

Immunotherapy in Biliary Tract Cancer: Worthy of a Second Look

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Abstract

Although immune checkpoint inhibitors (ICIs) have revolutionized the treatment landscape of several malignancies, the role of immunotherapy in biliary tract cancer (BTC) is currently under investigation and ICIs are still looking for their niche in this setting. In this Editorial, we discuss recently published data regarding ICIs in BTC, with a particular focus in terms of selection of patients and biomarker-driven trials.

Keywords

biliary tract cancer, cholangiocarcinoma, immunotherapy, nivolumab, pd-1, pembrolizumab, liver cancer, intrahepatic cholangiocarcinoma

In the last decade, the development of immune checkpoint inhibitors (ICIs) blocking the interaction of programmed death receptor 1 (PD-1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) with their specific ligands has had an outstanding impact on medical oncology.¹ Programmed death ligand 1 (PD-L1) protein expression, mismatch repair deficiency (dMMR), tumor mutational burden (TMB) and instable microsatellite (MSI) phenotype have been suggested to be predictive biomarkers of response to immunotherapy, according to previous reports.² In brief, dMMR / MSI-high phenotypes have been associated with higher overall response rate (ORR) and progression-free survival (PFS) in patients treated with ICIs; similarly, better responses to immunotherapy have been highlighted in a number of solid tumors with higher TMB.³ Based on these data, the US FDA approved in 2017 the anti-PD-1 agent pembrolizumab for the treatment of any dMMR or MSI-high malignancies, regardless of histological type.⁴

Immunotherapy has certainly represented one of the big breakthroughs of the past few years, which changed the treatment landscape of a number of hematological and solid malignancies⁵; unfortunately, this is not the case of biliary tract cancer (BTC). On the basis of the success of ICIs in advanced melanoma and several other tumors, a question remains: immune-checkpoint inhibition could be an option in a recalcitrant cancer such as BTC?

Recent evidence suggests that approximately 3% of BTCs report a dMMR phenotype or high TMB.⁶ And to date, only a limited number of studies have been performed to assess efficacy of ICIs in BTC, with available clinical data mainly limited to sub-analyses of basket trials and small single-arm trials.⁷ Thus, immunotherapy is still looking for its niche in BTC.

The phase Ib Keynote-028 trial firstly evaluated the anti-PD-1 agent pembrolizumab in 24 PD-L1 positive BTC patients - 20 cholangiocarcinomas and 4 gallbladder cancers.⁸ Among these subjects, 4 patients (17%) achieved stable disease (SD) and 4 (17%) partial response (PR). Subsequently, pembrolizumab was tested in the Keynote-158 trial, which enrolled 104 BTC patients whose disease progressed on at least one prior treatment regimen.⁹ Considering the cut-off value of 1% in terms of PD-L1 expression, the 60% of patients were PD-L1 positive while no MSI-high malignancies were included in the study. In this trial, an extremely disappointing

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ORR of 5.8% was achieved in unselected patients, with median PFS and OS of 2.0 months and 7.4 months, respectively.⁹ Despite these not encouraging results, several trials are ongoing assessing the role of anti-CTLA-4, anti-PD-1 and anti-PD-L1 agents as monotherapy or in combination with other anticancer drugs (e.g. chemotherapy, targeted agents, etc.).

And some weeks ago, Kim *et al* published a multicenter, phase II trial where nivolumab was administered in 54 BTC patients experiencing progression while being treated with between one and 3 lines of systemic therapy.¹⁰ According to the results of this study, 22% of patients receiving nivolumab achieved objective response and the disease control rate was 59%. Data regarding PD-L1 expression status were available for 42 patients, with 18% showing PD-L1 \geq 1% of tumor cells; interestingly, PD-L1 positive patients achieved a statistically significant prolonged PFS compared to PD-L1 negative tumors (mPFS 10.4 months versus 2.3 respectively, HR = 0.23, $p < 0.001$) while no statistically significant differences were detected in terms of OS (mOS not reached versus 10.8 months, $p = 0.19$).¹⁰ However, some issues deserve discussion.

Interestingly, all BTCs that responded to nivolumab treatment were not MSI-high, according to the results of this study; thus, since aberrations in DNA damage repair (DDR) genes have been reported in approximately 30% of BTCs (excluding MMR genes)^{11,12} and recent evidence suggested that homologous recombination deficiency (HRD) could be associated to high TMB and response to ICIs,¹³ it would be interesting to know how many patients with mutations in DDR genes achieved a response to nivolumab. Moreover, 10 (18.5%) out of 54 BTCs were locally advanced, non-metastatic tumors, something which could have represented a not insignificant source of bias in terms of patient selection.

Nonetheless, on the basis of the results of this trial, a role for immunotherapy in BTC cannot be excluded and more studies are warranted to explore ICIs as a novel therapeutic option in advanced disease. In fact, the key to success in this complex and aggressive group of malignancies could be to find a reliable biomarker helping clinicians in predicting response to ICI monotherapy or combination strategies.

Despite to date ICI monotherapy has shown limited efficacy in BTC, the meaningful and durable responses to ICIs in MMR-deficient and MSI-high malignancies including biliary cancers suggest that testing patients for MMR, MSI, TMB and PD-L1 expression is warranted.¹⁴ Considering the current therapeutic scenario and the grim prognosis of metastatic BTC, the option to treat this subset of patients which most likely could benefit from ICIs seems reasonable after failure of front-line chemotherapy. Probably, rather than using a limited, single biomarker, the usefulness of MMR, MSI, TMB and PD-L1 should be evaluated in concert. A wide number of clinical trials are currently underway and could help to understand how biomarkers and combination therapies could improve treatment selection for BTC patients, providing

effective measures that might soon modify the natural history of this aggressive, challenging entity.

Authors' Note

Our study did not require an ethical board approval because it did not contain human or animal trials.


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