

HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

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Nivolumab and Ipilimumab Combination Therapy for Second-Line Treatment of Hepatocellular Carcinoma



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G&H Could you discuss the evolution of the first- and second-line medical treatment options for hepatocellular carcinoma?

FB Hepatocellular carcinoma (HCC) is one of the fastest-growing cancers in the United States as well as one of the most common causes of cancer-related death. Currently, the only cure for early-stage disease remains liver transplantation. However, few patients qualify for transplantation, and often patients progress before a transplant is made available. More often, patients are diagnosed at an advanced stage that does not qualify for liver transplantation. Thus, physicians are left to offer palliative treatments to slow the progression of the disease and extend survival, as well as supportive care to address numerous comorbidities, such as viral infections, liver cirrhosis, and other organ dysfunctions.

The traditional antimitotic and other cytotoxic agents that have been used in other solid tumors and lymphomas have produced little improvement in the advanced stage of HCC until 2007, with the approval of the tyrosine kinase inhibitor sorafenib (Nexavar, Bayer), the first biologic for systemic frontline treatment of advanced HCC. Since then, doctors have been trying to improve on the clinical endpoints of overall survival and progression-free survival, and have looked for options for second-line treatment.

It took until 2017 for the first second-line treatment option, regorafenib (Stivarga, Bayer), to be approved in the

United States for use in patients who tolerated sorafenib for first-line therapy but needed further treatment. Subsequently, a new drug, cabozantinib (Cabometyx, Exelixis), was also approved for second-line treatment of patients whose disease did not benefit anymore from first-line sorafenib therapy.

Another option for first-line treatment of HCC is lenvatinib (Lenvima, Eisai), which was approved in 2018. Research showed that lenvatinib was noninferior to sorafenib when it comes to survival, although lenvatinib seemed to induce a good response rate and improved on progression-free survival compared with sorafenib.

Nivolumab (Opdivo, Bristol Myers Squibb) was the first checkpoint inhibitor approved by the US Food and Drug Administration for the treatment of advanced HCC when it received accelerated approval in 2017 for second-line treatment, based on the results of the multi-arm CheckMate 040 clinical trial. Last year, the first combination of 2 checkpoint inhibitors was approved for second-line HCC treatment with nivolumab and ipilimumab (Yervoy, Bristol Myers Squibb), based on a profound response rate. Another combination, atezolizumab (Tecentriq, Genentech) and bevacizumab (Avastin, Genentech), which consists of a checkpoint inhibitor and an antiangiogenic agent, was approved last year for frontline therapy.

Not to be forgotten, the monoclonal antibody ramucirumab (Cyramza, Eli Lilly) was approved in 2019 for

second-line HCC treatment after sorafenib in patients with a diagnosis of advanced disease and an alpha-fetoprotein value of 400 ng/mL or higher at baseline.

G&H What is the rationale for using nivolumab and ipilimumab in combination for the treatment of HCC?

FB Many treatments for cancer have tried to use programmed death ligand 1/programmed death 1 (PD-1) inhibitors such as nivolumab. Experience with melanoma and lung cancer has shown that combining 2 checkpoint inhibitors will disrupt PD-1 and cytotoxic T-lymphocyte-associated protein 4, which are 2 major negative regulators of T cells. Reversing the inhibition of T cells to activate them results in the additional benefit of mobilizing these cells to the cancer microenvironment, in addition to blocking regulatory T cells, which are working in favor of the cancer to inhibit the cytotoxic activity of the immune T cells against the malignant cells. Thus, the patient's immune system mobilizes T cells, recognizes malignant cells, and recruits other natural killer cells.

As mentioned earlier, in the multi-arm CheckMate 040 study, the single-agent nivolumab demonstrated a favorable overall response rate, which led to the approval of this agent for the treatment of HCC. In this trial, one arm used the combination of nivolumab and ipilimumab for a certain number of cycles, and then treatment was continued with only one agent. The combination demonstrated a very promising response rate, which was the primary endpoint of the study. Hence, the combination of both drugs received accelerated approval, contingent on providing phase 3 clinical trial data.

G&H How safe is this combination, and what are the most common adverse events that may occur?

FB Whenever one or more checkpoint inhibitors are used, the immune system is reactivated to target cancerous cells, so there is always the danger of causing immune-mediated inflammation of other organs in the body. Thus, it is important to look for signs and symptoms of inflammation. These can include pneumonitis colitis, hepatitis, nephritis, conditions related to the central or peripheral nervous system (eg, aseptic meningitis, uveitis encephalitis, mononeuropathy, polyneuropathy, Guillain-Barre-type inflammation, myasthenia gravis), myositis, and cardiomyopathy. Because nivolumab and ipilimumab are both monoclonal antibodies and are administered without premedication, infusion reactions may occur, although rarely. Among the common adverse events is skin toxicity, ranging from pruritus and macular

rash to more severe, immune-mediated Stevens-Johnson disease or toxic epidermal necrolysis. Last but not least, endocrine-related adverse events are relatively common, such as hypo- and hyperthyroidism. Adrenal insufficiency, hypophysitis, and type 1 diabetes also occur, but are less common. It is not surprising that trials of checkpoint inhibitors exclude the enrollment of patients with solid organ transplants who are on immunosuppressive agents because of the high likelihood of secondary organ rejection, as well as patients with active autoimmune disease requiring active immunosuppression. Caution must be exercised in clinical practice for such scenarios.

G&H How does the adverse-event profile of atezolizumab and bevacizumab combination therapy compare with that of nivolumab and ipilimumab combination therapy?

FB Atezolizumab and bevacizumab combination therapy, which is a first-line treatment option, carries the same risks of immune-mediated adverse events as nivolumab and ipilimumab. In addition, antiangiogenic adverse events from bevacizumab may occur, such as hypertension, proteinuria, delayed wound healing, bowel perforation, and hypercoagulable events. However, this combination has not been studied for its efficacy and safety in head-to-head clinical trials against ipilimumab and nivolumab.

Thus, there are 2 classes of adverse events when using atezolizumab and bevacizumab combination therapy and mainly 1 class of adverse events with nivolumab and ipilimumab combination therapy, although conclusions should not be drawn from this about the safety of one combination over the other. In addition to the fact that the 2 combinations have not been compared head-to-head, it should be emphasized that while atezolizumab and bevacizumab combination therapy has been studied and approved in the first-line setting, nivolumab and ipilimumab combination therapy has been studied in the second-line setting.

G&H Where does nivolumab and ipilimumab combination therapy fit in the treatment algorithm for HCC?

FB This combination should be one of the top options for patients with advanced HCC that has been treated with a first-line tyrosine kinase inhibitor such as sorafenib or with lenvatinib (ie, not with a checkpoint inhibitor) and has progressed. There are other second-line options such as regorafenib and ramucirumab (although the latter is restricted to a subset of patients with alpha-fetoprotein ≥ 400 ng/mL at diagnosis of stage IV disease), but it is up to the physicians and patients to consider the safety

profiles and decide on a treatment. Contraindications to nivolumab and ipilimumab combination therapy include solid organ transplantation, liver transplantation to treat recurrent metastatic HCC, active or prior autoimmune hepatitis, and any other active autoimmune disease. Thus, a majority of patients, but not all, with advanced HCC qualify for this combination if they have received prior sorafenib or lenvatinib. There is no approved indication for using nivolumab and ipilimumab combination therapy in patients who receive first-line atezolizumab and bevacizumab combination therapy, although clinical evidence supporting such usage may come to light in the future.

G&H Are there any advantages to using checkpoint inhibitors for second-line treatment as opposed to other treatment approaches?

FB We are still awaiting phase 3 clinical trials to directly compare different approaches (ie, single-agent or combination checkpoint inhibitors vs other agents). The only second-line agents that have been compared are tyrosine kinase inhibitors.

Over the last several years, a number of drugs have made it to market for HCC. Although overall survival has been the gold standard for determining the superiority of an intervention in a terminal illness, clinicians and regulators have also been considering the overall response rate, which has been achieved with a checkpoint inhibitor single agent or combination at a much higher percentage compared with tyrosine kinase inhibitors or even cytotoxic treatments.

I have no doubt that checkpoint inhibitor responses are also translating into improvements in survivorship because these responses are often very durable for solid tumors, including HCC. These are not just transient responses. In addition, a durable response often translates into a delay of disease progression, or at least improvement in survival in many diseases. However, this information comes from other disease states, so we are still waiting for clinical trial data to specifically address the magnitude of the impact on survivorship in the setting of advanced HCC.

G&H Can nivolumab and ipilimumab combination therapy be used for third-line treatment?

FB Nivolumab and ipilimumab combination therapy is a legitimate option for third-line treatment as long as checkpoint inhibitors have not been recycled; in other words, patients have not used checkpoint inhibitors in

the first or second line of treatment. The challenge is that patients with HCC can become sick sooner rather than later, and doctors should consider, on a case-by-case basis, how patients respond to the previous line of therapy and should consider the safety profile before choosing a treatment.

G&H What are the next steps in research in terms of using this combination in patients with HCC?

FB The hope is to use these checkpoint inhibitors very early in treatment, for example, in patients who are not immediately candidates for liver transplantation, perhaps to downstage them. Ultimately, in 1 of 10 transplanted patients, the disease will recur with distant metastasis. Thus, there is interest in studying this checkpoint inhibitor combination in borderline transplant candidates. Treatment with a checkpoint inhibitor combination or single agent is thought to induce an advantage in survivorship, so it is used for first-line therapy. However, it is not known whether this would translate into superiority of clinical endpoints without infringing on the safety of the combination.

Finally, for early HCC, clinical trials have been disappointing when it comes to combining tyrosine kinase inhibitors with local therapies such as radioembolization or transarterial chemoembolization. One wonders if any trials will show that the addition of checkpoint inhibitor therapy (either a single agent or combination) to a local therapy is safe and translates into improving outcomes.

Disclosures

Dr Braithe has received honoraria and speaker fees from BMS, Genentech, Exelixis, Bayer, Eisai, and Lilly.

Suggested Reading

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