a programmed death-ligand 1 inhibitor, and bevacizumab, an anti-vascular endothelial growth factor antibody, has become the standard first-line systemic treatment for advanced hepatocellular carcinoma after demonstrating superior survival outcomes compared with sorafenib in a pivotal phase III trial. Although patients with alcohol-related disease were underrepresented in randomized clinical trials, accumulating evidence from post-hoc analyses and real-world studies suggests that atezolizumab plus bevacizumab provides clinically meaningful benefit in alcohol-related hepatocellular carcinoma, particularly in patients with preserved liver function and adequately controlled portal hypertension. This review synthesizes current evidence on the pathogenesis, immune landscape, and clinical outcomes of alcohol-related hepatocellular carcinoma, with a focus on the efficacy and safety of atezolizumab plus bevacizumab and the importance of Child-Pugh status in treatment selection.

Keywords

Alcohol-related liver disease; Alcohol-related hepatocellular carcinoma; Immunotherapy; Atezolizumab; Bevacizumab; Immune checkpoint inhibitors; VEGF inhibition; Child-Pugh classification; Portal hypertension

1. Introduction

Hepatocellular carcinoma remains one of the leading causes of cancer-related mortality worldwide, with a steadily increasing incidence in many regions [1]. While chronic hepatitis B and C infections historically accounted for most cases, the epidemiology of hepatocellular carcinoma has shifted markedly over the past two decades. Alcohol-related liver disease has become a dominant etiological factor in Western countries and is increasingly recognized globally [2,3]. This epidemiological transition has major clinical

implications, as alcohol-related hepatocellular carcinoma frequently arises in patients with advanced cirrhosis, portal hypertension, and multiple comorbidities.

Hepatocellular carcinoma developing on a background of alcohol-related liver disease is characterized by chronic inflammation, progressive fibrogenesis, and profound immune dysregulation [4]. These features influence both tumor biology and therapeutic tolerance. The advent of immune checkpoint inhibitors has transformed the systemic treatment landscape of advanced hepatocellular carcinoma, with the combination of atezolizumab and bevacizumab demonstrating superior survival and quality-of-life outcomes compared with sorafenib in the first-line setting [5]. However, the applicability of immunotherapy-based regimens in alcohol-related disease has remained a matter of debate, given alcohol-induced immune dysfunction and the high prevalence of portal hypertension.

In this context, alcohol-related hepatocellular carcinoma represents a rapidly growing yet underrepresented etiological subgroup in clinical trials. Given the distinctive biological and immunological features associated with chronic alcohol exposure, extrapolation of immunotherapy data from viral-related disease may be insufficient. This review specifically focuses on alcohol-related hepatocellular carcinoma and integrates mechanistic insights, evidence from randomized trials, real-world clinical data, and liver function considerations to critically evaluate the role of atezolizumab plus bevacizumab in this population.

Pathogenesis of Alcohol-Related Hepatocellular Carcinoma

Chronic alcohol consumption promotes hepatocarcinogenesis through a complex interplay of toxic, inflammatory, and fibrogenic mechanisms. Ethanol metabolism generates acetaldehyde and reactive oxygen species, leading to oxidative stress, DNA damage, lipid peroxidation, and genomic instability [6]. Recurrent hepatocellular injury results in sustained activation of Kupffer cells and other innate immune cells, with persistent secretion of pro-inflammatory cytokines such as tumor necrosis factor-α and interleukin-6, which promote oncogenic signaling pathways [7].

Progressive fibrosis and cirrhosis represent the final common pathway of alcohol-related liver disease and constitute the principal substrate for hepatocellular carcinoma development. Stellate cell activation and extracellular matrix remodeling not only distort liver architecture but also create a pro-tumorigenic microenvironment [8]. In parallel, chronic alcohol exposure induces epigenetic alterations and impairs DNA repair mechanisms, further facilitating malignant transformation and tumor progression [9].

Immune Landscape in Alcohol-Related Hepatocellular Carcinoma

Alcohol-related liver disease is associated with profound alterations of both innate and adaptive immunity. Chronic alcohol exposure impairs antigen presentation, reduces cytotoxic T-cell activity, and promotes T-cell exhaustion, as reflected by increased expression of inhibitory receptors such as PD-1 and TIM-3 [10]. Expansion of regulatory T cells and myeloid-derived suppressor cells further contributes to an immunosuppressive tumor microenvironment, favoring immune escape [11].

In addition to immune dysfunction, vascular abnormalities driven by vascular endothelial growth factor signaling play a central role in immune exclusion within hepatocellular carcinoma. VEGF-mediated angiogenesis results in abnormal tumor vasculature, tissue hypoxia, and impaired immune cell trafficking [12]. VEGF inhibition may partially reverse these effects by restoring vascular normalization and enhancing immune infiltration, providing a strong biological rationale for combining bevacizumab with immune checkpoint blockade in alcohol-related hepatocellular carcinoma [13].

The biological and clinical rationale supporting the use of atezolizumab plus bevacizumab in alcohol-related hepatocellular carcinoma is summarized in **Figure 1.**

Clinical Evidence for Atezolizumab Plus Bevacizumab

The phase III IMbrave150 trial established atezolizumab plus bevacizumab as the preferred first-line therapy for unresectable or metastatic hepatocellular carcinoma, demonstrating significant improvements in overall survival, progression-free survival, and patient-reported quality of life compared with sorafenib [5,14]. Eligibility was restricted to patients with preserved liver function, defined as Child-Pugh class A, and controlled portal hypertension. Although alcohol-related liver disease accounted for a minority of cases, subgroup analyses suggested consistent benefit across etiologies.

Subsequent post-hoc analyses and real-world studies have provided important insights into outcomes among patients with alcohol-related hepatocellular carcinoma. Across multiple cohorts, atezolizumab plus bevacizumab demonstrated clinically meaningful antitumor activity in alcohol-related disease, with response rates and survival outcomes broadly comparable to those observed in viral-associated hepatocellular carcinoma [15–16].

Key studies are summarized in **Table 1**.

2. Discussion

The increasing incidence of alcohol-related hepatocellular carcinoma represents a major challenge for contemporary oncology and hepatology, as this etiological subgroup is frequently associated with advanced cirrhosis, portal hypertension, and profound immune dysfunction [1–3]. Historically, alcohol-related disease has been considered a negative prognostic factor, largely due to impaired liver function and limited therapeutic options. In the era of immunotherapy, however, accumulating evidence indicates that patients with alcohol-related hepatocellular carcinoma may derive substantial benefit from immune-based strategies when liver function is preserved.

Several systemic treatment options are currently available for advanced hepatocellular carcinoma. Tyrosine kinase inhibitors such as sorafenib and lenvatinib remain valid alternatives, particularly in patients with contraindications to immunotherapy or anti-VEGF agents; however, their clinical benefit is generally characterized by lower objective response rates and a more limited impact on quality of life compared with immunotherapy-based strategies [19,20]. More recently, the combination of durvalumab and tremelimumab has demonstrated an overall survival benefit over sorafenib and represents an additional immunotherapy-based option in the first-line setting [21]. Nevertheless, in patients with

alcohol-related hepatocellular carcinoma and preserved liver function, atezolizumab plus bevacizumab remains the preferred standard of care due to its consistent survival advantage, higher response rates, and favorable quality-of-life outcomes [5,14–17]. The use of anti-VEGF–based therapy must carefully balance the risk of gastrointestinal bleeding against the overall survival benefit, particularly in the context of portal hypertension, underscoring the importance of meticulous patient selection in Child-Pugh A disease [22,23].

The biological rationale supporting atezolizumab plus bevacizumab is particularly compelling in alcohol-related hepatocellular carcinoma. Chronic alcohol exposure induces an immunosuppressive tumor microenvironment characterized by impaired antigen presentation, T-cell exhaustion, expansion of regulatory T cells, and accumulation of myeloid-derived suppressor cells [10–12]. In parallel, VEGF-driven angiogenesis promotes abnormal tumor vasculature, hypoxia, and immune exclusion, thereby facilitating tumor progression [12,13]. VEGF inhibition may restore vascular normalization and enhance immune cell trafficking, creating a more permissive environment for immune checkpoint blockade. This dual mechanism provides a strong biological explanation for the preserved efficacy of atezolizumab plus bevacizumab in alcohol-related disease despite alcohol-associated immune dysfunction.

From a clinical perspective, liver function remains a critical determinant of treatment eligibility and outcome. Most available evidence supporting atezolizumab plus bevacizumab derives from patients with Child-Pugh A cirrhosis, and outcomes in this population appear comparable across etiologies when appropriate selection criteria are applied [5,15–17]. Patients with alcohol-related hepatocellular carcinoma frequently present with clinically significant portal hypertension, which increases the risk of gastrointestinal bleeding associated with bevacizumab. Consequently, current guidelines emphasize the importance of systematic endoscopic screening and prophylactic management of esophageal or gastric varices prior to treatment initiation [22,23]. When these precautions are implemented, real-world data suggest that the safety profile of atezolizumab plus bevacizumab is acceptable and consistent with that observed in other etiological subgroups [16,17].

Several limitations must be acknowledged. Alcohol-related liver disease remains underrepresented in randomized clinical trials, and much of the available evidence relies on post-hoc analyses and heterogeneous real-world cohorts [15–17]. In addition, the impact of ongoing alcohol consumption on immunotherapy efficacy and toxicity has not been adequately characterized. Finally, data regarding the use of atezolizumab plus bevacizumab in patients with Child-Pugh B cirrhosis remain limited and inconclusive, precluding routine use in this population outside carefully selected cases or clinical trials [18].

Overall, available clinical and biological evidence supports atezolizumab plus bevacizumab as the preferred first-line systemic therapy for patients with alcohol-related hepatocellular carcinoma and preserved liver function. Dedicated prospective studies focusing specifically on this etiological subgroup, with refined stratification by liver function, portal hypertension, and alcohol exposure, are urgently needed to further optimize treatment strategies and improve outcomes.

3. Conclusion

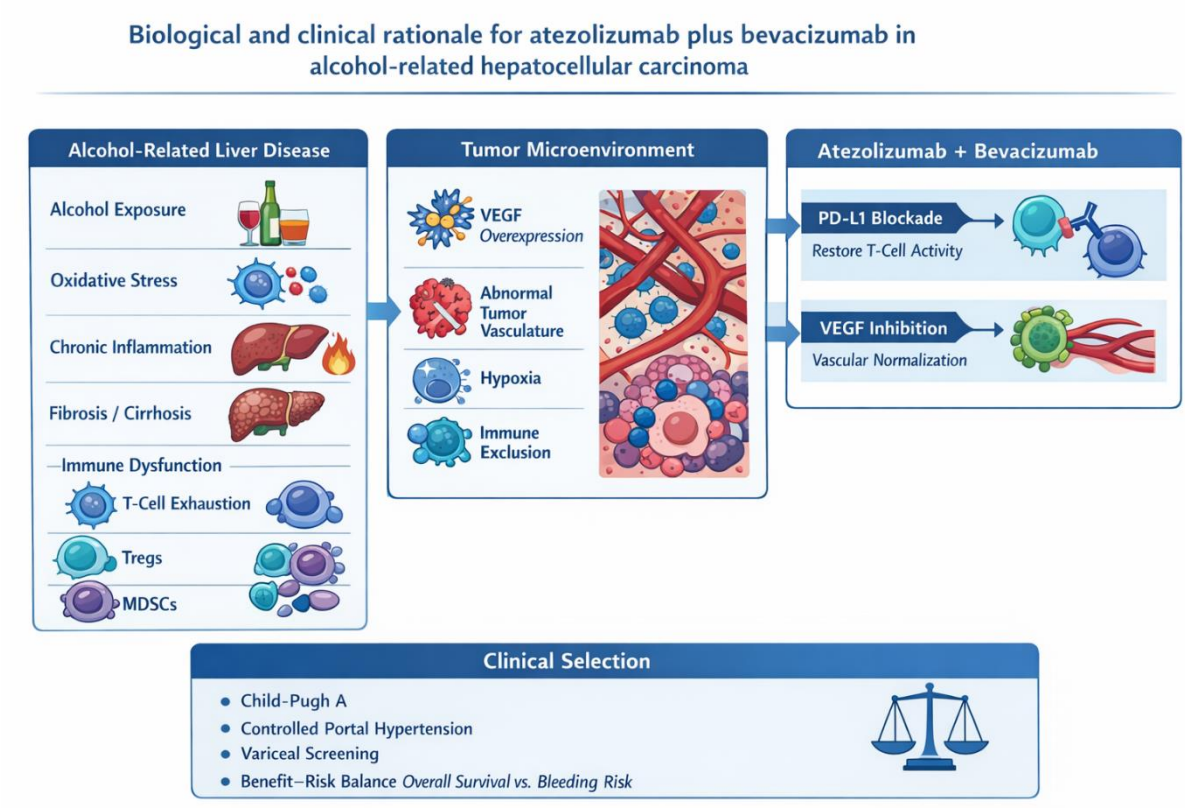
Alcohol-related liver disease is an increasingly important driver of hepatocellular carcinoma worldwide. In the era of immunotherapy, atezolizumab plus bevacizumab provides a substantial clinical benefit for patients with alcohol-related hepatocellular carcinoma who maintain Child-Pugh A liver function and adequately controlled portal hypertension. Dedicated clinical and translational research tailored to this growing population is essential to further optimize immunotherapy strategies and improve outcomes.

Table 1. Key clinical studies evaluating atezolizumab plus bevacizumab in alcohol-related hepatocellular carcinoma

Study (reference)	Study type	Total population (n)	Alcohol-related HCC (%)	Child-Pugh status	Key efficacy outcomes	Key safety notes
Finn et al., 2020 [5]	Phase III randomized trial IMbrave150)	501	~30% non-viral (ALD not isolated)	Child-Pugh A only	OS and PFS significantly improved versus sorafenib; ORR ~27%	Mandatory variceal screening; acceptable bleeding risk
Cheng et al., 2022 [14]	Updated IMbrave150 analysis	501	Non-viral subgroup	Child-Pugh A only	Sustained overall survival benefit and durable responses	No new safety signals
Rimassa et al., 2022 [15]	Post-hoc etiology analysis	501	ALD subgroup	Child-Pugh A only	Comparable efficacy across viral and non-viral etiologies	Similar toxicity profile
Casadei-Gardini et al., 2021 [16]	Multicenter real-world study	191	42% ALD	Predominantly Child-Pugh A; selected B	Objective response rate ~30%; clinically meaningful median OS	Inferior outcomes in Child-Pugh B patients
Kudo et al., 2022 [17]	Real-world cohort	171	36% ALD	Child-Pugh A only	Effectiveness consistent with	Bleeding events manageable

					IMbrave150	with screening
Rizzo et al., 2022 [22]	Real-world pooled analysis	>1000	Mixed etiologies	Mostly Child-Pugh A	No significant OS difference between ALD	Acceptable anti-VEGF safety profile

Figure 1. Biological and clinical rationale for atezolizumab plus bevacizumab in alcohol-related hepatocellular carcinoma



Chronic alcohol exposure promotes hepatocarcinogenesis through oxidative stress, chronic inflammation, fibrosis, and profound immune dysfunction, leading to an immunosuppressive tumor microenvironment characterized by T-cell exhaustion, regulatory immune cell expansion, and VEGF-driven abnormal tumor vasculature. VEGF overexpression contributes to immune exclusion and tumor progression. Combined PD-L1 blockade with atezolizumab and VEGF inhibition with bevacizumab synergistically restore antitumor immunity through immune reactivation and vascular normalization. This biological rationale supports the clinical efficacy of atezolizumab plus bevacizumab in carefully selected patients with

alcohol-related hepatocellular carcinoma, particularly those with Child-Pugh A liver function and adequately controlled portal hypertension.

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