HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

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Atezolizumab and Bevacizumab Combination Therapy for Hepatocellular Carcinoma

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G&H What are the current first-line medical treatment options for hepatocellular carcinoma?

AE-K Two drugs have been approved for the first-line treatment of hepatocellular carcinoma (HCC). The first was sorafenib (Nexavar, Bayer), which is an oral tyrosine kinase inhibitor that was approved around 10 years ago. Two international studies showed that sorafenib was superior to placebo in first-line treatment of HCC. Sorafenib has a low response rate, usually between 2% and 5%, but it does improve survival by stabilizing the disease. Then came the REFLECT trial, which was a noninferiority phase 3 study that compared lenvatinib (Lenvima, Eisai) and sorafenib. This study showed that lenvatinib was noninferior to sorafenib. Median overall survival rates were comparable (approximately 13 months for lenvatinib vs approximately 12 months for sorafenib). The hazard ratio along with the confidence interval met the noninferiority criteria. Thus, lenvatinib became another option for first-line treatment of HCC. Like sorafenib, it is an oral tyrosine kinase inhibitor. The difference between the 2 drugs is that lenvatinib is a more potent anti–vascular endothelial growth factor (VEGF) agent, and it also targets the fibroblast growth factor receptor axis, which plays an important role in HCC and in resistance to anti-VEGF therapy.

G&H What are the most significant challenges and limitations associated with these treatment options?

AE-K None of the treatment options for advanced HCC are curative, and the improvements in survival are modest. Another challenge is that oral tyrosine kinase inhibitors have toxicities. Whether those toxicities are fatigue, diarrhea, hand-foot skin reaction, or anorexia, the agents can be challenging to use at times and require dose interruptions and reductions. Therefore, there is still a need for more effective and tolerable first-line therapies for HCC.

G&H What is the mechanism of action of atezolizumab and bevacizumab combination therapy for HCC?

AE-K Atezolizumab (Tecentriq, Genentech) is an anti–programmed death-ligand 1 (PD-L1) antibody. It inhibits programmed cell death protein 1 (PD-1)/PD-L1 interaction, and thereby reinvigorates CD8-positive cytotoxic T cells to have an antitumor effect. Thus, this agent is similar to other anti–PD-1 and –PD-L1 agents that have shown single-agent activity in HCC. The most mature data have come from the anti–PD-1 antibodies nivolumab (Opdivo, Bristol-Myers Squibb) and pembrolizumab (Keytruda,

Merck), which have single-agent activity with a response rate generally between 15% and 20%.

Bevacizumab (Avastin, Genentech) is an anti-VEGF antibody. It has been used in multiple other tumor types, most commonly colorectal cancer. Initially, bevacizumab was investigated for HCC because of its well-known anti-angiogenic effects and because VEGF is an accepted target in HCC. Bevacizumab also has an immunomodulatory effect on the immune microenvironment. Preclinical data show that the addition of bevacizumab to anti–PD-L1 inhibition may help lower the activity of the inhibitory or immunosuppressive cells in the microenvironment, such as myeloid-derived suppressor cells and certain subtypes of macrophages that are immunosuppressive. Also, anti-VEGF therapy may be helpful in the recruitment of cytotoxic T cells into the tumor microenvironment. Thus, it is important to note that bevacizumab is not being used solely for its antiangiogenic effects; it is also being used for its immunomodulatory effects. That is why this combination was selected to undergo evaluation for the treatment of HCC.

The initial data showed a hazard ratio for overall survival of 0.58 in favor of atezolizumab and bevacizumab, meaning that there was a 42% reduction in the risk of death with the combination compared with sorafenib.

G&H What are the most recent clinical trial data on the use of this combination in HCC patients?

AE-K The combination was first evaluated in the setting of a phase 1/2 study and then in a randomized phase 2 study. Most recently, results were presented from the phase 3 randomized IMbrave150 trial. In this first-line international study, patients with HCC and Child-Pugh class A cirrhosis who had not received any prior systemic therapy were randomized 2:1 to receive atezolizumab and bevacizumab in combination vs sorafenib in the control arm. It is important to note that all of these patients had to undergo endoscopy within 6 months prior to the start of the study. If esophageal varices were noted, they had to be treated according to the local institutional standard (ie, either with banding or a beta-blocker such as propranolol). This safety precaution was taken because of the risk of bleeding associated with bevacizumab. The initial data showed a hazard ratio for overall survival of 0.58 in favor of atezolizumab and bevacizumab, meaning that there was a 42% reduction in the risk of death with the combination compared with sorafenib. The median overall survival for the combination has not been reached, but the median overall survival for sorafenib was approximately 13 months. Progression-free survival (PFS), a coprimary endpoint in the study, again favored the combination of atezolizumab and bevacizumab compared with sorafenib (median, 6.8 months vs 4.3 months, respectively; hazard ratio, 0.59). Similarly, the response rate was better with the combination (27% vs 12%, respectively) based on Response Evaluation Criteria in Solid Tumors 1.1 criteria. Thus, all endpoints were positive and quite encouraging for the atezolizumab and bevacizumab combination.

G&H How safe is the atezolizumab and bevacizumab combination, and what are the most common adverse events?

AE-K The combination appeared to be tolerable with a manageable toxicity profile. The risk of bleeding was as expected for bevacizumab as a single agent; there was no higher signal for bleeding in patients who received the combination. There was not a higher incidence of immune-mediated events either. The rate of all grade 3 and 4 events was in the 50% range and was similar in the 2 arms. Treatment-related grade 3 and 4 events occurred in 36% of patients receiving atezolizumab and bevacizumab vs 46% of patients receiving sorafenib. The rate of serious adverse events, including treatment-related serious adverse events, was nearly the same in the 2 arms (17% and 15%).

Many of the adverse events that occurred at a frequency of 10% or higher were more common with sorafenib compared with atezolizumab and bevacizumab. These events included diarrhea, hand-foot skin reaction, anorexia, abdominal pain, and fatigue.

G&H Are there any limitations to these data that should be taken into account?

AE-K Yes. This clinical trial, like any other, limited enrollment to patients with Child-Pugh class A cirrhosis. Safety data are not available for the use of this combination in patients with more advanced liver disease. This is an important point because patients with more advanced

liver disease, such as those with Child-Pugh class B cirrhosis, may have more portal hypertension and, therefore, may be at higher risk of bleeding complications. Thus, treating practitioners should be cautious about extrapolating the data on this combination to patients with more advanced liver disease. Additional safety data are needed in patients with more compromised liver function, such as Child-Pugh class B7 or B8 cirrhosis.

The combination is currently under review by the US Food and Drug Administration, but it is possible, and I would say likely, that it will become the new standard of care later in 2020.

In addition, patients in the study were carefully screened for bleeding risk, varices had to be treated prior to enrollment, and endoscopies had to be performed within 6 months prior to the start of the study. Endoscopies are not done routinely in patients with advanced HCC who are treated by medical oncologists, so it is important to remember the importance of multidisciplinary care and involve hepatologists to ensure the performance of endoscopies and management of varices.

Finally, there are well-established safety precautions that have to be taken with bevacizumab. Because of a slightly increased risk of arterial thrombotic events, patients with myocardial infarction or stroke within the previous 6 to 12 months are traditionally excluded from trials with this drug.

G&H Has there been any research specifically on the quality of life of patients receiving atezolizumab and bevacizumab?

AE-K Results of patient-reported outcomes were presented in January 2020 at the Gastrointestinal Cancers Symposium, which is sponsored by the American Society of Clinical Oncology and other societies. An important aspect of patient-reported outcomes is measuring the time to deterioration in regard to important parameters related to functioning and well-being. For all of these parameters, it appeared that the time to deterioration was longer for patients receiving atezolizumab and bevacizumab compared with patients receiving sorafenib. Thus, from a quality-of-life and patient-reported outcome perspective, the combination was superior to sorafenib.

G&H Do you think that the atezolizumab and bevacizumab combination will be the best first-line therapy for HCC by the end of this year?

AE-K The combination is currently under review by the US Food and Drug Administration, but it is possible, and I would say likely, that it will become the new standard of care later in 2020.

Nevertheless, it should be pointed out that there are other combinations currently under evaluation involving an anti–PD-1 or –PD-L1 agent with a tyrosine kinase inhibitor. Examples include pembrolizumab and lenvatinib, pembrolizumab and regorafenib (Stivarga, Bayer), and cabozantinib (Cabometyx, Exelixis) and atezolizumab. Both the pembrolizumab and lenvatinib combination and the cabozantinib and atezolizumab combination are in phase 3 studies. There is good rationale for these combinations, and the results are eagerly awaited. All of these combinations are being compared to sorafenib or lenvatinib as control.

Immunotherapy agents are also being studied together for first-line treatment. One example is an anti–PD-L1 agent and an anti–CTLA-4 agent, such as in the combination of durvalumab (Imfinzi, AstraZeneca) and tremelimumab in the phase 3 HIMALAYA trial, which is currently recruiting patients. This combination is being compared to durvalumab alone as well as sorafenib alone. Another trial is comparing the combination of nivolumab and ipilimumab (Yervoy, Bristol-Myers Squibb) to sorafenib in the phase 3 setting. These trials may impact the field as results are released.

G&H When the atezolizumab and bevacizumab combination is approved, which HCC patients should receive it for first-line treatment, and which should receive sorafenib or lenvatinib?

AE-K I believe that the majority of patients with advanced HCC, Child-Pugh class A cirrhosis, and no recent bleeding events or arterial thrombotic events will receive the combination of atezolizumab and bevacizumab once it is approved. However, as previously mentioned, the combination requires specific safety precautions. Patients who have had recent bleeding events, who are not able to undergo a screening endoscopy and have their varices treated, and so on should probably not be treated with atezolizumab and bevacizumab, and should instead be treated with sorafenib or lenvatinib. Similarly, patients who have contraindications to bevacizumab or to anti–PD-1 antibodies should not use the combination; this

includes patients with active autoimmune diseases and patients who recently had a stroke or myocardial infarction. If a patient recently had an arterial thrombotic event, there is also some risk involved with receiving sorafenib and lenvatinib, so some precaution should be taken and the patient should not be treated within 3 to 6 months of such an event. Thus, sorafenib and lenvatinib still have a role in first-line therapy for HCC patients who do not meet the standard criteria for atezolizumab and bevacizumab.

In terms of comparing sorafenib and lenvatinib, the REFLECT study showed that these drugs are noninferior to each other, although there are some nuances in terms of toxicities. Overall, the toxicities are relatively similar because both drugs are tyrosine kinase inhibitors. However, hypertension was more common with lenvatinib, whereas hand-foot skin reaction was more frequent with sorafenib. The REFLECT trial also showed that the secondary endpoints of PFS and response rate were superior with lenvatinib compared with sorafenib. If doctors are concerned about patients who are symptomatic or who have aggressive disease that is moving fast, they may prefer to select an agent that has a higher response rate or a superior PFS. In those patients, there may be a bias toward using lenvatinib compared with sorafenib; otherwise, choosing between these 2 drugs is relatively arbitrary.

G&H What are the next steps in research for atezolizumab and bevacizumab combination therapy in HCC patients?

AE-K We eagerly await more mature data and the median overall survival for the combination of atezolizumab and bevacizumab. Furthermore, the safety evaluation of atezolizumab and bevacizumab needs to be expanded. More real-world safety data are needed. The combination should also be explored in patients with more advanced liver disease, such as Child-Pugh class B cirrhosis. There will also likely be research focusing on triplets (ie, adding a third drug to the atezolizumab and bevacizumab combination). In addition, at this point there are no data on how to sequence agents after progression on atezolizumab and bevacizumab. By default, tyrosine kinase inhibitors such as sorafenib, lenvatinib, cabozantinib, and regorafenib will likely be used as second- and third-line therapy after atezolizumab and bevacizumab, but research should be conducted to come up with rationale sequences based on mechanism of resistance and biomarkers.

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Suggested Reading

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