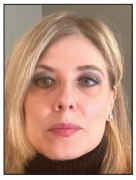
HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

Section Editor: Robert G. Gish, MD

Checkpoint Inhibitor Combinations for Hepatocellular Carcinoma Treatment



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G&H What are the advantages of using checkpoint inhibitors for treatment of hepatocellular carcinoma?

LK Immune checkpoint inhibitors (CPIs) were first studied in patients with advanced hepatocellular carcinoma (HCC), with up to 30% of patients demonstrating an objective response rate. Prior to the use of CPIs in patients with advanced HCC, providers used to quote a median overall survival of only approximately 6 months. Now, patients with advanced HCC are living up to 2 years and beyond. This has led to CPIs becoming the standard of care in patients with advanced HCC.

G&H Could you discuss key research on CPI combinations for HCC patients?

LK Like many therapies in cancer, CPI use started in patients with more advanced disease and limited life expectancy. Once a benefit is demonstrated, these therapies start to be studied in earlier-stage disease, particularly in the intermediate stage of HCC (Barcelona Clinic Liver Cancer class B). Studies are examining whether there is a real benefit to combining CPIs in patients who are receiving standard of care, which has generally been locoregional therapy, the backbone of which has been intra-arterial therapies with chemoembolization or radioembolization. There has certainly been an uptick in the use of radioembolization, particularly in the United States, while chemoembolization is the more commonly used intra-arterial therapy worldwide. Two trials, EMERALD-1 and LEAP-002, have looked at chemoembolization with placebo vs chemoembolization plus a CPI. EMERALD-1 examined the CPI durvalumab (Imfinzi, AstraZeneca) plus the anti–vascular endothelial growth factor antibody bevacizumab, whereas LEAP-002 examined the tyrosine kinase inhibitor lenvatinib (Lenvima, Eisai) plus the CPI pembrolizumab. The primary endpoint of both trials was progression-free survival, which was met in both. With longer follow-up, there is a question of whether overall survival will be significantly improved, which will be important in terms of deciding if combination therapies should become the standard of care. Some transplant centers have been utilizing the combination of locoregional therapy plus immunotherapy despite the fact that there have not been phase 3 trials clearly showing an improvement in overall survival. This may be because of the biological plausibility of this approach; locoregional therapy leads to the release of tumor antigens, which can then theoretically bolster the effects of CPIs on the immune system and lead to a more robust response against the cancer.

Additionally, ROWAN and EMERALD-Y90, which are ongoing single-arm trials, are looking at the use of radioembolization plus immunotherapy. ABC-HCC is another ongoing trial and is looking at chemoembolization vs atezolizumab (Tecentriq, Genentech) plus bevacizumab in unresectable HCC patients. What the control arms should be in future clinical trials in intermediate HCC is open for discussion because the standard of care may be changing. It is an exciting time in this field to be able to use the backbone of immunotherapy in combination with locoregional therapy, which had been the traditional treatment for patients with intermediate HCC. These trials are going to be paramount in deciding how providers treat patients with HCC.

G&H What are the major adverse events associated with CPI combinations that hepatologists need to know?

LK The issue with CPIs is that they try to unleash the immune system to control/kill the tumor, but in doing so, unfortunately, that strength may not only improve toward the tumor but can also increase the immune response to virtually any organ in the body. The more common immune-related adverse events are skin, gastrointestinal, or endocrine toxicities. Hepatotoxicity is one adverse event that everyone practicing in the gastroenterology space should be aware of. It has been reported in up to 15% of patients when trials have been performed in a prospective manner to over 50% of patients in retrospective trials. An important factor that determines if hepatotoxicity occurs is whether the combination of CPIs includes cytotoxic T-lymphocyte–associated antigen 4 plus a programmed death 1/programmed death ligand 1 vs monotherapy. The grade of the hepatotoxicity determines the therapy. For example, grade 1 is a mild asymptomatic elevation of liver enzymes and is the most common type of hepatotoxicity. In this case, CPIs can be continued; however, the patient has to be monitored closely for worsening of laboratory tests and development of symptoms. With grade 2, the agents should be held and corticosteroids started. With grades 3 and 4, the agents are supposed to be permanently discontinued. These patients should be followed with liver tests very frequently. If the hepatotoxicity becomes very severe and the patient develops fulminant liver failure, there may be a role for plasma exchange. It is also very important to make sure that there is not another cause that may have led to hepatotoxicity, remembering that 90% of these patients with HCC have underlying cirrhosis. In other words, could there be another drug reaction? Is the patient drinking? Does the patient have underlying steatohepatitis? Biopsies are not that helpful because immunosuppressive therapy should not be delayed and is generally empirically started with corticosteroids, followed by second-line therapy such as mycophenolate mofetil if there is not a response. A cholestatic presentation can also be seen, which tends to have a more ominous prognosis. A biopsy may be more helpful in such cases.

G&H What is the impact of CPI combinations on hepatitis B or C virus infection?

LK When these agents were being studied in clinical trials, there was concern in patients with hepatitis B because the immune system is very important in controlling this virus. There is an immunosuppressive nature associated with viral infections, and when something such as a CPI is given to ramp up the immune system, there is concern for a flare of hepatitis B in the presence of a more active immune system. Thus, generally patients were recommended to be on antiviral agents in trials to adequately control the hepatitis B viral load in order to prevent a flare of hepatitis B leading to liver decompensation.

As for hepatitis C, flares are not usually seen and there has not been as much concern for exacerbation of the virus occurring with immunotherapy. Some of the earlier trials showed a decrease in hepatitis C viral loads associated with immunotherapy. However, this was not enough to achieve sustained virologic response, so these patients still needed the use of direct-acting antiviral agents to cure hepatitis C virus infection.

G&H Can CPI combinations impact liver transplant timing?

LK The field of transplant oncology is rapidly expanding. When these agents were first being used, there was significant concern to not use them in patients being considered for liver transplant owing to the risk of severe rejection and possible graft loss. However, what has been seen is that among patients with advanced HCC in whom liver transplant is generally not an option, a robust and sustained response to CPIs occurred, which then led to consideration for transplant. I would not say that the initial fear of a higher risk of rejection has been completely eliminated, but what has been learned is that the longer away the patient is from their last dose of immunotherapy, the lower the chance of rejection. Thus, 3 months from the last administration of CPIs to transplant is better than 2 months, which is better than 1 month. Some guidelines have suggested a washout period of 2 to 3 half-lives of the CPI(s) being used before proceeding with liver transplant.

G&H Is there a role for using CPI combinations for Child-Pugh class B patients?

LK This is an unmet need. Patients in registry trials had to be Child-Pugh class A. If patients are Child-Pugh class B owing to extensive tumor burden, a rapid robust response to CPIs could potentially improve the underlying liver dysfunction/complications because it was the cancer that was driving them to be decompensated. However, if the patient is Child-Pugh class B owing to their underlying liver disease despite a tumor response, their overall survival remains lower than patients with Child-Pugh class A cirrhosis. Retrospective studies have looked at this issue. One study examined Child-Pugh class B patients who received atezolizumab plus bevacizumab compared with patients who received best supportive care. Child-Pugh class B patients who received atezolizumab plus bevacizumab had a longer overall survival in the range of

approximately 7.5 months compared with approximately 4 months for those who received best supportive care. There are ongoing prospective trials that are attempting to answer the question of using CPIs in patients with less preserved liver function. The SIERRA trial is looking at the use of the STRIDE (single-dose tremelimumab with regular interval durvalumab) regimen in patients who were excluded from the HIMALAYA trial, including those with Child-Pugh class B disease. Additionally, the prospective KIRROS trial is studying atezolizumab plus bevacizumab vs atezolizumab monotherapy in Child-Pugh class B patients who are not candidates for bevacizumab, so it is expected that more information will become available regarding this challenging group of patients. Thus far, it appears that Child-Pugh class B patients derive benefit from CPIs from a cancer standpoint, but unfortunately their overall survival is significantly lower than in patients who are Child-Pugh class A, bringing home the point that providers are dealing with dual risk of death owing to the underlying liver disease as well as the cancer itself.

It is essential for patients with HCC to be seen by a multidisciplinary team.

G&H What is the role of multidisciplinary care in the management of HCC patients receiving these combinations?

LK It is essential for patients with HCC to be seen by a multidisciplinary team. This has been seen with many other diseases as well, but HCC patients have cancer in addition to underlying chronic liver disease. Being seen by multiple disciplines simultaneously will increase the patients' chances of getting to therapy in an expeditious fashion, which will hopefully increase the chances of them getting to a potential curative option such as resection or transplant. I cannot overstate how important it is for doctors to refer their patients to a multidisciplinary team even if they have portal vein invasion or a large tumor that is outside the Milan criteria. It is critical that these patients be seen in an academic transplant center that has a multidisciplinary team to see whether they can be successfully downstaged and eventually get to the point of transplant or resection.

G&H What other studies on CPI combinations would you like to point out?

LK One study to mention is the MORPHEUS study, which added another type of CPI (the anti-TIGIT monoclonal antibody tiragolumab) to atezolizumab plus bevacizumab. Essentially, the thinking was that this addition could help overcome the immunosuppressive state seen in cancer, increasing the number of patients having radiographic response to 40%. This phase 2 trial saw an improvement in terms of overall survival in patients who were treated with this 3-drug combination, which led to the phase 3 SKYSCRAPER-14 trial. Results are awaited to see whether building on the current landscape will improve response rates as well as overall survival in patients with HCC.

G&H What are the main unmet needs in this area?

LK One unmet need involves patients who have portal vein thrombosis type 4 (main portal vein), who have been excluded from many trials, although not the IMbrave150 trial. These are the patients who tend to decompensate the fastest and are at the highest risk of having variceal bleeding. It is also going to be important to see whether patients who are decompensated will derive benefit from these therapies and potentially even improve their Child-Pugh classification by responding to HCC treatment. Most exciting in this field is seeing which patients can we try to downstage to liver transplant. Instead of starting a patient on HCC therapy, seeing that they have a response, and then considering transplant, what is being done now is looking upfront at a patient and purposely giving them immunotherapy alone, or in combination with locoregional therapy, with the goal of downstaging them to liver transplant.

Disclosures

Dr Kulik has had a relationship with AstraZeneca and Genentech.

Suggested Reading

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