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Immunotherapy in the Treatment of Biliary Tract Cancer: The Future?

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Abstract

Biliary tract cancer is known for its dismal prognosis, both due to late diagnosis as well as to the short width span of therapeutic options available. Although much more common in Asian countries, the number of patients with these tumours has been rising in European and American countries, mainly due to the increased rates of chronic hepatic diseases. Currently the only curative treatment revolves around surgical resection, although only possible in roughly 10-15% of patients. First line systemic therapies include chemotherapy with gemcitabine and cisplatin, unfortunately with also poor results with a 5-year survival rate of only 10-20%. With this in mind, the need for other therapeutic options has been proved, with the rising popularity of immunotherapy leading to several studies analysing the use of immune checkpoint inhibitors in the treatment of patients with biliary tract cancer.

Keywords: Gemcitabine and Cisplatin; Cholangiopancreatography; Intrahepatic Cholangiocarcinoma; Extrahepatic Cholangiocarcinoma; Sclerosing Cholangitis; Hepatolithiasis; Gallbladder Polyps; Cirrhosis; Neoantigens

Abbreviations: BTC: Biliary Tract Cancer; CTLA-4: Cytotoxic T-Lymphocyte Associated Antigen 4; DOR: Duration Of Response; ERCP: Endoscopic Retrograde Cholangiopancreatography; EGFR: Epithelial Growth Factor Receptor; ICI: Immune Checkpoint Inhibitor; MCRP: Magnetic Resonance Imaging With Cholangiopancreatography; ORR: Overall Response Rate; OS: Overall Survival; PD-1: Programmed Death 1; PD-L1: Programmed Death Ligand 1; PFS: Progression Free Survival; PR: Partial Response; TIL: Tumour Infiltrating Lymphocytes; TME: Tumoural Microenvironment; VEGF: Vascular Endothelial Growth Factor

Introduction

Biliary tract cancers (BTC) are responsible for less than 1% of the malignant tumours [1], mostly occurring in men around 70 years of age. Despite being more commonly found in eastern countries [2], the incidence of BTC has been increasing worldwide due to better diagnostic options and the increased rates of chronic liver disease seen in western countries [1,3]. These tumours tend to have poor response to therapy if not diagnosed at early stages candidates to surgical approaches, with not many options following 1st line chemotherapy [4] and ultimately resulting in low survival rates [1,5]. With this knowledge, the need for new therapeutic options to offer to patients with BTC is of the utmost importance, with the advances in immunotherapy in other types of tumours giving BTC a new therapeutic approach [4,6].

Biliary Tract Cancer

BTCs are commonly divided based on their location regarding the liver, into intrahepatic cholangiocarcinoma

when originating from the biliary tract in the liver and extrahepatic cholangiocarcinoma when outside of the liver [1,6]. Currently the best diagnostic tool is magnetic resonance imaging with cholangiopancreatography (MRCP) followed by tissue analysis of biopsies collected via ERCP [1]. When it comes to risk factor typically associated with BTC, the most commonly found are primary sclerosing cholangitis, hepatolithiasis, gallbladder polyps, cirrhosis and hepatic viral infections [1]. BTC is a type of cancer with typically very poor outcomes with a 5-year survival rate of only 10-20% [6].

Current Therapies

When referring to early stage BTC, the first line therapy revolves around surgery that can be followed by chemotherapy +/- radiotherapy [5,7]. However, in locally advanced or metastatic disease therapeutic options fall on chemotherapy, target therapy and best supportive care [1,8]. Besides, only around 10-15% of patients with BTC are surgical candidates at presentation [2,7]. Systemic chemotherapy extends survival in BTC patients with a combination of cysplatin and gemcitabine the 1st line therapy [3,6,8]. Unlike many other tumours, there is no established 2nd line therapy when tumour progression is seen after 1st line therapy, but the use of fluoropyrimidine-based therapies is an option [1,7], such as FOLFOX scheme with a median OS of 6 months after progression with 1st line therapy [8]. After these two lines of therapy there are currently no other treatments approved for unselected patients [7]. Given the poor results seen with chemotherapy in the treatment of these patients, the need for targeted therapies is clear. Monoclonal antibodies targeting EGFR and VEGF have been studied with controversial results as in some studies showed benefit in the addition to chemotherapy and other none at all [8], highlighting even more the need for a better understanding of the BTC pathological pathways and of new therapeutic approaches [1].

Immunotherapy for BTC

Immunotherapy strategies in BTC included immune vaccinations, autologous cell transfers and immunomodulation with ICIs [8]. In fact, most BTC arise from chronic inflammatory states resulting in a high infiltration of immune cells such as Natural Killer cells and TILs like T CD4 and T CD8 cells, usually associated with better prognosis whereas high numbers of infiltrating macrophages tend to result in more advanced disease and worse response to chemotherapy and therefore poorer outcome [2,8]. The most studied ICIs are monoclonal antibodies against PD-1 and PD-L1, with several studies showing worse outcomes in tumours with high expression of PD-L1 and other immune checkpoints, highlighting the immune suppression associated with these markers that ultimately enabled tumour progression [8], while also being the fundamental reason for the rationale behind the use of ICIs. In the Keynote 028 trial, the use of the monoclonal antibody against PD-1 pembrolizumab was evaluated in the treatment in BTC, showing an ORR of 13%, mOS 5.7 months and mPFS of 1.8months [2,7]. On the other hand, there was one patient with a durable response of >50months, notably the one with established microsatellite instability [7]. However, in a larger study (Keynote 158) pembrolizumab use in these patients reported an ORR of only 5.8% [3,8]. In another study the use of another PD-1 blocker, nivolumab, was evaluated as a single agent vs combination treatment with cisplatin and gemcitabine in the treatment of BTC cancer. In the monotherapy cohort there were no complete responses and one PR in a patient with deficient mismatch repair. Nonetheless, in tumours with PD-L1 positive tumour cells the mOS was 11.6months vs 5.2months in PD-L1 negative cells.

In another study evaluating the use of nivolumab, median Os was 14.22 months with a durable response of more than one year [8]. Besides, the combination of nivolumab+gemcitabine+cisplatin showed promising results within 37% PR, mPFS of 4 months and mOS of 15 months [2,6,8]. The use of the anti-PD-L1 antibody durvalumab was also evaluated in the treatment of patients with BTC, both as a single agent and in combination treatment. In the monotherapy group there was a 5% PR and a mOS of 8.1months [6,8]. Furthermore, studies analysing the use of combination therapies have also been conducted, such as the combination of durvalumab and tremelimumab (an ICI targeting the CTLA-4 axis), showing 11% PR, 8.5months DOR and mOS of 10 months [7,8]. In addition, the use of the PD-1 blocker camrelizumab and gemcitabine+oxaliplatin has been evaluated in the treatment of patients with advanced BTC. In this study the 6 months PFS was 50% and mOS 11.8 months, with an ORR of 54% and a progressive disease in only 3% of patients [7]. Treatment related adverse events are also tolerable with grade 3-4 events reported in 13-17% of patients in the pembrolizumab studies, 13-20% in the nivolumab studies [8] and roughly 20% in durvalumab studies [6]. On the other hand, combination of immunotherapies results in an increased number of treatments related adverse events, with one death reported due to drug toxicity in the durvalumab + tremelimumab group [3].

The studies evaluating ICIs as monotherapies did not show promising results, emphasising the importance of combination therapies [3]. Some studies suggest beneficial responses when combining chemotherapy with ICIs, given the enhanced immune checkpoint expression and immune cell infiltration seen with the use of chemotherapy drugs due to the increased number of neoantigens formed by cell killing, therefore easing the use of ICIs [7,8].

Conclusion

BTC remains a tumour with very poor prognosis, both due to its intrinsic biological characteristics and to the late diagnosis, as well as less than optimal therapies available. In a setting with so few therapeutic options such as the one seen in BTC, the promising results seen in studies evaluating the use of ICIs in combination with other immunotherapies or chemotherapy schemes might be revolutionary. In addition, the use of ICIs in the treatment of BTC is tolerable and manageable and with a low adverse event rate. With the advances in the development of new therapeutic options arises the need for a better understanding of the biological pathways that underlie these tumours. Furthermore, there is an urge to identify which patient subtypes might respond better to ICIs, namely looking for biomarkers of response to these drugs. Besides, further studies evaluating the use of ICI in the treatment of BTC are needed. In addition, the study of combination therapy using ICIs and chemotherapy seems to be one of the possible routes when treating patients with BTC.

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