First-line Use of Antiangiogenic Agents in Unresectable Hepatocellular Carcinoma: A Double-Edged Sword?

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Abstract: Treatment options for hepatocellular carcinoma (HCC), the most prevalent primary liver malignancy, have historically been limited, particularly in unresectable cases with underlying cirrhosis. Initial systemic therapy with antiangiogenic agents, notably vascular endothelial growth factor (VEGF) inhibitors such as sorafenib, showed modest survival gains but lacked durable responses. Subsequent trials with more potent VEGF pathway inhibitors failed to improve overall survival significantly, raising concerns about the long-term utility and potential hepatic and renal toxicities of prolonged VEGF blockade. The advent of immune checkpoint inhibitors (ICIs) marked a paradigm shift. Trial results demonstrating that dual-ICI regimens induced more durable responses and achieved higher long-term survival rates have challenged the prior VEGF-centric therapeutic approach and suggest that early use of dual ICIs may offer a more transformative effect on disease trajectory. Although anti-VEGF therapies remain valuable for initial tumor shrinkage, prolonged use may compromise liver regeneration and worsen portal hypertension. A refined treatment strategy emphasizing VEGF inhibition for a limited duration followed by or combined with ICIs may optimize both efficacy and safety. Future research should focus on identifying predictive biomarkers for ICI response and on developing regimens that maximize long-term survival in unresectable HCC.

Keywords
Antiangiogenic agents, immune checkpoint inhibitors, unresectable hepatocellular carcinoma, VEGF inhibitors

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and ranks as the third most frequent cause of cancer-related deaths worldwide.[1,2] Owing to the competing risk of death

from the underlying cirrhosis, meaningful improvement in outcomes has almost exclusively been studied and observed in patients with preserved liver function, as evaluated with the Child-Pugh scoring system (ie, Child-Pugh A). The prognosis for unresectable HCC, deemed a disease relatively refractory to cytotoxic therapy, remained dismal until very recently owing to a lack of effective systemic therapies. HCC is a hypervascular tumor with a complex microenvironment consisting of tumor-supporting stromal cells, including cancer-associated fibroblasts, and characterized by an immune imbalance with a predominance of suppressive cells (eg, myeloid-derived suppressor cells, regulatory T cells, and type 2 macrophages) and a paucity of effector T cells. Insights into the biology of HCC have informed the development of the treatment landscape during the past 15 to 20 years.[3]

The Use of Antiangiogenesis

Early attempts to treat unresectable HCC with conventional chemotherapy had limited success, given the chemoresistant nature of the disease and limited tolerability due to underlying liver dysfunction. The recognition of the role of angiogenesis in solid tumors and the development of antiangiogenic therapies in the early 2000s led to the availability of a limited repertoire of agents to be tested in a multitude of malignancies, including HCC.[4] Although the first-in-class anti–vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab was not further pursued as a single agent in HCC, mainly because of safety concerns, the rapid parallel development of multitarget tyrosine kinase inhibitors (TKIs) inhibiting the VEGF receptor led to new hope for this challenging disease. In 2008, the SHARP trial demonstrated an improvement in overall survival (OS) with sorafenib (Nexavar, Bayer HealthCare/Onyx) vs best supportive care, the first systemic therapy to extend survival in advanced HCC.[5] Sorafenib subsequently became the standard of care for unresectable HCC. Alas, 4 subsequent negative phase 3 trials with additional anti-VEGF TKIs (sunitinib, brivanib, linifanib, and erlotinib + sorafenib) failed to show results better than or at least noninferior to sorafenib alone.[6-9] Given the modest improvement in OS (2.8 months) with sorafenib over best supportive care, the failure of other anti-VEGF TKIs to match this low bar may have suggested that just because a certain target (in this case the VEGF pathway) is druggable, it is not necessarily the best initial target.

More than a decade later, in 2018, REFLECT was the first positive phase 3 trial in unresectable HCC since the introduction of sorafenib.[10] However, even with a more potent anti-VEGF receptor inhibitor (ie, lenvatinib [Lenvima, Eisai]), noninferiority of OS compared with sorafenib was observed, but no improvement. This was surprising because lenvatinib nearly doubled both progression-free survival (PFS) and overall response rate (ORR) according to the Response Evaluation Criteria in Solid Tumors, version 1.1. (RECIST 1.1).[10] One could have deduced that cutting off the blood supply to an HCC tumor might lead to a transient shrinkage in size, and although a more potent inhibitor could achieve that feat for twice as long, neither therapy changed the behavior of the tumor. Thus, more than a decade of high-level data in unresectable HCC suggested that starting with antiangiogenesis is more of a Band-Aid than a long-term solution.

The Advent of Immunotherapy

A significant paradigm shift occurred with the advent of immunotherapy. Early-phase studies of immune checkpoint inhibitors (ICIs), such as CheckMate 040 with nivolumab (Opdivo, Bristol Myers Squibb), demonstrated not only objective responses in patients with later-line unresectable HCC but also, perhaps more importantly, durable responses in a subset of patients.[11] This tail of durable response indicated that these therapies altered the disease trajectory, achieving durable responses in a subset of patients rather than simply delaying disease progression. These findings of objective and durable responses with ICIs, and early-phase single-arm data for ICIs in combination with anti-VEGF–directed therapies, fueled new hope for synergy and a breakthrough in the systemic treatment for unresectable HCC.[12] Therefore, several late-phase trials evaluated the efficacy of anti-VEGF agents in combination with ICIs in first-line unresectable HCC. The IMbrave150 trial, which evaluated the combination of atezolizumab (Tecentriq, Genentech) and bevacizumab, was the first to show significantly improved OS, PFS, and ORR for combination therapy in comparison with sorafenib monotherapy, and combination therapy was thenceforth regarded as the new standard of care.[13]

However, other phase 3 trials combining anti-VEGF agents with ICIs, including LEAP-002 (lenvatinib and pembrolizumab [Keytruda, Merck]) and COSMIC-312 (cabozantinib and atezolizumab), did not demonstrate improvements in OS when these combinations were compared with anti-VEGF monotherapy (lenvatinib alone and sorafenib alone, respectively).[14,15] Importantly, despite higher ORRs in the arms in which ICIs were combined with VEGF inhibitors, no apparent durable responses were reported with longer follow-up in these trials. Updated analysis of IMBrave150 in 2022, with an additional 12 months of follow-up data, showed a median OS of 19.2 months (lower than the "not reached" median OS in the original publication) but no available evidence of a subset with durable response in either arm, despite

sufficient follow-up time to obtain the data (ie, no flattening of the curve, or "tail").[16]

Unlike the patients in the aforementioned trials, which evaluated immune checkpoint inhibition in combination with VEGF inhibition, the patients with advanced HCC in the nonrandomized CheckMate 040 trial received nivolumab either alone or in combination with one of 2 doses of ipilimumab (Yervoy, Bristol Myers Squibb), an anti–cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) monoclonal antibody.[11] Although both treatment-naive and sorafenib-pretreated patients with unresectable HCC were included, the group that received the higher dose of ipilimumab (3 mg/kg) + nivolumab demonstrated the highest ORR and the highest durable response rate, at the cost of a higher rate of immune-related adverse events (irAEs).[11] Importantly, a recent update of the study reported a 5-year survival rate of 29% with the combination of higher-dose ipilimumab + nivolumab.[17]

On the basis of the findings of CheckMate 040 and other trials, the paradigm of dual checkpoint inhibition in first-line unresectable HCC (without the use of an anti-VEGF agent) was tested in 2 large, randomized, global phase 3 trials.[18] The first trial to report was HIMALAYA, which compared a single dose of the anti–CTLA-4 agent tremelimumab (Imjudo, AstraZeneca) plus the anti–programmed death ligand 1 (anti–PD-L1) agent durvalumab (Imfinzi, AstraZeneca) every 4 weeks (the STRIDE regimen) with sorafenib.[18] The trial, originally published in 2022, met the primary endpoint of improved OS.[19] Notably, yearly survival updates have been provided for this trial since 2022, with the most recent update in 2024 demonstrating a 5-year survival rate with the STRIDE regimen of 19.6% (vs 9.4% in the sorafenib arm), the longest reported 5-year survival in a randomized phase 3 trial for unresectable HCC.

The other phase 3 trial with a dual-ICI regimen, CheckMate 9DW, was based on CheckMate 040 and compared ipilimumab at 3 mg/kg + nivolumab vs the control arm of lenvatinib or sorafenib (almost 90% of the patients received lenvatinib). The primary endpoint was met, with a median OS of 23.7 months in the experimental arm vs 20.6 months (hazard ratio [HR], 0.79) in the control arm. The ORRs were 36% and 13%, respectively. Importantly, the 3-year survival rates were 38% and 24%, respectively.[20]

Despite sufficient follow-up time for all the major global phase 3 trials in first-line unresectable HCC, only those 2 trials that did not include an anti-VEGF–directed therapy have reported long-term survivors. We believe that these clinical observations might have implications for trial design and timing of the introduction of antiangiogenic agents in the treatment of HCC.

Despite numerically higher response rates with VEGF inhibitors than with ICI-based regimens, these do not appear to translate into long-term survival for patients with unresectable HCC. This suggests that the frontline use of VEGF inhibition may have temporary benefits, whereas longer-term use may be less effective or even detrimental. Until recently, with median OS in the 10- to 13-month range for unresectable HCC, the potentially late adverse effects of anti-VEGF inhibitors in unresectable HCC were not apparent because long-term survival was not expected in these patients. Thus, not observing a "tail" became a self-fulfilling prophecy, with all drug development efforts focused on maximizing median OS, PFS, and other values without regard for long-term outcomes. With HIMALAYA and CheckMate DW9 data now showing long-term survival, the conceptual framework should be revisited.

Dual immune checkpoint blockade may induce long-term tumor immunity in a subset of patients and alter the natural history of the disease without adversely affecting underlying liver function, a possibility that might not be reflected as an anatomical change in tumor size (ie, an objective response) by RECIST 1.1. This notion is supported by prior data suggesting that radiographic response in patients receiving ICIs, as characterized by RECIST 1.1, may not be indicative of pathologic response.[21,22] Neoadjuvant trials with ICIs convincingly demonstrate that a major pathologic response is more closely related to disease-free survival than is radiographic response to ICIs. This finding can be attributed in part to ICI-mediated tumor necrosis and tumor clearance, which may be underestimated by RECIST 1.1.[23] Given the importance of pathologic response in recurrence-free survival, stark discrepancies in radiographic and pathologic response may in part explain survival differences in patients receiving ICIs despite inferior ORRs.[24]

Although conventional wisdom may suggest that this lack of efficacy can be explained by drug resistance and subsequent tumor progression, systemic effects on the liver may partially explain poor outcomes resulting from VEGF inhibition. These could include impaired liver regeneration, worsening portal hypertension, and increased risk of portal hypertension–related complications.

Liver regeneration is driven in part by angiogenesis, which aids in the delivery of oxygen and nutrients to hepatocytes.[25] As such, subsequent inhibition of angiogenesis may hinder the regenerative capacity of the liver, particularly in patients with cirrhosis and disrupted architecture. To date, VEGF inhibition in mice has been shown to interfere with liver regeneration and to reduce protection against hepatic injury.[26] Although studies to date on bevacizumab treatment before portal vein embolization and hepatectomy did not show inhibition of liver

regeneration, the short duration of treatment in these studies limits insights into the effect of long-term VEGF inhibition on liver regeneration.[27,28]

Beyond compromising liver regeneration, some evidence suggests that VEGF inhibition may exacerbate portal hypertension, particularly in patients with cirrhosis. Angiogenesis regulates portal pressures via several mechanisms, including vascular resistance.[29] As such, VEGF inhibition may exacerbate portal hypertension via endothelial injury and reduced nitric oxide production.[30-32] Both endothelial injury and nitric oxide dysfunction directly promote vasoconstriction and increase systemic vascular resistance, leading to increased portal pressures.[30-32]

Patients on lenvatinib were found to have increased portal venous congestion, further strengthening this assertion.[33] Beyond increased portal hypertension, patients on anti-VEGF therapy may experience increased rates of portal hypertension–related complications, including variceal bleeding, ascites, and hepatic encephalopathy.[34,35] In a prospective cohort of patients receiving bevacizumab, variceal bleeding and ascites in particular were associated with higher rates of mortality.[35] Patients with cirrhosis have altered portal flow and in some cases even hepatofugal portal flow. Therefore, arterial supply plays a greater role in hepatocyte survival in these patients, and the compromise of arterial flow affects liver function and health.

Beyond compromise of the liver, VEGF inhibition may indirectly impair renal function through several mechanisms, further contributing to poor patient outcomes. VEGF inhibition can lead to significant hypertension, with a meta-analysis demonstrating a 7- to 8-fold increase in hypertension risk in patients on bevacizumab.[36] In turn, increased blood pressure may promote renal injury and the progression of chronic kidney disease.[37] Beyond indirect injury from hypertension, VEGF inhibitors can cause direct injury to podocytes expressing VEGF.[38] In turn, podocyte injury may predispose patients to nephrotic syndromes, such as minimal change disease or focal segmental glomerulosclerosis.[38] Consistent with this hypothesis, patients on VEGF inhibitors experienced concurrent increases in proteinuria in the aforementioned meta-analysis.[36] Lastly, VEGF-induced endothelial injury predisposes patients to thrombotic microangiopathies (TMAs).[39] Patients who have TMAs present with hypertension, proteinuria, and thrombocytopenia.[39,40] In some instances, VEGF-induced TMA can progress to end-stage renal disease, posing a significant potential source of morbidity in patients on long-term VEGF inhibitors.[40] Although angiogenesis inhibitors have shown efficacy in patients with HCC, the spectrum of renal toxicities in these patients cannot be ignored in considering the implications for long-term survival.

Thus, available data suggest that despite potentially superior initial tumor responses due to the antiangiogenic effects of VEGF inhibitors, these effects are not durable and may be potentially detrimental owing to long-term systemic side effects. In contrast, although ICI treatments may induce smaller radiographic responses, the ripple effects of ICIs on immune modulation and tumor control result in more durable responses. As such, although the VEGF axis is a validated actionable target in patients with HCC, the presence of a target does not inherently make it the best initial target.

On a clinical level, some evidence is provided via post hoc analysis of the IMbrave150 and HIMALAYA trial data on underlying liver function. In patients treated with bevacizumab + atezolizumab, a survival difference was observed only in those with excellent liver function according to the albumin-bilirubin (ALBI) score (ie, ALBI grade 1), whereas in patients with ALBI grade 2 or 3, no OS benefit was seen when the combination of bevacizumab + atezolizumab was compared with sorafenib.[41] In contrast, the STRIDE regimen of tremelimumab + durvalumab showed a survival benefit in comparison with sorafenib across all ALBI scores.[42]

If prolonged VEGF inhibition in patients with HCC causes detrimental outcomes after a transient period of tumor control, then the implications are more concerning for those patients who might be treated with these regimens earlier in the disease course. The lack of OS benefit has been apparent to date in 3 reported phase 3 trials of earlier-stage HCC. In IMbrave050, 12 months of adjuvant atezolizumab + bevacizumab improved recurrence-free survival vs placebo in high-risk resected HCC, but the transient benefit was lost once the treatment was completed, and numerically higher rates of death were reported in the experimental arm (HR for death, 1.42).[43] In intermediate-stage HCC, the EMERALD-1 (durvalumab + bevacizumab) and LEAP-012 (lenvatinib + pembrolizumab) trials compared locoregional therapy with transarterial chemoembolization (TACE) vs TACE plus an anti-VEGF + ICI combination.[44] Both trials met the primary endpoint of improving median PFS. Although EMERALD-1 has not yet reported median OS, LEAP-012 was negative for improvement in median OS. On the basis of the above considerations for potential liver damage with systemic anti-VEGF, longer-term follow-up of these trials is eagerly awaited to determine whether a delay in disease progression (ie, PFS) in limited HCC might not only fail to improve survival but also result in worse outcomes after 2 to 3 years.

Conclusion and Future Directions

Looking ahead, the use of limited-duration VEGF inhibition could allow maximization of the initial tumor

response while limiting systemic toxicity in patients with unresectable HCC. As ICIs move to the forefront of systemic therapies for advanced HCC, combination therapy is the most promising option for long-term survival and durable responses in these patients. To date, the HIMALAYA and CheckMate 040 trials have demonstrated notable promise with ICI combination therapy, consisting of anti–PD-L1 and anti–CTLA-4 agents, to treat unresectable HCC.[11,19] In theory, combining limited-duration VEGF TKIs with these therapies could benefit patients.[45]

Although sorafenib and subsequent VEGF inhibitors provided an incremental benefit in patients with HCC, the lack of reported long-term survival is concerning and suggests that the first target discovered is not necessarily the optimal target. Further research is required to better identify patients who will benefit from first-line dual-ICI regimens and to develop strategies for those with primary refractory disease or disease that becomes resistant to ICI-containing regimens, without compromising their chance of long-term survival.

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