Liver transplant and resection are preferable for the management of hepatocellular carcinoma (HCC), but ultimately, tumor location, biology, and patient condition often dictate treatment decisions. At the NCCN 2022 Annual Conference, a panel of experts presented the current liver-directed and systemic therapy options in this clinical context. Moderated by Daniel B. Brown, MD, FSIR, the session focused on 3 case studies, which were used to develop an evidence-based approach for the treatment of similar patients. Panelists included Rajiv Agarwal, MD, Assistant Professor of Medicine, Division of Hematology and Oncology, and Lea K. Matsuoka, MD, Associate Professor of Surgery, and Program Director, Vanderbilt ASTS Transplant Surgery Fellowship, both of Vanderbilt University Medical Center.

Case 1: Resection, Transplantation, and Bridging Therapy

The first case presentation focused on a patient with a 2-cm HCC in segments VI and VII of the liver and an ECOG performance status of 0. The tumor was situated over the branches of the right posterior portal vein. No portal vein invasion or other suspicious masses were reported. “Initial considerations should include liver resection or liver transplant,” Dr. Matsuoka explained. In terms of resection, the risk and efficacy of the surgery itself should be taken into account.

In the 1970s, the rate of resection-associated mortality was high; currently, the rate has decreased to <5% based on the results of a 20-year analysis by Fan et al. In addition to safety, there are also data supporting the efficacy of resection. Based on an intention-to-treat analysis, the 5-year survival rate of resection was 51% in the overall population and 74% in those without portal hypertension. According to Dr. Matsuoka, this study emphasized the potential benefits of resection with proper patient selection and its potential superiority over transplantation when considering organ scarcity and the waitlist dropout rate.

A couple of studies were published that reviewed 2 randomized controlled trials of well-compensated patients with early-stage HCC and revealed moderate evidence favoring resection over radiofrequency ablation in terms of overall survival (OS) and 2-year survival. In another trial, patients within Milan criteria who underwent resection experienced improved survival outcomes and a lower recurrence rate compared with those who underwent transarterial chemoembolization followed by radiofrequency ablation.

“Liver resection should be considered in patients with early-stage HCC and well-compensated liver disease with minimal portal hypertension,” Dr. Matsuoka commented. “The disease should be resectable, with an adequate liver remnant remaining, and the patient should, overall, be a reasonable surgical candidate.”

To comment on the efficacy of transplantation in early-stage HCC, Dr. Matsuoka presented a landmark trial of patients with small, unresectable disease. After transplantation, a 4-year OS rate of 75% was reported. “This study supported HCC as an indication for liver transplant and established what became known as the Milan criteria, which is a single tumor <5 cm or up to 3 tumors, each <3 cm,” Dr. Matsuoka remarked. “In the United States, patients with HCC who fall within this Milan criteria are granted exception points and a Model for End-Stage Liver Disease (MELD) score equal to the median MELD at transplantation – 3 for that region; therefore, these patients will move higher on the liver transplant waitlist.”
Surgical resection or transplantation is recommended in the current Barcelona Clinic Liver Cancer (BCLC) guidelines in patients with early-stage and very early-stage HCC.8 “For patients with a small focal tumor that is targetable, ablation is the next best option,” Dr. Brown remarked. “For those who cannot go through tumor ablation, the BCLC group provided an option in which they thought locoregional therapy options could be considered.”

The current NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Hepatobiliary Cancers recommend resection as the primary treatment option in this setting; however, locoregional therapies are frequently used for patients ineligible for transplantation or who are being bridged to transplantation (Figure 1).9 In 2018, 92.4% of patients had undergone at least 1 locoregional therapy, compared with 42.3% in 2003.

A seemingly equivalent alternative to arterial locoregional therapy, yttrium-90 (Y-90) radioembolization has been a clinical topic of interest. In the LEGACY study, patients with a solitary unresectable tumor ≤8 cm underwent segmental infusion of radioactive Y-90. The 3-year OS rates were 86.6% and 92.8% in all patients and in those bridged to transplantation or resection, respectively.10

“One of the more common questions that medical oncologists get asked is [whether there] is a role for systemic treatment as a bridge or neoadjuvant therapy,” Dr. Agarwal commented. “Currently, there are no definitive data to support the use of systemic therapy [with tyrosine kinase inhibitors or immunotherapy] as a bridge to transplantation or as neoadjuvant therapy prior to resection.” Multiple ongoing studies are currently testing tyrosine kinase inhibitors or immunotherapy in the neoadjuvant and bridge settings.

**Case 2: Downstaging and Combination Therapies**

The second case focused on a patient with a solitary 6-cm HCC in the left lateral segment. Dr. Matsuoka noted that, similar to this patient, the majority of those with HCC do not fall within the Milan criteria for transplant candidacy. “With the advent of locoregional therapies, we questioned whether we could downstage our patients with HCC and they could undergo transplantation subsequently with acceptable outcomes,” Dr. Matsuoka explained.

A prospective study enrolled patients who did not initially fall within the Milan criteria. However, they did meet 1 of the following criteria: single lesion ≤8 cm, 2 or 3 lesions each ≤5 cm with the sum of maximal tumor diameters ≤8 cm, or 4 or 5 lesions each ≤3 cm with the sum of maximal tumor diameters ≤8 cm. A total of 65% of the patient population underwent successful downstaging with locoregional therapy and were listed for a transplant. The intention-to-treat survival outcomes did not seem to differ between patients who underwent downstaging and those who were initially within the Milan criteria.11 Based on these data, in 2017 the standardized United Network for Organ Sharing (UNOS) downstaging protocol was adopted.

“Patients with tumor burden within [the UNOS downstaging criteria] undergo locoregional therapy and are hope-fully successfully downstaged to within Milan criteria,” Dr. Matsuoka explained. “They are then also eligible for the same MELD exception points on the transplant list.”

Most frequently, chemoembolization and Y-90 radio-embolization are applied for downstaging; however, based on data from the MERITS-LT Consortium, the probabilities of successful downstaging do not seem to differ between these arterial therapies.12 “These therapies are institutionally

**Figure 1.** NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Hepatocellular Carcinoma: clinical presentation, surgical assessment, treatment, and surveillance [HCC-4]. Version 1.2022. © 2022 National Comprehensive Cancer Network, Inc. All rights reserved. These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN®. To view the most recent and complete version of the NCCN Guidelines, go to NCCN.org.
dependent regarding expertise,” Dr. Brown commented. “[However, these data show] there is no one right way to do this.”

In terms of “pushing the boundaries” to identify eligible patients for downstaging, there appears to be an upper limit in tumor burden beyond which successful transplantation may be unrealistic. Patients exceeding the standard downstaging criteria seemed to experience a significantly lower probability of transplantation and inferior intention-to-treat survival.

“As we are talking about more locoregional options, a common space that is now being investigated is combined systemic with liver-directed therapy,” Dr. Agarwal remarked. In the phase III LAUNCH trial, patients were randomly assigned to receive first-line lenvatinib with or without transarterial chemoembolization. Median durations of OS (17.8 vs 11.5 months; hazard ratio [HR], 0.45) and progression-free survival (10.6 vs 6.4 months; HR, 0.43) were prolonged with transarterial chemoembolization; a higher overall response rate was also reported (54.1% vs 25.0%).

“This analysis did not exclude extrahepatic disease … [which] raises the question of [whether] it is appropriate to combine systemic therapy with locoregional therapy while we also are making strong advancements in our systemic therapy options,” Dr. Agarwal commented. “The underperformance of the control arm compared with the REFLECT study raises the question again of [whether] there is a true difference.”

Case 3: Systemic and Locoregional Therapies
The third case presentation focused on an 82-year-old patient with nonalcoholic steatohepatitis who was diagnosed with a 12-cm advanced HCC. According to Dr. Brown, this patient was classified as BCLC stage C and Child-Pugh class A, with an ECOG performance status of 0. The tumor invaded the right portal vein, but no varices were detected via imaging or endoscopy.

Recommendations regarding first-line systemic therapy are included in the current NCCN Guidelines. The preferred regimen, atezolizumab + bevacizumab, is indicated for patients with Child-Pugh class A disease. Other recommended regimens include sorafenib (Child-Pugh A or B7) or lenvatinib (Child-Pugh A), durvalumab, and pembrolizumab. Nivolumab is recommended in patients classified as Child-Pugh class A or B who are ineligible for treatment with an anti-VEGF or tyrosine kinase inhibitors (Figure 2).

“The IMbrave150 study demonstrated the superiority of atezolizumab with bevacizumab,” Dr. Agarwal explained. Median durations of OS (19.2 vs 13.4 months; HR, 0.66) and progression-free survival (6.8 vs 4.3 months; HR, 0.59) were...
prolonged with this combination compared with sorafenib. The objective response rate by RECIST 1.1 was 29.8%.\textsuperscript{15,16}

“Atezolizumab + bevacizumab has been the standard of care, when appropriate, [which] raises the question of what the evolving landscape is for systemic treatment options,” Dr. Agarwal commented. To provide insight, he presented the results of the multicenter, global, phase III HIMALAYA trial. Patients who were treated with a single priming dose of tremelimumab + regular-interval durvalumab (STRIDE) experienced a prolonged median duration of OS compared with those who received sorafenib (16.4 vs 13.8 months; HR, 0.78). Furthermore, durvalumab monotherapy seemed to be non-inferior to sorafenib (median OS, 16.6 vs 13.8 months; HR, 0.86). Objective response rates were 20.1%, 17.0%, and 5.1% with STRIDE, durvalumab monotherapy, and sorafenib, respectively.\textsuperscript{17}

“This potential role for durvalumab monotherapy is important to think about when we are also balancing quality of life and immune-mediated events,” Dr. Agarwal explained. The rates of grade 3 or 4 adverse events (12.6% vs 6.4%) and adverse events requiring high-dose steroids (20.1% vs 9.5%) were higher with STRIDE compared with durvalumab alone; however, he noted that increased incidences of toxicities are expected with combined checkpoint inhibition.\textsuperscript{17}

“It is very clear that systemic therapy … is the principal method for treating patients with advanced HCC,” Dr. Brown commented. “There have been studies looking at locoregional therapy … but recent studies did not work out as positive.” In the phase III SARAH trial, the objective response rate was higher with Y-90 than with sorafenib; however, upon the inclusion of those who were unfit for treatment, it did not translate to an OS benefit.\textsuperscript{18}

In a single-arm cohort study, after undergoing Y-90 radioembolization, the median duration of OS was 304 days in patients with branch portal venous thrombosis and 134 days in those with main portal venous thrombosis.\textsuperscript{19} “This has informed the medical oncology studies as well now because … main portal vein thrombosis is not being included in all of the current trials,” Dr. Brown explained.

Unpublished data, which will be presented in June 2022 at the Society of Interventional Radiology annual meeting, seem to support the use of locoregional therapy in this clinical context. “For patients who present with [Child-Pugh A disease and an ECOG performance status of 0], there may be a role for locoregional therapy,” Dr. Brown commented. “That would be what I would focus on in randomized prospective trials moving forward in this patient group.”

References


