Editorial

Targeted therapies in cholangiocarcinoma: light at the end of the tunnel?

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Comment on: Munugala N, Maithel SK, Shroff RT. Novel biomarkers and the future of targeted therapies in cholangiocarcinoma: a narrative review. Hepatobiliary Surg Nutr 2022;11:253-66.

Keywords: Cholangiocarcinoma (CCA); targeted therapy; biomarkers

Submitted May 16, 2023. Accepted for publication Jun 23, 2023. Published online Jul 03, 2023.
doi: 10.21037/hbsn-23-255
View this article at: https://dx.doi.org/10.21037/hbsn-23-255

The genetic landscape of cholangiocarcinoma (CCA) remains largely unexplored. It is one of the deadliest cancers (1), with the gold standard treatment for all anatomical forms (intrahepatic—iCCA, perihilar—pCCA and distal—dCCA) being surgical resection (with adjuvant capecitabine also recommended in the newest guidelines) (2,3). The importance of genetic markers in terms of postoperative and oncological outcomes is being increasingly recognized, but few actionable mutations have been identified so far (2,4). This is particularly pertinent for patients with advanced/irresectable disease, who rely on systemic therapy. Survival outcomes are poor in these patients [5-year survival up to 10%—(5)] and they would profit the most from novel, targeted therapies.

In their narrative review, Munugala *et al.* deliver a thorough overview of biomarkers and targeted therapies, focusing on those with existing clinical trials, either completed or ongoing (4). As the authors state early in their article, there have been no major advances in the treatment of irresectable CCA since the establishment of combination gemcitabine-cisplatin in 2010 (4,6). Despite the high toxicity of this regimen, survival remains poor among patients receiving it, necessitating more effective treatments. The authors focus on the identification of clinically relevant genetic biomarkers as the next step, which will unlock the potential of targeted therapies for CCA. To this end, next generation sequencing (NGS) is presented as the key technology, which will enable broad genetic analysis and provide molecular insights. Indeed, the study by Jusakul *et al.* is provided as an example, where stratification of CCA in genomic clusters influenced survival outcomes more than traditional anatomical classification (7). The review then focuses on actionable mutations, such as *IDH1/IDH2* and *FGFR2*, and current available targeted therapies.

Ivosidenib is the only *IDH*-inhibitor described by the authors with tangible results in a phase III trial (4), which demonstrated significantly improved PFS, compared to placebo. Other *IDH*-inhibitors are being investigated in ongoing trials. As for *FGFR*-inhibitors, results are presented regarding Infigratinib, TAS-120 and Pemigatinib. The first showed promising results in a multi-centre phase II study, and is currently being evaluated against gem-cis in the PROOF phase III randomized controlled trial (4). Furthermore, TAS-120 is the subject of an ongoing phase II trial, with interim results from 67 patients showing a 37% overall response rate (ORR), without grade 4 treatment-related adverse events (4). Additionally, Pemigatinib is being investigated in the FIGHT-202 phase II trial, with interim results showing an ORR of 35% for patients with *FGFR2* translocations (4). A phase III trial is underway, including patients with unresectable or metastatic CCA with *FGFR2* rearrangements. For *KRAS*, *BRAF*, *BRCA* and *PARP*

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mutations, only results from early-phase and/or basket trials are outlined. Finally, various monoclonal antibodies have been tested against *Her-2*-overexpressing tumors, with poor results for Lapatinib and pending results from ongoing trials with various *Her-2*-positive tumor types, including CCA (4).

Regarding immunotherapies, the clinical trials described in the review have demonstrated poor results for Pembrolizumab so far, suggesting it is unsuitable as a monotherapy for CCA (4). Further studies with combined Atezolizumab plus Cobimetinib have shown some promise with PFS, but overall survival (OS) results are pending. Nivolumab has shown encouraging results in patients with PD-L1 positive tumors and is being investigated in an ongoing phase II study (4). As the authors point out, the efficacy of immunotherapy is hampered by the low rate of mismatch repair (MMR) deficiency in CCA, which has been reported as <1% (3).

The efforts of Munagala *et al.* are laudable, in painting a picture of the status quo regarding CCA biomarkers with tested targetable therapies. A possible critique would be the failure to mention differences in genomic profiles according to anatomical location. For example, *IDH* mutations have been reported in 10–30% of iCCA, but rarely in extrahepatic CCA (eCCA, 1–3%) (2). The opposite trend is observed in *HER2/3* mutations, which can be detected in up to 8% of iCCA and up to 15% of eCCA (2). Furthermore, there is no mention of *NTRK* fusions, which have been detected in about 4% of iCCA, and can be targeted with TRK inhibitors, such as Larotrectinib or Entrectinib (2,3). Admittedly, they are very rare in biliary tract cancers overall, occurring in <0.1% of cases (3).

The picture painted by the authors is relatively bleak, but accurately reflects the clinical reality when the review was written. Meanwhile, several reports such as from the TOPAZ-1 trial have been published, showing a significant benefit by adding the PD-L1 antibody durvalumab to standard chemotherapy (8). This emphasizes the dynamic development of the field and there is additional hope for the future, with novel emerging therapies and clinical trials being underway. Further evaluation of the efficacy of targeted therapies for current actionable mutations, as well as identification of further targets is faced with some challenges. Firstly, the rarity of CCA itself, compared to other malignancies (e.g., colorectal cancer), limits the available patient pool for studying this disease. Secondly, the pathophysiology and anatomical properties of perihilar and distal CCA make tissue procurement for genetic analysis more difficult. This is mentioned by Munugala *et al.* and reflected in the statistics they present regarding genomic profiles, which are based on intrahepatic CCA. Thirdly, individual mutations identified so far are rare within CCA cohorts, so that targeted therapies would only benefit a small number of patients, as things stand. However, advancements in genomic sequencing, such as NGS, may identify new biomarkers and combinations thereof, which may serve as targets for new therapeutic agents.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Hepatobiliary Surgery and Nutrition*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-255/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Amygdalos I, Neumann UP, Lang SA. Targeted therapies in cholangiocarcinoma: light at the end of the tunnel? HepatoBiliary Surg Nutr 2023;12(4):631-633. doi: 10.21037/hbsn-23-255