Editorial Commentary

Review of practice informing data and current state of NCCN consensus guidelines in hepatobiliary cancers

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The most important recent updates to the US National Comprehensive Cancer Network (NCCN) guidelines include the addition of new immunotherapy agents to the armamentarium for both hepatocellular carcinoma (HCC) and biliary tract cancers (1). The publication and subsequent the US Food and Drug Administration (FDA) approval of the Single Tremelimumab Regular Interval Durvalumab (STRIDE) regimen established in the phase III HIMALAYA trial (2) adds an important option for first-line systemic treatment of advanced HCC and was included in the NCCN guidelines with the 4.2022 update as a category 1, preferred recommendation. Although several recent FDA approvals have advanced targeted therapies in the 2nd line for advanced biliary tract cancers including FGFR2 (3,4) and IDH1 (5) targeting agents, there have been few recent approvals in the front line setting for unresectable biliary tract cancer until the recent FDA approval of gemcitabine, cisplatin, with durvalumab. The 2.2022 update of the NCCN guidelines acknowledged the positive results of the phase III TOPAZ-1 (6) study evaluating gemcitabine, cisplatin, durvalumab versus gemcitabine and cisplatin alone and moved the recommendation for this treatment combination from category 2A to category 1 as a preferred regimen. The addition to the NCCN guidelines of immunotherapy regimens in hepatobiliary cancers, underscores the efficacy of immunotherapy for gastrointestinal cancers as well as the pivotal role that this treatment modality can play in improving patient outcomes. However, there is an ongoing critical need for further studies that explore the potential benefits of immunotherapy alone and in combination with other agents to better inform clinical decision-making and to continue to advance the field for patients with hepatobiliary cancers.

The NCCN guidelines include recommendations for screening, diagnosis and treatment of cancer (7). These guidelines are developed by a panel of experts based on review of the most recent data and the highest levels of evidence available. Evidence for each recommendation is graded on a scale from category 1 (highest level of evidence and strongest expert consensus) to category 3 (NCCN experts disagree about intervention). These guidelines are widely used by oncologists in the US and around the world to establish standards for treatment recommendations and are often used in the determination of standard therapies for insurance coverage in the US. When compared to other organizations that develop treatment guidelines, particularly in HCC, including American Society of Clinical Oncology (ASCO) (8), European Society for Medical Oncology (ESMO) (9), American Association for the Study of Liver Diseases (AASLD) (10), American Gastroenterological Association (AGA) (11), European Association for the Study of the Liver (EASL) (12,13), among others, the NCCN

guidelines, are more frequently updated and reflect the latest available evidence. Of note, due to the increased complexity of liver cancers and their treatments, in March of 2023, the NCCN guidelines for hepatobiliary cancers were split into two separate sections—biliary tract cancer and HCC.

In HCC, the positive results of the HIMALAYA study were recently added to the NCCN guidelines. The HIMALAYA study was a global open-label phase III study comparing 3 regimens in unresectable HCC. The study compared the STRIDE regimen with single-agent durvalumab and single-agent sorafenib, with the primary endpoint being the superiority of overall survival (OS) for STRIDE *vs.* sorafenib. The study included patients with advanced or unresectable HCC, Child-Pugh Class A cirrhosis. This study notably excluded patients with main portal vein invasion. In total 1,171 patients were enrolled with 393 in the STRIDE arm 389 in the single agent durvalumab arm and 389 in the sorafenib arm. The median OS for the STRIDE group was 16.43 months versus 13.77 months with sorafenib [hazard ratio (HR) =0.78, P=0.0035]. Median progression-free survival (mPFS) for STRIDE was 3.78 months, and 4.07 months with sorafenib. Median PFS was not significantly different among the groups. The overall response rate (ORR) for STRIDE was 20.1% versus 5.1% with sorafenib. In the STRIDE arm 50.5% of patients experienced grade 3 or 4 treatment emergent adverse events, compared to 52.4% of patients in the sorafenib arm. The success of the STRIDE regimen led to FDA approval on October 21, 2022. The addition of the STRIDE regimen as a preferred category 1 regimen for systemic treatment of advanced HCC broadens the options for patients in the front-line setting. In addition to the comparison of STRIDE with sorafenib, the HIMALAYA trial also included a secondary endpoint with a non-inferiority comparison of single agent durvalumab with sorafenib for OS. The trial demonstrated that the mOS for single agent durvalumab was 16.56 months, versus 13.77 months with sorafenib, with OS HR in comparison with sorafenib of 0.86, meeting the endpoint of non-inferiority. Given the non-inferiority endpoint was met for single-agent durvalumab, the NCCN guidelines include the addition of durvalumab as a category 1 recommendation under the category "other recommended regimens".

Previously, atezolizumab and bevacizumab was the only category 1 preferred regimen for patients with advanced HCC and Child-Pugh A cirrhosis, based on the success of the IMBRAVE 150 trial, comparing atezolizumab and bevacizumab to sorafenib in the front line setting (14,15). IMBRAVE 150 was the first recent trial to show significant improvement in both ORR and OS in advanced HCC with ORR of 30% and median OS of 19.2 months. Treatment-related grade 3 or 4 adverse events occurred in 43% of patients receiving atezolizumab and bevacizumab, compared to 46% in the sorafenib arm. Six patients experienced grade 5 bleeding events in the atezolizumab and bevacizumab arm (14). Although both are considered category 1 preferred regimens, the NCCN guidelines do not specifically state which agent should preferentially be used. Direct cross trial comparisons are not possible, and determination of the most appropriate frontline approach must consider the individual characteristics of each patient. Given the risk of bleeding with bevacizumab, one proposed strategy is to preferentially use the STRIDE regimen in patients at the highest risk of bleeding or with contraindications to bevacizumab for other reasons (10). Given that nearly all agents in HCC in both the first line and 2nd line (16) have never been compared head-to-head, the next major advance in the treatment of this disease will be determining treatment algorithms to better sequence therapies to optimize responses. In addition, there is a significant need for future trials for patients with more advanced liver disease including with Child-Pugh B cirrhosis.

Despite several recent negative trials evaluating combination therapy with tyrosine kinase inhibitors and immunotherapy including the negative COSMIC-312 evaluating cabozantinib and atezolizumab versus sorafenib which was negative for OS, but positive for PFS (17), as well as LEAP-002 assessing lenvatinib and pembrolizumab versus lenvatinib alone (18), there have also been other recent advances in the first line setting. For example, the positive phase III camrelizumab and apatinib was the only trial incorporating a tyrosine kinase inhibitor with immunotherapy to meet its' primary endpoint of improved OS (19). In addition, RATIONALE-3 that incorporated the novel anti-programmed death 1 (PD-1) monoclonal antibody tislelizumab versus sorafenib in the first line setting of advanced HCC, was another positive trial after meeting the endpoint of noninferiority to sorafenib (20). Finally, sintilimab plus a bevacizumab biosimilar (IBI305) was evaluated in the ORIENT-32 trial and met the primary endpoint of improved OS and response versus sorafenib (21). It remains to be seen when and how these new positive trials will be incorporated into the next iteration of the NCCN guidelines for hepatobiliary cancers.

Another important advance in HCC is the recent announcement that the IMBRAVE 050 phase III trial of adjuvant atezolizumab and bevacizumab after curative resection or ablation was positive (22,23). This trial randomized patients who had received resection or ablation for localized HCC with high risk of recurrence to adjuvant atezolizumab and bevacizumab for 1 year or to active surveillance. The primary endpoint of this trial is recurrence-free survival (RFS) as assessed by an independent review facility (IRF). For patients with early-stage HCC and with adequate hepatic reserve, the current NCCN guidelines recommend considering resection, transplantation, or logoregional therapy including ablation, however, to 60–80% of patients who undergo curative intent resection or ablation will recur (24). The IMBRAVE 050 results were presented at the 2023 AACR Annual meeting showing that adjuvant atezolizumab and bevacizumab for patients status post curative intent resection or ablation with high risk of recurrence, was associated with improved RFS as assessed by an IRF. The intent to treat analysis included 334 patients in each arm with a median follow-up of 17.4 months, with RFS of 78% in the adjuvant atezolizumab and bevacizumab arm at 1 year versus 65% in the surveillance arm with a hazard ratio of 0.72 (P=0.012) (23). This is the first phase III trial in the adjuvant setting in HCC. Given the potential to change the treatment landscape of early HCC, it will likely be added to NCCN guidelines if atezolizumab and bevacizumab are FDA-approved in this setting. This regimen has already been added to the newest version of the AASLD HCC guidelines (10).

Most recent advances in biliary tract cancers have focused on targeted agents in the second line or later settings. This includes the recent FDA approvals of agents targeting FGFR2 fusions or rearrangement such as pemigatinib (4) and infigratinib (3) as well as ivosidenib (5) for tumors with IDH1 mutations. The NCCN guidelines also include futibatinib for FGFR2 positive disease as well as entrectinib and larotrectinib for NTRK gene fusion positive tumors, pembrolizumab and dostarlimab-gxly for MSI-H/dMMR tumors, dabrafenib and trametinib for BRAF V600E tumors and trastuzumab with pertuzumab for HER2 positive tumors. In the 3.2022 update of the NCCN guidelines selpercatinib (25) was added as a category 2B recommendation for RET gene fusion positive tumors.

The most important recent change to the NCCN guidelines in biliary tract cancers was the transition of gemcitabine, cisplatin and durvalumab from a category 2B recommendation to a category 1, preferred regimen. This change in recommendation status reflects improved evidence and consensus amongst members of the NCCN committee in the 2.2022 revision of the guidelines. This was based on FDA approval of this combination as per the TOPAZ-1 trial (2), which compared the first line standard of care, the combination of chemotherapy with gemcitabine and cisplatin with gemcitabine and cisplatin plus durvalumab. The proof of concept for this experimental combination was established in a phase II trial comparing cisplatin and gemcitabine with the addition of durvalumab and durvalumab and tremelimumab (26). The phase II trial, which was a single institutional study in South Korea, included 49 patients in the gemcitabine and cisplatin plus durvalumab group, with an ORR of was 72%, mPFS of 11.8 months, and mOS of 20.2 months, which were truly extraordinary outcomes in this deadly cancer. In the reported data the median duration of follow up was 26 months (26). TOPAZ-1 (6) is a double-blind placebo-controlled phase III trial for patients with unresectable or metastatic biliary tract cancer with a primary endpoint of OS, with secondary endpoints of ORR and safety. This trial included 341 patients randomized to the durvalumab, cisplatin, and gemcitabine arm and 344 patients in the placebo, gemcitabine, and cisplatin arm. Approximately half of enrolled patients had intrahepatic cholangiocarcinoma. In the reported data as of a planned interim analysis at a median follow up 16.8 months in the chemotherapy and durvalumab arm, the median OS in the experimental arm was 12.8 months, compared to 11.5 months in the placebo arm (HR =0.80, P=0.021). The mPFS in the experimental arm was 7.2 versus 5.7 months in the placebo arm (HR =0.75, P=0.001). The ORR in the investigator arm was 26.7% versus 18.7% in the placebo arm. Treatment related adverse effects occurred in 62.7% of patients in the durvalumab arm and 64.9% of patients in the placebo arm. Although these results are significant, they are much less impressive than the data from the phase II proof of concept study. The improved ORR is promising, and hopefully with further follow up this trial will show ongoing improvement in survival. Given the success of the TOPAZ-1 trial this regimen has become the new standard of care for first line treatment in advanced or unresectable biliary tract cancer and the NCCN guidelines have been appropriately updated to reflect this new development.

In addition to the positive trial of gemcitabine and cisplatin with durvalumab, the combination of immunotherapy and chemotherapy with cisplatin,

gemcitabine, and pembrolizumab was evaluated in the KEYNOTE-966 trial. This was a phase III randomized control trial comparing gemcitabine and cisplatin with gemcitabine, cisplatin, and pembrolizumab. Unlike in TOPAZ-1, in KEYNOTE-966 after completion of 8 cycles of gemcitabine, cisplatin, and pembrolizumab, both pembrolizumab and gemcitabine were continued until progression. In TOPAZ-1 durvalumab was continued as a monotherapy. This trial met the primary endpoint of improved OS. At a median follow up of 25.6 months, median OS was 12.7 months in the pembrolizumab group versus 10.9 months in the placebo group with a hazard ratio of 0.83, P=0.0200) (27). The results of this trial were recently reported in *The Lancet*, and gemcitabine, cisplatin, and pembrolizumab will likely be incorporated into the NCCN guidelines soon.

Although the above data is focused on success stories in hepatobiliary cancers, recently the guidelines may also shift to reflect other less promising outcomes. The combination of gemcitabine, cisplatin, and albumin-bound paclitaxel (GAP) in advanced or unresectable biliary tract cancers was studied in a phase II trial (28), with promising results including mPFS of 11.8 months, ORR of 45% and mOS of 19.2 months. Based on this preliminary data, the NCCN guidelines list the combination of gemcitabine, cisplatin and albumin-bound paclitaxel as a category 2B recommendation in the neoadjuvant setting and under "other recommended regimens" in the metastatic or unresectable setting. GAP was also recently evaluated in the SWOG 1815 study presented at GI ASCO 2023 (29). This was a phase III randomized control trial in patients with newly diagnosed advanced biliary tract cancer who were randomized to receive gemcitabine, cisplatin alone *vs.* GAP. The primary endpoint was OS. The results show that the addition of albumin-bound paclitaxel did not result in a statistically significant improvement in OS. In this study mOS with GAP was 14 versus 12.7 months with gemcitabine and cisplatin alone (HR =0.93, P=0.58). ORR was 34% with GAP *vs.* 25% with gemcitabine, cisplatin (P=0.11) and mPFS was 8.4 months with GAP versus 6.4 months (HR =0.92, P=0.47). The addition of albumin-bound paclitaxel led to significantly increased treatment related adverse effects as compared to gemcitabine, cisplatin alone. GAP showed great promise in the phase II trial, however, in the phase III trial the addition of albumin-bound paclitaxel led to more toxicity without clinical benefit. The phase III SWOG 1815 study is a cautionary reminder that it is essential to complete robust phase III trials to thoroughly assess novel combination regimens to ensure efficacy and patient safety. Given the results of this trial, it is likely that future updates to the NCCN guidelines will reclassify the role of the GAP regimen in biliary tract setting in the neoadjuvant setting and/or in the setting of advanced or unresectable disease.

The NCCN guidelines are a critical resource for oncologists around the world in the treatment of nearly all cancer types, providing the highest level of evidence and most up-to-date recommendations. In both HCC and biliary tract cancers the most recent version of the guidelines have been updated to reflect recent data showing the success of the STRIDE regimen, with efficacy demonstrated in the recent HIMALAYA study (2) and the addition of durvalumab to gemcitabine and cisplatin as studied in TOPAZ-1 (6). However, further research is needed, not only to expand upon the success of these trials with additional research into immunotherapy and combination treatments, but also to better identify predictive biomarkers. In addition, as new approvals roll out, further studies are needed to clarify optimal sequencing of treatments. The next frontier will be identifying which patients benefit the most from each treatment, which will allow truly personalized regimens, improving efficacy and minimizing side effects. In liver cancers, this is especially important, as oncologists must treat cancer in the setting of cirrhosis and baseline liver dysfunction. Looking forward to the next decade it is our hope that new treatment regimens will continue to transform the treatment landscape of hepatobiliary cancers offering further hope for patients and their families.

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