HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

Section Editor: Robert G. Gish, MD

The Use of Checkpoint Inhibitors in Patients With Hepatocellular Carcinoma

Ghassan K. Abou-Alfa, MD, MBA
Attending Physician
Memorial Sloan Kettering Cancer Center
Professor of Medicine
Weill Medical College at Cornell University
New York, New York

G&H Why have checkpoint inhibitors been studied in the setting of hepatocellular carcinoma?

GAA The liver is an important organ through which toxins and microbial products are eliminated. It is like an immunogenic machine. It has to be tolerant of the immune mobilization of the nearby gut and of exposure to all of the products that the body can encounter (eg, bacteria and food). Checkpoint inhibitors, which are critical immunotherapy players, can alter immune reactions in liver cancer cells in the liver or metastatic disease sites, and the immune system can, as such, fight off disease.

G&H Does response to checkpoint inhibitors vary based on the risk factor or etiology of the cancer in the liver?

GAA So far, there is no difference in response to checkpoint inhibitor therapy based on the etiology or risk factor of hepatocellular carcinoma (HCC). However, there has been concern of possible reactivation of hepatitis B or C virus infection when using checkpoint inhibitor therapy, so close monitoring is needed.

G&H Which checkpoint inhibitors have been studied the most in HCC patients?

GAA Numerous checkpoint inhibitors have been studied in HCC patients. Tremelimumab and durvalumab (Imfinzi, AstraZeneca) are currently being evaluated as part of the HIMALAYA trial. Atezolizumab (Tecentriq, Genentech) is being investigated in combination with bevacizumab (Avastin, Genentech) based on intriguing response data. However, the checkpoint inhibitors with the most data so far are the programmed cell death protein 1 (PD-1) inhibitor nivolumab (Opdivo, Bristol-Myers Squibb) and the PD-1 inhibitor pembrolizumab (Keytruda, Merck). Both nivolumab and pembrolizumab have received conditional approval by the US Food and Drug Administration (FDA) as second-line monotherapy for patients with HCC. Nivolumab and pembrolizumab were conditionally approved based upon their phase 2 trial data, which included response rates close to 20% and, more

Nivolumab and pembrolizumab were conditionally approved based upon their phase 2 trial data, which included response rates close to 20% and, more importantly, impressive durations of response ...

importantly, impressive durations of response—up to 9.9 months with nivolumab, and 67% of patients were still on therapy at the time the data were reported.

However, the conditional FDA approvals for nivolumab and pembrolizumab are dependent upon the results of their phase 3 trials, which are currently underway and are examining nivolumab vs sorafenib (Nexavar, Bayer) as first-line therapy and pembrolizumab vs placebo as second-line therapy. No results are available yet for either trial.

G&H Does the sequencing of checkpoint inhibitors seem to matter?

GAA There is no question that checkpoint inhibitors work in HCC. However, it is unclear so far whether they would ultimately be most beneficial as first- or second-line treatment. It may not matter when patients receive a checkpoint inhibitor—as first-line therapy (as in the nivolumab trial) vs later (as in the pembrolizumab trial). It is important to note that the survival outcomes of the ongoing phase 3 nivolumab and pembrolizumab trials may be influenced not only by the therapy being evaluated, but by the therapy that may follow or that has been given beforehand.

There are several possible scenarios. If the data on nivolumab vs sorafenib first-line treatment are positive, showing improved survival in favor of nivolumab, and if the data on pembrolizumab vs placebo second-line treatment are negative, then the sequence of the therapies may matter, and checkpoint inhibitors should be the first-line systemic therapeutic intervention. If both studies have positive results, then checkpoint inhibitors prove their agnostic effectiveness and it does not matter when they are given—as first-line treatment, second-line treatment, or perhaps even later. A third scenario, more complex yet still possible, is if the nivolumab vs sorafenib study does not show a survival advantage in favor of nivolumab in the first-line setting, but pembrolizumab proves to enhance survival vs placebo in the second-line setting. These findings may imply that the sequencing of the checkpoint inhibitors does not matter, as the patients who were randomized to sorafenib could have received a checkpoint inhibitor as second-line treatment or later, thus matching any potential survival advantage that the nivolumab arm may have had. There could, however, be a complex explanation for the possible scenario of negative outcomes in the nivolumab vs sorafenib study. Sequence may matter, and not only may nivolumab do well like pembrolizumab in second-line treatment, but the prior exposure to sorafenib may help enhance the effect of checkpoint inhibitors, as has been suggested in the combination of tyrosine kinase inhibitors and checkpoint inhibitors.

G&H What are the most common adverse events that are associated with the use of checkpoint inhibitors in HCC patients?

GAA Anything that a patient taking checkpoint inhibitors may complain of can be an adverse event until proven otherwise. With the use of immunotherapy, every organ in the body can experience anti-immune activities. Side effects may include diarrhea, skin irritation or redness/inflammation, joint pain, diabetes, and a subtle change in thyroid functionality that can only be seen on laboratory workup and is not necessarily symptomatic; such scenarios can be managed easily and may not limit the use of the checkpoint inhibitor. Liver function may worsen, and may result in complications ranging from the development of inflammation in the liver to autoimmune hepatitis or the reactivation of viral infections such as hepatitis B or C. Checkpoint inhibitor–related hepatic toxicity may occur and may involve portal and periportal inflammation and liver cell necrosis with infiltrating lymphocytes, plasma cells, and eosinophils. Such hepatotoxicity may thus be associated with a reduction in the necrosis of liver cells in the border zone and few infiltrating T cells. This is in contrast to autoimmune hepatitis, in which most patients have a characteristic high titer of serum autoantibodies, such as antinuclear antibodies, anti–double-stranded DNA antibodies, and smooth muscle antibodies. Most cases of checkpoint inhibitor immune-mediated hepatitis, when tested, do not show the presence of any serum autoimmune hepatitis autoantibodies. It has not yet been determined whether the risk of immune-mediated hepatitis is related to exposure to checkpoint inhibitors or whether the infiltrating tumor cells promote the activation of inflammatory pathways that may induce immune-mediated hepatitis. Some patients taking checkpoint inhibitors may not experience any side effects; however, deleterious side effects may occur, although they are not common. Therefore, physicians need to extensively evaluate any suspicious or concerning signs and/or symptoms that patients may develop while taking checkpoint inhibitors.

G&H What are the next steps for research regarding the use of checkpoint inhibitors for HCC treatment?

GAA There has been excitement regarding data on the combination of bevacizumab plus atezolizumab in HCC patients. An impressive response rate of over 60% was originally reported at the American Society of Clinical Oncology meeting in June 2018. However, updated data, reported at the European Society of Medical Oncology meeting in October 2018, revealed a response rate of close to 30%, which may be explained by the antiangiogenic

effect against the infiltration of T cells into the tumors. Research on other checkpoint inhibitor combinations is currently underway, including nivolumab plus cabozantinib and pembrolizumab plus lenvatinib (Lenvima, Eisai). The possibility of adding a tyrosine kinase inhibitor to a checkpoint inhibitor is intriguing and requires further investigation; however, there is currently a lack of understanding of any mechanism of action that may explain this potential synergistic effect, which may just be an additive effect.

As previously mentioned, the HIMALAYA study is currently examining the combination of the PD-1 inhibitor durvalumab and the CTLA-4 inhibitor tremelimumab. The concept of "priming" the immune system with a CTLA-4 inhibitor and enhancing anticancer activity with a PD-1 inhibitor is intriguing.

G&H Is there any research (past or present) on the use of checkpoint inhibitors in earlier stages of HCC?

GAA To date, the use of checkpoint inhibitors in the setting of HCC has focused on patients with metastatic HCC. Checkpoint inhibitors are also being investigated for locally advanced disease based on the altered lymphocyte/neutrophil ratio and immune set-up induced by the use of local therapy. There is also ongoing interest and research on checkpoint inhibitors in the adjuvant setting.

Dr Abou-Alfa has conducted research with ActaBiologica, Agios, Array, AstraZeneca, Bayer, BeiGene, BMS, Casi, Celgene, Exelixis, Genentech, Halozyme, Incyte, Lilly, MabVax, Novartis, OncoQuest, Polaris, Puma, QED, and Roche; and has consulted with 3DMedcare, Agios, AlignMed, Amgen, Antengene, Aptus, Aslan, Astellas, AstraZeneca, Bayer, BeiGene, Bioline, BMS, Boston Scientific, BridgeBio, Carsgen, Casi, Celgene, Cipla, CytomX, Daiichi, Debio, Delcath, Eisai, Exelixis, Genoscience, Gilead, Halozyme, Hengrui, Incyte, Inovio, Ipsen, Janssen, Jazz, Kyowa Kirin, LAM, Lilly, Loxo, Merck, Mina, Newlink Genetics, Novella, Onxeo, PCI Biotech, Pfizer, Pharmacyclics, PharmaCyte, Pieris, QED, RedHill, Sanofi, Servier, Silenseed, Sillajen, Sobi, Targovax, Tekmira, Twoxar, Vicus, Yakult, and Yiviva.

Suggested Reading

El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet*. 2017;389(10088):2492-2502.

Harding JJ, El Dika I, Abou-Alfa GK. Immunotherapy in hepatocellular carcinoma: primed to make a difference? *Cancer*. 2016;122(3):367-377.

Ikeda M, Sung MW, Kudo M, et al. A phase 1b trial of lenvatinib (LEN) plus pembrolizumab (PEM) in patients (pts) with unresectable hepatocellular carcinoma (uHCC) [ASCO abstract 4076]. *J Clin Oncol.* 2018;36(15)(suppl).

Lee KH, Hsu CH, Lee MS, et al. Atezolizumab + bevacizumab in hepatocellular carcinoma (HCC): safety and clinical activity results from a phase Ib study [ESMO abstract]. *Ann Oncol*. 2018;29(9)(suppl):mdy432.002.

Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. *Lancet Oncol.* 2018;19(7):940-952.