Editorial Commentary

Insights on liver-directed surgical innovations, targeted therapies, and immunotherapy for biliary tract cancer: navigating the new European Society for Medical Oncology (ESMO) Clinical Practice Guidelines

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Cancers of the bile duct, including gallbladder cancer, extrahepatic cholangiocarcinoma, hilar and intrahepatic cholangiocarcinoma, present a significant treatment challenge. Characterized by their notorious difficulty to diagnose or biopsy, intricate anatomical locations and diverse clinical presentations, these malignancies collectively contribute to a significant burden on global health. The epidemiology of bile duct cancers reveals worldwide variations in incidence, prevalence, and mortality rates, emphasizing the need for a nuanced understanding of each subtype and the local environmental etiologies. Challenges in early diagnosis further compound the complexity of managing these cancers, often leading to advanced stage at the time of detection and treatment delays. Surgery remains the cornerstone of curative-intent treatment of bile duct cancers, yet the rate of recurrence and metastases underscores the importance of comprehensive multidisciplinary therapeutic strategies. Pivotal randomized clinical trials have been performed; however, they have been challenged by the lack of active agents, a limited number of accrued patients, and a grouping of all patients together regardless of where in the biliary tract the tumor originates. This has resulted in variations in treatment strategies and multiple treatment options that range from immunotherapy to radiation to hepatic artery infusion therapy (more on this later). A greater understanding of the mutational landscape of biliary tract cancers has resulted in optimism around appropriately targeted agents and combination immunotherapies. Yet, many of these regimens await robust outcomes data, and it is questionable if they significantly move the needle forward to improve overall survival. Thus now, more than ever, there is a need for updated treatment guidelines.

There are two pitfalls to many of the available guidelines for this disease. First, most do not separate treatment strategies based on anatomical location, e.g., gallbladder, intrahepatic/hilar/extrahepatic cholangiocarcinoma, though we understand these to be different tumors with unique progression and metastatic patterns, and certainly with different surgical approaches. Second, most treatment algorithms do not take into account the etiology of the cancer, e.g., liver fluke, stone disease, autoimmune, underlying infection or hepatitis, etc., despite this likely playing a pivotal role in the biology of tumor formation. This problem is to no fault of their own as the limited data and trials do not stratify patients by these clinical features. Further, a more recent understanding of underlying patient factors like diabetes, obesity, and viral hepatitis is coming to light, however, they have not translated into targeted treatment strategies. Secondary to these limitations, and

increasing but limited clinical trials data, most of the current guidelines are recommendations based on collective expert opinion (1).

The ESMO guidelines begin with recommendations on work-up. The main level I evidence and grade A recommendation is to perform molecular analysis for patients eligible for systemic treatment, which is a significant advance. Though core biopsy for diagnostic pathology is recommended (III, A), there is not specific mention of what to do if tissue biopsies are inconclusive. It is important to note that these tumors are notorious for eluding diagnostic certainty (2), and thus remain an exception to the rule where treatment is sometimes necessary without tissue diagnosis. The difficulties in securing tissue confirmation are exacerbated by the limited accessibility of percutaneous or endoscopic ultrasound-guided biopsies for prospective transplant recipients with hilar cholangiocarcinoma, owing to the perceived risk, however minimal or theoretical, of seeding or carcinomatosis (3). Newer scopes and instruments have improved tissue yield compared to relying on brushings alone.

The ESMO guidelines follow with staging and risk assessment. All recommendations are based on level III evidence that includes appropriate cross-sectional imaging to evaluate diagnosis, stage, and resectability. Discussion then turns to management of localized disease and focuses on surgery to obtain an R0 margin and appropriate lymphadenectomy apropos to the location of the tumor. Surgical approach, e.g., minimally invasive compared to open, it is not addressed here. These are often very complex surgeries in challenging areas to access, thus most of the literature is based on open procedures. Needless to say, biology trumps technique, and for surgeries that can be done minimally invasively there is a future. Certainly, an ever-increasing number of gallbladder cancers are being addressed minimally invasively, and our recent review has concluded that robotic surgery for biliary tract cancer appears non-inferior to open surgery when compared to published contemporary data (4).

The caveat, of course, is that the current literature on the topic is limited, and future prospective/randomized studies are needed.

There is a IV, C recommendation to remove laparoscopic port sites during curative intent gallbladder cancer re-resection that is worth attention. When the role of port site resection for this disease over 17 years at Memorial Sloan Kettering Cancer Center was evaluated, it was determined that port site metastases were indeed associated with peritoneal disease and decreased survival, which makes sense. Nevertheless, removing the port sites was deemed disfiguring and showed no correlation with enhanced survival or reduced disease recurrence, leading to the conclusion that it is not mandatory in definitive surgical treatment (5). This reasoning and reference have remained part of the NCCN guidelines.

Adjuvant therapy recommendations include the use of capecitabine since the 2019 BILCAP trial (6). The trial is considered level II data here, but in the absence of any superior data is for all intents and purposes the standard of care for resected patients in the West. The guidelines then continue with recommendations for advanced and metastatic disease, recommending gem-cis-durva as the new first-line standard of care based on the recently reported TOPAZ-1 trial (7). It is exciting to have a new level I vetted treatment regimen for the first time in over a decade since the UK ABC-02 trial (8). It does remain to be elucidated though which patients are receiving the advantage of durvalumab. About 99% of the patients have microsatellite stable tumors and the addition of durvalumab to chemotherapy benefited patients regardless of PD-L1 expression levels. Further, the absolute difference in median overall survival gained with the addition of immunotherapy to gem-cis was 1.3 months. Certainly, this marks a positive stride; however, the quest for a true "David" to combat this disease is still ongoing. The incorporation of durvalumab indeed demonstrates a divergence in the overall survival Kaplan-Meier curve beyond the initial six months of treatment. This lends support to the notion that priming the immune system against biliary tract cancers is a plausible strategy. Undoubtedly, significant efforts are underway in adoptive cell transfer for this disease, although refinement is imperative before its integration into guideline-based care (9).

Clearly, there is newfound hope for bile duct tumors harboring targetable mutations, and the latest ESMO guidelines seamlessly integrate these findings into their recommendations. Notably, for IDH1 mutant tumors, constituting 1–13% of bile duct cancers, the observed approximately 5-month improvement in overall survival over placebo, post-correction for crossover, merits the consideration of ivosidenib (10). Furthermore, FGFR inhibitors have a discernible role in patients with FGFR2 fusion-positive cholangiocarcinoma, with reported overall response rates ranging from 20% to 40%. Although HER2/neu (ERBB2) mutated tumors constitute a minority, there is reported activity from HER2-directed agents. BRAF mutations are notably rare, meaning that while there are

available options for patients with V600E mutations, the affected population remains limited in number.

For patients with intrahepatic cholangiocarcinoma that are not candidates for liver resection, it is important to consider regional therapy, and specifically hepatic arterial infusion pump (HAIP) therapy. Three phase II trials employing HAIP showcased a response rate ranging from 39% to 56%, with up to a 43% 3-year overall survival. In comparison, the ABC trials reported a response rate of 21% with gem-cis (11-14). At ASCO-GI this year, the three center Dutch PUMP-2 phase II trial was presented (n=50) making it the largest HAIP trial to date in intrahepatic cholangiocarcinoma (15). The combination of HAIP and gem-cis supported prior studies with a 46% partial response rate and 3-year overall survival of 33% at 29-month median follow-up. While the ESMO guidelines provided a grade C recommendation for HAIP in liver-limited intrahepatic cholangiocarcinoma, the forthcoming publication of this trial will bolster the data, particularly in the absence of other significant clinical enhancements over gem-cis alone or a higher incidence of actionable mutations.

There are several organizations and medical societies that provide practice guidelines for the management of bile duct cancer [e.g., National Comprehensive Cancer Network (NCCN), ESMO, American Society of Clinical Oncology (ASCO), European Association for the Study of the Liver (EASL), Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS)]. These current ESMO guidelines provide a useful algorithm with associated levels of evidence and grade of recommendation, with the greatest added strength being inclusion of targeted therapies for actionable mutations. Future guidelines will undoubtably benefit from increased data in newer surgical techniques, HAIP, use of circulating tumor DNA, targeted biologics, and immunotherapies as we strive to make significant improvements over the traditional workhorses for this disease.

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