Updates in the Management of Hepatobiliary Cancers
Presented by Mitesh J. Borad, MD

ABSTRACT

Hepatobiliary cancers are aggressive tumors that affect the liver and biliary tract and are responsible for nearly 550,000 deaths per year. The most common malignancy is hepatocellular carcinoma, and risk factors include viral hepatitis infection, nonalcoholic steatohepatitis, and excessive alcohol use. Other etiologies include Wilson’s disease, a1-antitrypsin deficiency, and cryptogenic cirrhosis. Clinicians should be aware of underlying conditions and how they influence treatment decisions.

“We are seeing a shift with hepatitis being less common because of vaccinations and use of antiviral therapies that can eliminate hepatitis C in most cases . . ., [with] nonalcoholic steatohepatitis and metabolic syndrome likely becoming the predominant etiology in the years to come,” stated Mitesh J. Borad, MD, Associate Professor; Consultant, Division of Hematology/Oncology; and Consultant, Department of Molecular Medicine; Director of the Cancer Cell, Gene, and Virus Therapy Lab, of the Liver and Biliary Cancer Research Program; and of Precision Cancer Therapeutics at the Center for Individualized Medicine, Mayo Clinic Comprehensive Cancer Center, Scottsdale, Arizona, and member of the NCCN Hepatocellular Carcinoma and Biliary Tract Cancers Panels, at the NCCN 2023 Annual Conference. During his presentation, Dr. Borad discussed current therapeutic strategies for advanced hepatocellular carcinoma (HCC) and biliary tract cancers, as well as the genomic landscapes in this patient population.

First-Line Treatments for HCC

Sorafenib is a multikinase inhibitor that had been the standard of care for patients with advanced or metastatic disease prior to the advent of immunotherapy. It works by inhibiting tumor cell proliferation and tumor angiogenesis, while simultaneously increasing the rate of apoptosis. It also inhibits the serine–threonine kinases Raf-1 and BRAF, as well as the receptor tyrosine kinase activity of VEGFRs and PDGFRβ. This agent has been tested in 2 pivotal trials: the phase III SHARP trial and the Asia-Pacific trial.1,2

Both the SHARP and Asia-Pacific trials enrolled patients with advanced HCC who were then randomly assigned to receive sorafenib or best supportive care. Despite similar inclusion and exclusion criteria, Asian patients alone were enrolled in the latter study, and participants were more likely to be younger, have hepatitis B–related disease, be symptomatic, and harbor more tumor sites than those in the SHARP trial. Results from these trials demonstrated an improvement in overall survival (OS) and progression-free survival (PFS), and modest response rates. At the time, the data deemed sorafenib as an appropriate treatment option for these patients.1,2

Sorafenib remained the standard of care for nearly a decade, until a phase II study evaluating lenvatinib—an oral multikinase inhibitor that targets VEGFR-1, -2, and -3; FGFR1, -2, -3, and -4; PDGFRα; RET; and KIT—showed activity in HCC.3 To build on these findings, the REFLECT study randomly assigned patients to receive lenvatinib or sorafenib, but was statistically designed for noninferiority.4 “There was some numerical improvement with lenvatinib over sorafenib, but this was noninferior, so in the clinic you could pick either one,” commented Dr. Borad.

Immunotherapy

The combination of antiangiogenics with immune checkpoint inhibitors (atezolizumab + bevacizumab) is a recommended option for certain patients. “We know that hepatocellular cancers have a tumor microenvironment in a subset of patients, at least where there is T-cell infiltration, particularly CD8-positive T cells, that you could leverage with immune checkpoint inhibitors,” Dr. Borad noted.

This sparked the IMbrave150 study, which compared atezolizumab + bevacizumab versus sorafenib alone in this patient population. The interim analysis for this study was stopped because of significantly improved OS in the experimental arm compared with the standard arm.
available options for perhaps a subset of patients, lumab agents. Dr. Borad concluded. It is important to note that auto-immune toxicities of the liver are prevalent with this combination, so consistent patient monitoring is recommended.

Another area of therapeutic intervention for HCC is the concept of dual inhibition of PD-1, PD-L1, and CTLA-4 checkpoints in the interaction between T cells and the tumor microenvironment. The phase III HIMALAYA study compared durvalumab with or without a single dose of the CTLA-4 inhibitor tremelimumab versus sorafenib monotherapy in patients with advanced or metastatic disease.6

“OS was improved with the STRIDE regimen [single dose of tremelimumab followed by treatment with durvalumab] compared with sorafenib, and was noninferior between durvalumab and sorafenib,” Dr. Borad concluded. “Even using a single dose of CTLA-4 antibody would provide superiority.”

“Both sorafenib and lenvatinib still remain clinically available options for perhaps a subset of patients,” concluded Dr. Borad. “Atezolizumab + bevacizumab and durvalumab + tremelimumab are more contemporary options, given their superiority over sorafenib, and lenvatinib and durvalumab could also be considered as single agents.” Note that pembrolizumab, nivolumab, and nivolumab + ipilimumab are also recommended first-line systemic therapy options for certain patients with HCC.

First-Line Treatments of Biliary Tract Cancers
Cancers of the biliary tract comprise intrahepatic and extrahepatic cholangiocarcinomas, as well as gallbladder cancer, and they are the second most common set of hepatobiliary cancers. “Globally, we can see that in the Western world, this is an uncommon cancer,” stated Dr. Borad. “High-incidence regions of the world include southeast Asia, where due to liver flukes, this is a carcinogenic event. In fact, the incidence is as high as 85 per 100,000 [people] compared with 2 per 100,000.”

The global standard of care for biliary tract cancer was established more than a decade ago due to the ABC-02 trial, which evaluated gemcitabine ± cisplatin in this patient population.9 The results of this trial, which favored the doublet regimen with a significant improvement in OS, paved the way for SWOG 1815, which compared gemcitabine, cisplatin, and nab-paclitaxel with gemcitabine + cisplatin. Although there was a numerical improvement in PFS, OS, and response rates among the triplet regimen, none of the results were statistically significant.9

The results of these studies influenced the TOPAZ-1 trial, which evaluated gemcitabine, cisplatin, and durvalumab versus gemcitabine + cisplatin in patients with advanced biliary tract cancer.10 According to Dr. Borad, “There were no big differences in the toxicity of the triplet versus the doublet regimen, so even though immunotherapy was added, there were no significantly meaningful differences in terms of toxicity. The combination of gemcitabine and cisplatin + durvalumab represents a new standard of care. OS, PFS, and response rates were all superior.”

Genomic Landscape and Gene Therapy
The incidence of gene fusions among patients with intrahepatic cholangiocarcinoma is approximately 10%. Known mutations involve the FGFR, IDH, and BRAF genes. The incidence of FGFR2 mutations among this population is between 10% and 15%, and there have been several studies evaluating FGFR inhibitors.11–13 The phase II FIGHT-202 trial evaluated FGFR2 inhibitor therapy with pemigatinib among patients with locally advanced or metastatic cholangiocarcinoma harboring gene fusions.14

“In this study, 70% to 80% of patients had some tumor shrinkage, RECIST response rates were in the 30% range, and the duration of response in responders was 7.5 months,” Dr. Borad stated. Both PFS and OS were improved among patients harboring gene fusions, with diminishing effects in those with other alterations or none. Other FGFR inhibitors included futibatinib and infigratinib, which demonstrated response rates that ranged from 30% to 40%, 6 to 9 months for PFS, and 1 to 2 years for 2-year OS.15,16

Although pemigatinib and infigratinib have demonstrated efficacy, futibatinib may be able to overcome many of the resistance mutations, especially polyclonal mutations, that other agents cannot target. According to Dr. Borad, “newer agents are under investigation. One of the most exciting ones is RLY-4008, which is an allosteric inhibitor, and this has shown considerable activity, even in patients who progressed on agents such as futibatinib. Patients who have fusions or mutations in biliary tract cancers and other diseases showed a significant clinical benefit in early evaluations.”

IDH1 mutations are found in 10% and 15% of patients, resulting in higher levels of a neomorphic metabolite 2-hydroxyglutarate and therefore altering the epigenetic landscape. The ClarIDHy study evaluated the IDH1 inhibitor ivosidenib versus placebo in the second-line setting.17 “You can see that there’s an early and significant difference statistically, but median PFS was 2.7 versus 1.4 months. Given that this drug is not very toxic, this can be particularly meaningful,” explained Dr. Borad.

At a 5% incidence, alterations affecting the BRAF pathway are important in biliary tract cancers. The phase II ROAR trial involved several different cancers, including biliary tract cancers, and administered combination dabrafenib + trametinib to these patients. Approximately 80% of patients in the biliary tract cancer cohort had tumor shrinkage, with a response rate of 50%, and duration of response was 9 months. The
results of this study supported this combination on a tumor-agnostic basis, offering patients with aggressive biliary tract cancer a more reliable and effective treatment option.\textsuperscript{18}

“Genomic profiling is the standard of care in the management of these cancers,” concluded Dr. Borad. “There are many more targetable alterations in biliary tract cancer; as this is the most targetable and actionable gastrointestinal tract cancer, so many novel agents targeting a host of mutations will be clinically available therapies in the not-too-distant future.”

Disclosures: Dr. Borad has disclosed no relevant financial relationships.

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References