HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

Section Editor: Robert G. Gish, MD

How to Choose Second-Line Treatment for Hepatocellular Carcinoma

Catherine Frenette, MD
Director, Liver and Hepatocellular Cancer Program
Scripps MD Anderson Cancer Center
La Jolla, California

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

CF Recently, there has been a significant progression in the options that are available for hepatocellular carcinoma (HCC) treatment. The tyrosine kinase inhibitor (TKI) sorafenib (Nexavar, Bayer) was approved by the US Food and Drug Administration (FDA) in 2007, but there were no other medical options until several years ago, when the TKI lenvatinib (Lenvima, Eisai) was approved. Immunotherapy for first-line HCC treatment became possible last year, with FDA approval of atezolizumab (Tecentriq, Genentech) and bevacizumab (Avastin, Genentech) combination therapy, which consists of a checkpoint inhibitor and an antiangiogenic agent. The National Comprehensive Cancer Network (NCCN) recently updated its guidelines to state that atezolizumab/bevacizumab should be the preferred first-line treatment regimen for HCC and that sorafenib and lenvatinib monotherapy should be used only if there is a reason that patients cannot use atezolizumab/bevacizumab. Reasons include if patients have esophageal varices, if they are mildly decompensated (in which case sorafenib is the only TKI recommended by the NCCN), if there is a contraindication to immunotherapy, or if there are concerns about bevacizumab's vascular endothelial growth factor (VEGF) inhibition.

Studies have clearly shown that atezolizumab/bevacizumab has improved overall survival directly compared with sorafenib (>19 months vs ~12 months, respectively). Lenvatinib has been shown to be noninferior to sorafenib, but has an improved response rate and a different side-effect profile. For example, more hand, foot, and skin reactions may be seen with sorafenib, whereas hypertension is more likely to be seen with lenvatinib. More real-world research has been conducted with sorafenib, which has been helpful in terms of side-effect management and tolerance concerns for patients who may be a little frailer or may have a little more decompensated liver disease.

The NCCN lists nivolumab (Opdivo, Bristol Myers Squibb) as useful in certain circumstances, which I think is appropriate. The study of first-line nivolumab did not show improved survival compared with sorafenib; however, patients who respond to nivolumab can have a more prolonged response and do well for quite some time. Thus, nivolumab is reserved for patients who cannot receive a TKI or other angiogenic agents, such as patients with very poorly controlled hypertension, patients who are concerned about side effects, and patients who have significant proteinuria, which can be worsened by VEGF.

G&H When should a second-line treatment be used?

CF It depends partly on what is used for first-line treatment and how the patient is tolerating it. With any of these therapies, one of my first thoughts is tolerance, especially with TKIs. Dose adjustments may be needed so that the patient can tolerate treatment and still have a good quality of life. When a patient starts therapy, I usually see him or her relatively frequently in the office. Patients typically undergo scans approximately 8 to 12 weeks into therapy, depending on which treatment they started and how they are doing. If they are experiencing more adverse events and are having difficulty tolerating treatment, they may be scanned earlier so that the clinician can see if they are starting to have a response.

With immunotherapy, patients may improve, but the full response may not be seen right away because of pseudoprogression or delay in response, which can be seen as late as 4 months in some patients. Pseudoprogression occurs when patients start responding and cells of the immune system infiltrate the tumor, and the patient appears to have a mild progression, but the enlargement is not related to tumor growth. If the patient continues on immunotherapy, a response may be seen at the next scan. Thus, if the tumors are not significantly progressed on a scan at 8 to 12 weeks on an immunotherapy such as atezolizumab/bevacizumab, the clinician may consider continuing therapy as long as the patient can tolerate it and would wait to see the next scan before switching treatment. When many options are available, it is tempting to switch patients to different treatments frequently, but it is better for the patient to maximize the benefits from each therapy before moving on.

G&H What are the options that are currently approved for second-line treatment of HCC, and how do they compare in terms of efficacy and safety?

CF Several options are available for second-line treatment, including the TKIs regorafenib (Stivarga, Bayer) and cabozantinib (Cabometyx, Exelixis). The monoclonal antibody ramucirumab (Cyramza, Lilly) has been approved by the FDA for patients with an alpha-fetoprotein (AFP) level of 400 ng/mL or higher. The immunotherapies nivolumab and pembrolizumab (Keytruda, Merck) were approved as single agents based on phase 2 data, although the phase 3 study of second-line pembrolizumab did not meet its primary endpoint. Finally, nivolumab and ipilimumab (Yervoy, Bristol Myers Squibb) combination therapy has been approved recently for second-line treatment. NCCN guidelines also list lenvatinib and sorafenib as single-agent options in subsequent therapy, but those 2 therapies have not been studied in the second line and are not approved by the FDA in this setting.

When comparing second-line TKIs, it should be noted that the patient populations studied in clinical trials differed. Patients could only be included in the regorafenib study if they had tolerated at least a 400-mg dose of sorafenib for at least 20 of the previous 28 days. The cabozantinib study was more liberal with inclusion and exclusion criteria, as patients were able to enroll even if they had not tolerated their first-line therapy, and they could still enroll if they had more than 1 line of therapy. In approximately one-third of patients, cabozantinib was used as the third line of treatment.

Ramucirumab only showed benefits in patients who had an AFP level of 400 ng/mL or higher. Regorafenib, cabozantinib, and ramucirumab had relatively similar overall survival. Cross-study comparison is not possible, but the 3 treatments had relatively similar hazard ratios. The hazard ratio for the ramucirumab study was not quite as strong as that for the regorafenib or cabozantinib studies, but that is not surprising because patients who have an AFP level of 400 ng/mL or higher tend to have more aggressive disease that progresses a little faster.

In phase 2 studies, nivolumab and pembrolizumab showed survival benefits as well as good response rates. Although the phase 3 study of pembrolizumab as second-line treatment failed, response was quite long when it occurred, as previously mentioned. Thus, there appears to be a clinical benefit for certain patients, similar to nivolumab.

Interestingly, the study on nivolumab/ipilimumab looked at 3 different dosing regimens, and patients had quite a long survival with the dosing regimen that was ultimately chosen. However, this was a phase 2 study, so the data were not quite as strong as those of the other second-line treatments. Overall survival was quite good at 22 months; however, approximately half of the patients required corticosteroids for immunotherapy-related side effects. Therefore, it is important to discuss the risks and benefits of treatment with patients and their families, and patients have to be monitored closely.

In terms of side effects and safety, regorafenib, cabozantinib, and ramucirumab are relatively similar. However, ramucirumab is an intravenous therapy, which some patients might prefer, and it is not associated with as many instances of diarrhea and hand, foot, and skin reactions as regorafenib and cabozantinib.

G&H In patients who received atezolizumab/bevacizumab for first-line treatment, how should clinicians decide on second-line treatment?

CF This is a question that clinicians are struggling with right now. All of the aforementioned second-line

treatments were studied after sorafenib first-line therapy. Every study required patients to be treated with sorafenib before going on to second-line treatment because sorafenib was the standard of care when those studies were planned. Thus, there are not much data on what to do for second-line treatment after a patient has received atezolizumab/bevacizumab. However, data are starting to come out. For example, a small study presented at this year's American Society of Clinical Oncology Gastrointestinal Cancers Symposium found that some patients can still have a benefit using the combination of nivolumab/ipilimumab after immunotherapy, although not quite as much as that seen when using the combination after a TKI. Thus, nivolumab/ipilimumab may be an option once HCC progresses on atezolizumab/bevacizumab. In addition, in the atezolizumab/bevacizumab study, quite a number of patients went on to treatment with a TKI, suggesting that TKIs would be appropriate in this setting, although further research is needed.

At my center, my colleagues and I usually decide on second-line treatment based on what happened in the first line. For example, if a patient's HCC did not seem to respond at all to atezolizumab/bevacizumab and progressed relatively quickly, we are somewhat reluctant to move to an immunotherapy in the second line because the patient has already shown that he or she is not responding to immunotherapy. We are more likely to choose a TKI in that patient population. If a patient's HCC responded to atezolizumab/bevacizumab and tolerated it well, we may decide to try nivolumab/ipilimumab because the patient had a response to an immunotherapy in the first line. Atezolizumab/bevacizumab has not been available very long, so there are not many patients yet who were doing well and had stable disease or response for a long time whose disease started to progress, but a few such patients were seen in the clinical trial for the combination.

Choosing which TKI to use for second-line treatment always requires discussion. We are a little reluctant at this point to use regorafenib if a patient has not tolerated or used sorafenib previously because safety and tolerance data are not yet available in this scenario; however, this is currently being studied, so data may be available in the next several years. The decision of which TKI to use is generally based on the other comorbidities of the patient and which side effects are most common for that treatment. For example, if a patient already has poorly controlled hypertension, we may be less likely to choose a TKI that is associated with more hypertension. If a patient is an avid gardener and is worried about hand, foot, and skin reactions, we may be less likely to choose an agent that has worse reactions.

G&H How should clinicians decide on second-line treatment for patients who received sorafenib or lenvatinib in the first line?

CF Data are not available for second-line therapy after lenvatinib because, as mentioned, all of the second-line treatments were studied after sorafenib. Generally, after a patient has been on a TKI for first-line treatment, my colleagues and I consider whether he or she is a candidate for some type of immunotherapy in the second line. That decision is made based on why the patient received a TKI as opposed to immunotherapy in the first line. It may be that the patient started treatment before atezolizumab/bevacizumab was available, so he or she has not had the opportunity to use an immunotherapy and does not have contraindications. In that case, we would probably choose an immunotherapy as the second line. If the patient did not use atezolizumab/bevacizumab because he or she has a contraindication to immunotherapy, we would go back to a TKI and choose based on the adverse-event profiles of the drugs as well as on the similarities between the patient and the clinical trial participants. For example, we might choose ramucirumab for a patient with a very high AFP. For a patient who has never had sorafenib and was on lenvatinib, we may move to cabozantinib rather than regorafenib because of the way that the studies were conducted.

G&H In general, what are the advantages of using immunotherapy as opposed to TKIs for second-line treatment, and vice versa?

CF It depends on the patient, but I think the main advantage of using immunotherapy in the second line is tolerance, except for nivolumab/ipilimumab, which is associated with more immune-mediated adverse events and the need for corticosteroids. The single-line immunotherapies are tolerated very well, and patients generally do quite well.

One of the benefits of using TKIs in the second line is the ability to adjust the dose to a specific patient to ensure that the medicine will be well tolerated. Often, patients need to be on a lower dose than what is the FDA-recommended dose in order to maintain their quality of life, but they still will have a survival benefit from treatment. In addition, most infusion therapies may be given every 2 to 6 weeks depending on the regimen and dose, and some patients are reluctant to come in for infusion therapies, especially during the COVID-19 pandemic. Thus, another benefit of TKIs is that they can be shipped to the patient and dosed at home, and follow-up can be done via telemedicine, which patients may be more comfortable with. Also, patients may not

live close to their specialty centers or may want to travel, so coming in for infusion therapy every few weeks may be difficult.

G&H For which patients is it especially challenging to decide which second-line treatment to use?

CF Often, by the time that patients reach second-line treatment, they may be starting to have decompensation in their liver, their laboratory test results may be worsening, and they may be starting to become malnourished owing to cancer progression and side effects of therapy. For these patients, it can be very challenging to decide whether they can even go on a second-line therapy because they may not be able to tolerate anything; if they can, it may not be clear which therapy they will be able to tolerate that will not worsen their decompensation. We worry about these patients because although they may benefit from therapy, it can be especially challenging to ensure tolerance for the therapy. By the time patients with HCC receive their second line of treatment, approximately half are starting to decompensate. Thus, it is fairly common that decompensation can affect the ability to move to the next line of therapy.

G&H Do you have any advice on how clinicians should select second-line treatment for HCC?

CF My biggest advice is to involve patients and their families in the treatment decision. Clinicians should explain the advantages and disadvantages of the different options and decide what may be best for each patient based on everything else in their life. In addition, great strides are being made in cancer treatment with immunotherapies, and it can be very tempting to continue to jump from one immunotherapy to the next. However, if patients are not responding at all to first-line immunotherapy, it does not make sense to me to continue the same type of therapy. Clinicians should not be shy about using a TKI, even with the adverse events that have to be managed aggressively. Some clinicians think that TKIs are very difficult to use and that their side effects are not worth the survival benefit that may be achieved. In my experience, with aggressive dose adjustment and side-effect management, patients can remain on therapy and have a good response for a long time.

Disclosures

Dr Frenette has served on the speaker's bureau for Bayer, BMS, Eisai, Exelixis, and Genentech; served as a consultant for Bayer, Eisai, Genentech, and Merck; received research support from Bayer, Exelixis, and Merck; and served on the advisory board for AstraZeneca, Eisai, Exelixis, Genentech, and Merck.

Suggested Reading

Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *N Engl J Med*. 2018;379(1):54-63.

Bruix J, Qin S, Merle P, et al; RESORCE Investigators. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2017;389(10064):56-66.

Finn RS, Ryoo BY, Merle P, et al; KEYNOTE-240 Investigators. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: a randomized, double-blind, phase III trial. *J Clin Oncol*. 2020;38(3):193-202.

Sonbol MB, Riaz IB, Naqvi SAA, et al. Systemic therapy and sequencing options in advanced hepatocellular carcinoma: a systematic review and network meta-analysis. *JAMA Oncol*. 2020;6(12):e204930.

Yau T, Kang YK, Kim TY, et al. Efficacy and safety of nivolumab plus ipilimumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib: the CheckMate 040 randomized clinical trial. *JAMA Oncol*. 2020;6(11):e204564.

Zhu AX, Kang YK, Yen CJ, et al; REACH-2 study investigators. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019;20(2):282-296.