

HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

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The Evolving Role of Combination Systemic Therapies in Hepatocellular Carcinoma



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H&O What are the treatment goals in hepatocellular carcinoma?

RK In hepatocellular carcinoma (HCC), the treatment goals depend on the stage of the cancer. For early-stage cancers, the goal is always curative. Increasingly, for intermediate-stage disease and cancers that are limited to the liver, clinicians are using treatments that can provide long-term disease control or even a cure. For more-advanced cancers—tumors with extensive involvement of both lobes of the liver, those that have invaded a major vessel, or those that have spread outside the liver (so-called “extrahepatic spread”)—treatment goals have evolved to include symptom palliation and prolongation of life. Thankfully, in recent years, advances in systemic therapies have made these goals much more achievable. There are now regimens that can substantially prolong survival and shrink tumors while also preserving quality of life.

H&O How has the treatment of HCC evolved over the past few years?

RK In 2007, the multikinase inhibitor sorafenib became the first systemic therapy approved by the US Food and Drug Administration (FDA) for the treatment of advanced stages of HCC. Sorafenib remained the only therapy with regulatory approval in this setting for approximately a decade. In 2017, a renaissance in HCC therapy was

initiated by a succession of FDA approvals of next-generation multikinase inhibitors, which have distinct kinase inhibition profiles from sorafenib. These drugs improved outcomes in patients who developed progressive disease during treatment with sorafenib.

The most substantial recent change to the management of HCC has been the advent of immunotherapy for advanced stages of disease. One of the first immune checkpoint inhibitors to show activity was tremelimumab, a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitor. Treatment with tremelimumab led to deep responses in a small subset of patients with hepatitis C virus associated with HCC. Afterward, studies of programmed death 1 (PD-1) checkpoint inhibitors, including nivolumab (Opdivo, Bristol Myers Squibb) and pembrolizumab (Keytruda, Merck), showed deep and durable responses in approximately 15% of patients.

These findings led to the current era of combination immunotherapy. In 2020, the FDA approved the combination of atezolizumab (Tecentriq, Genentech) plus bevacizumab as first-line treatment of HCC that has spread or is unresectable. Atezolizumab inhibits the programmed death ligand 1 (PD-L1) checkpoint. Bevacizumab is a vascular endothelial growth factor (VEGF)-targeted monoclonal antibody. The phase 3 IMbrave150 trial evaluated this combination among patients with unresectable HCC who had not received prior systemic therapy. The trial established atezolizumab plus bevacizumab as the

new global standard for first-line therapy. The median overall survival was 19.2 months with the combination vs 13.4 months with sorafenib (hazard ratio, 0.66; 95% CI, 0.52-0.85; descriptive $P < .001$). Remarkably, the combination of atezolizumab plus bevacizumab has shown that it is possible to achieve substantial tumor shrinkage in a meaningful number of patients. In the IMbrave150 trial, the objective response rate was 30% with atezolizumab plus bevacizumab vs 11% with sorafenib. A complete response was reported in 8% vs less than 1%, respectively. Some of the complete responses in the combination arm are still ongoing. The potential for a complete response, meaning all tumors disappear and are no longer radiographically apparent, was inconceivable just 5 years ago. It is now a reality, admittedly not in all patients, but still in a meaningful proportion.

H&O How is research into the molecular pathogenesis of HCC guiding new treatment strategies?

RK In the clinic, it is apparent that some patients have remarkable responses to immunotherapy, but most do not. For immune checkpoint inhibitors, the response rate is approximately 15%. In rare cases, the patients achieve a complete response that lasts for years. Treatment can be life-altering for these patients.

These responses indicate that something unique is happening on a biologic level, and they raise several questions. For example, what are the molecular underpinnings of the responses, and how can we achieve them in more patients? The potential for response has prompted research that aims to identify the mechanisms of primary resistance. Why is immunotherapy unsuccessful in 85% of patients? How can we inhibit the mechanisms of resistance with new drugs or combinations to obtain much higher rates of response, and allow more patients to achieve prolonged survival?

The combination regimen of atezolizumab plus bevacizumab provides a good example of how this type of research led to a new treatment that improves outcome. Preclinical studies in the laboratory, as well as translational research using human samples, showed that inhibiting angiogenesis with the VEGF monoclonal antibody bevacizumab can promote a more immune-permissive microenvironment and inhibit some of the immunosuppressive elements, resulting in a stronger antitumor response.

H&O Which types of patients are candidates for systemic therapy?

RK A challenge in the management of HCC is that the condition often represents 2 diseases in 1. Most patients with HCC have underlying liver disease, which was the

cause of their cancer. Patients who have borderline or decompensated liver function may not be candidates for all of the systemic therapies that are available. Many of these drugs are metabolized in the liver. In a patient who is very sick or who has many comorbidities, these drugs may cause greater degrees of toxicity or cause toxicities that overlap with other vulnerabilities. Many therapies are not safe for patients who have extensive hepatic dysfunction.

Currently, most of the data for systemic therapy in HCC are drawn from patients with preserved liver function (Child-Pugh class A). These treatments should now undergo study in patients with Child-Pugh class B hepatic dysfunction. These studies will help broaden the treatment options for all patients.

H&O Do you treat patients with single immuno-oncology agents, such as nivolumab, pembrolizumab, and ipilimumab?

RK I treat with single immuno-oncology agents in certain contexts. Currently, data are lacking regarding the next steps for patients who develop progressive disease during first-line treatment with a 2-drug immunotherapy regimen, such as atezolizumab plus bevacizumab or tremelimumab plus durvalumab (Imfinzi, AstraZeneca). It is not known whether or how to use immunotherapy in this second-line setting.

There are many patients who receive first-line therapy with a non-immunotherapy-based treatment, such as lenvatinib (Lenvima, Eisai) or sorafenib, and then require a second-line therapy once they develop progressive disease. In this scenario, I evaluate the patient's fitness level and liver function. I consider using a combination immuno-oncology regimen, such as nivolumab plus ipilimumab (Yervoy, Bristol Myers Squibb), in patients who are fit and able to handle the potential risk of immune-related toxicity. The rates of immune-related toxicity are higher with a 2-drug immunotherapy combination compared with single-agent immunotherapy.

Among patients who are more fragile and who have more borderline liver function, such as those with Child-Pugh class B liver function, I tend to use a single-agent immune checkpoint inhibitor, such as pembrolizumab or nivolumab. There are safety and efficacy data from a prospective cohort of patients with Child-Pugh class B liver function treated with nivolumab in the CheckMate 040 study. This analysis showed that the rates of immune-related hepatic decompensation were no higher than in Child-Pugh class A cohorts. A subset of the Child-Pugh class B patients experienced prolonged responses, suggesting that single-agent immune checkpoint inhibitors are effective even in this setting.

H&O What are the roles for durvalumab and tremelimumab in patients with HCC?

RK The randomized phase 3 HIMALAYA trial evaluated tremelimumab plus durvalumab in patients with unresectable HCC who had not received prior systemic therapy. Results were published in June 2022. The trial compared 3 treatment arms: tremelimumab at a single dose of 300 mg administered on day 1 of treatment, plus durvalumab at a dose of 1500 mg given every 4 weeks; durvalumab administered alone at 1500 mg every 4 weeks; and sorafenib administered alone at 400 mg twice daily continuously. (These treatment arms reflect an amendment to the original design, which included an arm in which tremelimumab was given at 75 mg every 4 weeks for 4 doses in combination with 1500 mg of durvalumab given every 4 weeks.) The trial found that the combination of durvalumab plus tremelimumab improved survival compared with the control arm of sorafenib, and that durvalumab as monotherapy was noninferior to sorafenib. The rate of overall survival at 36 months was 30.7% with tremelimumab plus durvalumab, 24.7% with durvalumab alone, and 20.2% with sorafenib alone. The objective response rates were 20.1%, 17.0%, and 5.1%, respectively. The median overall survival was 16.4 months with tremelimumab plus durvalumab vs 13.8 months with sorafenib.

The combination of durvalumab plus tremelimumab does not have an antiangiogenic component, so it does not substantially alter the patient's baseline bleeding risk.

As a clinician, I am particularly struck by the landmark data showing that the survival rate at 3 years was 30% for the combination of tremelimumab plus durvalumab compared with 20% for sorafenib alone. This difference is clinically meaningful. Oncologists who treat patients with HCC are hopeful that the combination of durvalumab plus tremelimumab will receive regulatory approval for the treatment of advanced disease.

It is not yet known how the role of tremelimumab plus durvalumab will compare with that of atezolizumab plus bevacizumab. Durvalumab and tremelimumab are both immunotherapies; durvalumab is a PD-L1 inhibitor and tremelimumab is a CTLA-4 inhibitor. The regimen does not include an antiangiogenic component, in contrast to the atezolizumab/bevacizumab regimen. This difference has clinical relevance. Many patients with advanced HCC have underlying liver dysfunction and associated comorbidities. With antiangiogenic therapy, some of the key adverse events of concern in this setting are bleeding and blood clots. Among patients with advanced liver disease, there are higher rates of portal hypertension and associated complications, such as esophageal or gastric varices that are at risk for bleeding. Bevacizumab is known to increase the risk for serious bleeding events, including variceal bleeding. For that reason, the IMbrave150 trial required all patients to undergo an endoscopy within 6 months prior to the start of treatment. Patients were eligible for the combination treatment only if they had no high-risk varices or untreated varices at risk for bleeding.

The combination of durvalumab plus tremelimumab does not have an antiangiogenic component, so it does not substantially alter the patient's baseline bleeding risk. Among patients who are at higher risk for bleeding or vascular complications with an antiangiogenic agent, treatment with durvalumab plus tremelimumab offers a new option that may be safer.

H&O How do you sequence treatment when sorafenib fails as first-line therapy and immuno-oncology fails as second-line therapy?

RK Among patients treated with first-line sorafenib followed by pembrolizumab, nivolumab, or nivolumab plus ipilimumab in the second-line setting, I tend to use another multikinase inhibitor, such as cabozantinib (Cabometyx, Exelixis), as third-line treatment. Cabozantinib was approved by the FDA and many other regulatory agencies based on results from the phase 3 CELESTIAL trial. This trial enrolled patients who were candidates for second-line or third-line therapy after developing disease progression during prior treatment with sorafenib and up to 1 other therapy. Cabozantinib is a very reasonable option in the third-line setting. A multikinase inhibitor that has not been previously used in this setting, such as lenvatinib, might also be an option for this type of patient. Lenvatinib has a different target profile from sorafenib.

H&O What is the rationale behind the use of triple systemic therapy for HCC?

RK The IMbrave150 trial showed that antiangiogenic

therapies, in combination with checkpoint inhibitors, can promote immune responses. However, the response rate is only about 30%. Although this outcome marks a substantial improvement from prior therapies, it is still much lower than we want, and raises the question of how to further modulate the immune microenvironment to benefit more patients. Increasingly, investigators in contemporary clinical trials are collecting blood samples and obtaining tumor biopsy samples from patients to study the tumor immune microenvironment. The aim is to identify mechanisms of primary or acquired resistance to guide the addition of another drug, such as a different checkpoint inhibitor (eg, a CTLA-4 inhibitor or a lymphocyte-activation gene 3 [LAG-3] inhibitor), in hopes of inhibiting one of the pathways causing primary or acquired resistance.

H&O In HCC, do triple systemic therapies typically include drugs with different mechanisms of action?

RK We are at the beginning of the era of triple systemic therapies in HCC. Currently, there are no FDA-approved or established triple systemic therapies in HCC. The drug combinations in clinical trials sometimes have overlapping mechanisms. For example, a triple systemic regimen might consist of complementary immune checkpoint inhibitors, such as an inhibitor of PD-1 or PD-L1, plus a CTLA-4 inhibitor, plus an antiangiogenic agent. This type of regimen is probably the most common combination being studied right now. In addition, there are targeted therapies that inhibit other pathways related to angiogenesis. These therapies might be combined to

To move a combination regimen forward, it is necessary to have a close understanding of how each component contributes to both efficacy and toxicity.

address other escape pathways or mechanisms of resistance. The goal is to increase the proportion of patients who are able to achieve an immune response and thereby prolong survival.

These studies are all in very early stages. A challenge

with these types of trials is that the addition of more drugs increases the potential for toxicity, particularly among patients who have liver dysfunction. To move a combination regimen forward, it is necessary to have a close understanding of how each component contributes to both efficacy and toxicity.

H&O What are some ongoing trials evaluating triple systemic therapy combinations?

RK One interesting ongoing study is the phase 1b/2 Morpheus-Liver trial (NCT04524871). This study is using a backbone of atezolizumab plus bevacizumab as the platform standard of care. It has multiple treatment arms, which are being compared with a continuous control arm of atezolizumab plus bevacizumab. The treatment arms consist of novel combinations given in parallel, checkpoint inhibitors and other immunomodulatory drugs, and targeted therapies combined with atezolizumab plus bevacizumab. All of the triple combinations were guided by preclinical or translational data suggesting that the third drug might inhibit or modulate a particularly important target or an aspect of the immune microenvironment that might promote a response. Data are not yet available. This type of trial design is a great approach to obtaining data for contemporary combinations.

There are other ongoing trials of triplet therapies, but so far, very few have reported results. One example of a study with preliminary results was a triplet combination arm within the CheckMate 040 study, which was a multi-arm, phase 1/2, open-label, noncomparative, dose-escalation and expansion trial of the PD-1 inhibitor nivolumab. A small randomized phase 2 cohort of the CheckMate 040 trial evaluated the combination of nivolumab, ipilimumab, and cabozantinib, along with a separate 2-drug combination arm of nivolumab plus cabozantinib without ipilimumab. Results were presented at the 2020 American Society of Clinical Oncology Gastrointestinal Cancers Symposium. Notably, the triplet arm had a higher response rate, but also higher rates of toxicity, compared with the doublet arm.

H&O Do the treatments used in triple systemic therapies appear to have synergistic effects?

RK The answer to this important question is not yet known. When evaluating combination regimens in oncology, it is very difficult to discern the component contributions of treatment combinations, making it especially important to have a concurrent control arm or arms when feasible. Eventually, randomized studies are needed to determine if an additional agent is additive or

synergistic in a combination. It can be difficult to discern additive effects, synergistic effects, and even potential detrimental effects in combination regimens without careful randomization and stratification.

H&O How might triple systemic therapy be incorporated into the treatment of patients with HCC?

RK It is not yet known whether triple systemic therapy improves efficacy in a safe way. From a clinical perspective, the question is whether triple systemic therapy should be administered in the upfront setting or if it should be reserved for rescue therapy, wherein a drug would be added to the doublet therapy when the response is inadequate. In a clinical trial, it would be difficult to measure whether the sequential addition of another therapy is beneficial. From a biological perspective, the right strategy is not yet known.

H&O Are there any other promising areas of research?

RK The advent of immuno-oncology as an effective treatment for subsets of patients with advanced stages of HCC raises the possibility that patients with earlier stages of HCC could benefit, as well. Immuno-oncology agents with higher rates of response are now being studied in the adjuvant or neoadjuvant setting, before or after surgery. These agents might also be used at earlier stages in combination with liver-directed therapies. It may one day be possible to develop neoadjuvant approaches or to augment local control in the intermediate-stage setting by combining systemic therapy with agents that are more effective than those used in the past. Beyond immune checkpoint inhibition, studies in immuno-oncology are also evaluating novel cellular therapies, such as chimeric antigen receptor T-cell therapy that targets a specific tumor antigen or antigens, in HCC and other solid tumors.

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Suggested Readings

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