Developments in Hepatocellular Cancer Treatment

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Presenter's disclosure of conflicts of interest is found at the end of this article.

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Abstract

The treatment landscape of hepatocellular cancer has changed significantly within the past few years. At JADPRO Live Virtual 2020, Bridget O'Brien, DNP, APRN, FNP-BC, AOCNP®, provided an overview of developments in hepatocellular cancer treatment and clinical pearls for how advanced practitioners can manage common adverse events.

The death rate from hepatocellular cancer (HCC) has more than doubled in the past 30 years as the incidence of this disease continues to rise worldwide. However, the recent approvals of targeted agents and immunotherapies have dramatically changed the treatment landscape of HCC and should impact these numbers over time.

During JADPRO Live Virtual 2020, Bridget O'Brien, DNP, APRN, FNP-BC, AOCNP®, of Rush University, reviewed the diagnostic evaluation for HCC in newly diagnosed patients at all stages of disease and discussed treatment options, including new systemic approaches. Dr. O'Brien also discussed the role of advanced practitioners in managing treatment-related adverse effects of novel agents.

COMPLEXITIES OF TREATING HCC

As Dr. O'Brien explained, treating HCC is uniquely complex because it is composed of two diseases with overlap: cancer and liver disease. Although these two diseases go hand in hand for most patients, said Dr. O'Brien, the functionality of the liver is a key component of decision-making regarding treatment.

"Patients with end-stage liver disease have a different treatment algorithm than patients with very isolated disease," said Dr. O'Brien. "Unfortunately, most patients present with more significant disease."

"Because patients with Child-Pugh class C may not benefit from systemic treatment or many treatment options, for that matter, it's best to capture patients earlier in the course of their disease," she added.

In addition to different toxicities for locoregional therapies vs. systemic therapy options, goals of treatment are an important consideration. For some patients, bridge therapy (usually a locoregional treatment) can be used to carry patients to surgery or transplant. For other patients, down-

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staging therapy can improve overall quality of life. Patients with more limited disease who have better liver functionality and can undergo surgery, however, may be candidates for curative therapy (either surgery or liver transplant). Finally, there are patients who need to be addressed with palliative care to limit their tumor burden and the complexities of their liver function.

"It really is a complex discussion when we diagnose a new patient in terms of what's best for their individual circumstance," said Dr. O'Brien. "Shared decision-making with both the providers and patients is an important part of the process."

DIAGNOSING HCC

Diagnosis of HCC is often based on noninvasive imaging: triple-phase CT or MRI. Biopsy is not always needed, but when it is warranted, imaging is still needed for guidance, said Dr. O'Brien.

Laboratory testing is then used to determine the severity of underlying liver disease. These tests include the following: complete blood count, comprehensive metabolic panel, coagulation studies, and alpha-fetoprotein (AFP). AFP is elevated in 75% of cases, which correlates conversely with prognosis, said Dr. O'Brien, who noted that AFP greater than 400 ng/mL predicts HCC with specificity greater than 95% (Peng et al., 2004).

An upper endoscopy is also important with a new diagnosis for evaluation of varices to predict bleeding risk and to eliminate potential systemic therapies that may cause increased bleeding.

Child-Pugh classification is important in diagnosing HCC because it provides an indication of overall prognosis and liver function. Because a number of systemic treatment options have only been tested in the Child-Pugh A category, this evaluation is also needed for treatment selection (Table 1).

Another useful tool is the CLIP scoring system, which is comprised of the Child-Pugh classification along with additional information about tumor morphology, AFP levels, and the presence of portal vein thrombosis.

When looking at newly diagnosed patients with HCC, health-care providers should also think about additional toxicities related to worsening liver dysfunction, said Dr. O'Brien. These toxicities include new or worsening ascites, encephalopathy, increased bilirubin, decreased albumin, and variceal bleeding. Imaging evaluation also can reveal portal hypertension, which could be associated with varices, splenomegaly, abdominal collaterals, or thrombocytopenia (Table 2).

Table 1. Child-Pugh Classification

Finding	1 Point	2 Points	3 Points
Encephalopathy grade	None	Mild	Severe
Ascites	Absent	Mild to moderate	Severe, refractory
Serum bilirubin (mg/dL)	< 2	2–3	> 3
Serum albumin (g/dL)	> 3.5	2.8–3.5	< 2.8
INR	< 1.7	1.71–2.20	> 2.20

Note. Child Pugh A: 5–6 points; Child Pugh B: 7–9 points; Child Pugh C: 10–15 points. INR = international normalized ratio. Information from Child & Turcotte (1964).

FIRST-LINE SYSTEMIC THERAPY

For more than 10 years, patients with newly diagnosed HCC who require systemic therapy have received sorafenib (Nexavar), an oral multikinase inhibitor, based on results of the SHARP trial, which showed almost 3-month improvement in median overall survival vs. placebo (Llovet et al., 2008).

In 2018, the REFLECT trial, which compared lenvatinib (Lenvima), a VEGF inhibitor, to sorafenib, demonstrated noninferiority in the first-line setting (13.6 months median overall survival vs. 12.3 months) and provided an additional treatment option for patients with newly diagnosed HCC (Kudo et al., 2018).

Table 2. What We Know About Treatment Decisions

- Staging patients is important (physiologic and anatomic)
- The only curative approach is surgery (resection or transplant)
- Most patients are not candidates for surgery
- Chemoembolization (TACE) and radio frequency ablation (RFA) can improve survival in selected patients
- Most patients will require systemic treatment if they live long enough
- Cytotoxic chemotherapy has not had any real impact on this disease
- Molecularly targeted and immunotherapeutic agents have helped expand the treatment landscape in HCC

More recently, results of the phase III IMbrave150 trial, which tested atezolizumab (Tecentriq), an immunotherapy, plus bevacizumab (Avastin), a VEGF inhibitor, vs. sorafenib in unresectable or metastatic HCC, led to the approval of the combination in patients who have not received prior systemic therapy (Finn et al., 2020). Although serious adverse events were slightly higher in the combination arm, results also showed improved overall and progression-free survival.

According to Dr. O'Brien, this is the first time a treatment has demonstrated superiority to sorafenib in a decade. Importantly, the hazard ratio demonstrates a strong benefit (hazard ratio = 0.58), and there was improved quality of life with the combination.

Given the improved outcomes and a very good overall safety profile, atezolizumab plus bevacizumab will likely become the first-line therapy for the majority of patients, said Dr. O'Brien.

SECOND-LINE THERAPY AND ADVANCED DISEASE

The treatment landscape for second-line therapy has become increasingly complex given the proliferation of novel agents. Although a biopsy is not necessarily warranted in patients with newly diagnosed HCC, said Dr. O'Brien, it is recommended prior to starting treatment for metastatic disease or following disease progression. A CT scan of the chest and a bone scan may also be helpful to consider in most patients, she said.

The multiple options in advanced HCC include the following:

- Regorafenib (Stivarga; Child-Pugh A only) approved according to improved overall survival
- Nivolumab (Opdivo; Child-Pugh A or B) approved according to durable objective response rate
- Cabozantinib (Cabometyx; Child-Pugh A only) had positive overall survival benefits
- Ramucirumab (Cyramza; AFP > 400 only) failed in REACH but positive in REACH-2
- Lenvantinib (Child-Pugh A only)
- Nivolumab plus ipilimumab (Opdivo and Yervoy; Child-Pugh A only)
- Sorafenib (Child-Pugh A or B)
- Pembrolizumab (Keytruda; Child-Pugh A only)

As Dr. O'Brien explained, in the original REACH trial, ramucirumab initially showed no survival advantage vs. placebo (Zhu et al., 2015). However, after subset analysis of patients with AFP greater than 400 identified a survival difference, the REACH-2 trial was conducted specifically for this patient population and led to the approval of ramucirumab (Zhu et al., 2019).

"This was one of the first positive studies in HCC that looked at a biomarker-defined patient population, and it shows the potential impact of genomic testing," said Dr. O'Brien. "It also validated angiogenesis as a therapeutic target."

EMERGING TARGETS AND COMBINATION THERAPIES

According to Dr. O'Brien, immunotherapy is "exploding" in HCC, and the list of immune checkpoint inhibitors includes the following: nivolumab (targets PD-1); ipilimumab (targets CTLA-4); pembrolizumab (targets PD-1); tremelimumab (targets CTLA-4); durvalumab (Imfinzi; targets PD-L1); tislelizumab (targets PD-1); camrelizumab (targets PD-1); and avelumab (Bavencio; targets PD-L1).

Results of the CheckMate 459 trial of nivolumab vs. sorafenib showed a median overall survival of 16.4 months vs. 14.7 months as first-line treatment of patients with advanced HCC (Yau et al., 2019). Overall response rates, however, were more than twice as high with nivolumab, reported Dr. O'Brien.

Phase III studies have not shown an overall survival benefit for single-agent immunotherapy in the first- or second-line setting, but the combination of ipilimumab and nivolumab demonstrated an overall response rate of 33% in the second-line treatment of advanced HCC (Yau et al., 2020).

"Several new drugs have been developed for HCC in the past 2 years alone, but sequencing of treatments can be difficult due to limited data and the quickly evolving treatment landscape," said Dr. O'Brien. "If you don't treat a lot of HCC, I recommend looking at the NCCN Category 1 recommendations and considering how the side effect profile of each agent may affect your individual patient."

MANAGEMENT OF COMMON ADVERSE EVENTS

Dr. O'Brien also underscored the importance of management of toxicities. Common toxicities of tyrosine kinase inhibitors (TKIs) and anti-VEGF therapies include hypertension; palmar-plantar erythrodysesthesia syndrome (PPES); fatigue; cardiac ischemia and/or myocardial infarction; hepatotoxicity; and wound healing and bleeding.

Hypertension is typically mild to moderate and managed with antihypertensive therapy, said Dr. O'Brien, who recommended monitoring blood pressure weekly for the first 6 weeks and then periodically thereafter.

PPES, a group of symptoms affecting the hands and/or feet, is a common side effect of antiangiogenic therapies and usually occurs during the first few weeks of treatment, said Dr. O'Brien, who noted that early intervention may prevent progression of symptoms and avoid treatment interruption or dose reduction. Patients are advised to use liberal creams on hands and feet, soak in Epsom salt bath with warm but not hot water, wear comfortable soft-soled footwear, and wear cotton socks and shoe pads.

Patients should also be aware of the potential for fatigue prior to initiating therapy.

"We want patients to stay as active as possible while paying attention to their body," said Dr. O'Brien. "We want to really help them with energy as well as sleep, have them maintain normal activities, and be aware of any significant change in their performance status."

Cardiac ischemia and/or myocardial infarction have also been reported with some TKIs and should result in permanent discontinuation of the treatment, said Dr. O'Brien.

"This is very rare, but it's something we need to keep a close eye on," she said. "Monitor electrolytes, bradyarrhythmia, and avoid any concomitant QT-prolonging drugs, including antiemetics."

Sorafenib-induced hepatitis may result in hepatic failure or death, so liver function tests should be monitored closely, and sorafenib should be discontinued with increased transaminases.

Bleeding from esophageal varices was seen in 2.4% of patients on sorafenib and 4% on placebo and can lead to fatal outcomes. Bleeding necessitates medical intervention and therapy may need to be permanently discontinued.

Immune checkpoint inhibitor toxicities are due to overactivity of the patient's immune system. Early assessment of toxicities is needed with prompt intervention, said Dr. O'Brien, who noted that the most common immune-mediated toxicities are rash/dermatitis, diarrhea/colitis, mucositis, hepatoxicity, and fatigue. Although less common, endocrinopathies (hypophysitis, thyroiditis, diabetes), pneumonitis, arthralgia, neuropathy, nephritis, and encephalitis are also seen. There is no standard does reduction with immune-mediated toxicities, said Dr. O'Brien, but a dose can be held for significant adverse events.

"The management of toxicities is a key role of the advanced practitioner," said Dr. O'Brien. "They become symptom management experts and the best advocates for patients in terms of keeping them on these therapies, maintaining a good quality of life, and positively impacting patient outcomes." ●

Disclosure

Dr. O'Brien had no conflicts of interest to disclose.

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