Commentary

Anti–PD-1 Therapy for Patients with Advanced Cholangiocarcinoma: Ready for Prime Time?

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Biliary tract cancers (BTCs) comprise a heterogeneous population of tumors, including intrahepatic and extrahepatic cholangiocarcinoma and gallbladder cancer. The development of chronic hepatic inflammation, leading to fibrosis and cirrhosis associated with BTCs, is linked to viral hepatitis, cholelithiasis, primary sclerosis cholangitis, and obesity as leading risk factors in the United States, although in most patients, risk factors remain unknown. Most patients are diagnosed with advanced-stage disease, and the prognosis is poor, with approximately 15% surviving 2 years. In the advanced setting, the ABC-02 trial was a landmark study that showed a survival benefit of 11.7 months with gemcitabine and cisplatin, compared to gemcitabine monotherapy (hazard ratio [HR] 0.64; 95% CI, 0.52–0.80; $p < 0.001$), establishing gemcitabine/cisplatin as first-line therapy for metastatic BTC.[1] More recently, the TOPAZ-1 and KEYNOTE-966 studies reported a modest improvement in survival with the addition of immunotherapy to chemotherapy.[2,3] The recently published SWOG 1815 trial failed to show improvement in survivalfavoring a triplet chemotherapy regimen.[4] For patients whose disease progresses despite first-line treatment and who do not have targetable alterations (e.g., HER2, IDH1, FGFR2, *BRAF* V600E, MSI-H), second-line options are limited, providing minimal benefit, and there is no established third-line option (Table 1).[5–7] Therefore, there remains an unmet need to improve treatment and outcomes in patients with advanced BTC.

In this issue of the *Journal of Immunotherapy and Precision Oncology*, Naing and colleagues[8] present their data on the safety and early efficacy of toripalimab in patients with cholangiocarcinoma. Toripalimab, an anti–programmed cell death-1 (anti–PD-1) inhibitor, was investigated in a heavily pretreated patient population with advanced or recurrent/unresectable BTC. Most of these patients (69%) had intrahepatic cholangiocarcinoma, and 31% had extrahepatic cholangiocarcinoma, including one patient with ampullary and three patients with gallbladder cancers. Patients received toripalimab infusion at a dose of 240 mg as a single agent every 3 weeks until unacceptable toxicity or disease progression. Forty-two patients were enrolled, and no prior anti–PD-1, anti–programmed cell death ligand-1 (anti–PD-L1), or anti–programmed cell death ligand-2 (anti–PD-L2) treatment was allowed. Approximately 40% of patients had 5–10 prior lines of therapy. Most patients were female (66.7%). The most common treatment-emergent adverse effects (TEAEs) included fatigue (47.6%), abdominal pain (40.5%), decreased appetite (33.3%), constipation (31%), increased transaminase levels (31%), nausea (23.8%), and increased bilirubin levels (21.4%). TEAEs leading to discontinuation or interruption of toripalimab therapy occurred in 4.8% and 14.3% of patients, respectively. Three patients developed grade 5 adverse events, including respiratory failure, biliary tract infection, and cerebrovascular accident. The authors concluded that toripalimab was well tolerated and showed antitumor activity as a single agent in patients with heavily pretreated BTCs.

With a median follow-up time of 4.4 months, the objective response rate (ORR) was 4.8% (95% CI, 0.58–16.16), the disease control rate (DCR) was 40.5% (95% CI, 25.63–56.72), and median progression-free survival (mPFS) was 2.1 months (95% CI, 1.91–3.88). There was no significant difference in response based on PD-L1 status. Median overall survival was not reported.

With the approval of immunotherapy in combination with chemotherapy in treatment-naïve patients with BTC,[9] the role of toripalimab in second-line therapy is questionable. This study excluded patients with previous prior exposure to anti–PD-1/PD-L1, and response rates were low as a single agent. In fact, in a similar patient population with refractory disease, patients receiving the anti–PD-1 antibody nivolumab achieved a higher investigator-assessed ORR of 22% with an mPFS of 3.68 months (95% CI, 2.3–5.7) and median overall survival (mOS) of

Table 1. Current therapies for advanced biliary tract cancers

Therapy	ORR, %	mPFS, mo	mOS, mo	Any-Grade TRAE, %	Grade 3–5 TRAE, %
Gemcitabine/cisplatin[1]	26.1	8	11.7		70.7
GC + durvalumab[2]	26.7	7.2	12.8	92.9	62.7
GC + pembrolizumab[3]	29	6.5	12.7	93	72
GC + nab-paclitaxel[4]	31	7.5	14		71
FOLFOX[5]	5	4	6.2	84	38
5FU/LV + nal-IRI (Asia)[7]	14.8	7.1	8.6		
5FU/LV + nal-IRI (Europe)[6]	14	2.6	6.9	53[a]	
Toripalimab[8]	4.8	2.1	—	64.3	21.4

[a]A total of 293 TRAEs were reported in 48 patients.
FOLFOX: 5-fluorouracil/leucovorin and oxaliplatin; 5FU/LV: 5-fluorouracil/leucovorin; GC: gemcitabine and cisplatin; mOS: median overall survival; mPFS: median progression-free survival; nal-IRI: nanoliposomal irinotecan; ORR: overall response rate; TRAE: treatment-related adverse event.

14.2 months (95% CI, 5.98–NR [not reached]).[10] Results from KEYNOTE-028 also found that the anti–PD-1 antibody pembrolizumab achieved an ORR of 17% in pretreated BTCs.[11] Taken together, these studies suggest that single-agent immunotherapy has limited activity in refractory BTCs, even when immune checkpoint inhibitor (ICI)–naïve. The relationship between chronic inflammation and immune modulation is likely a driver in the pathogenesis of BTC, and combination strategies with chemotherapy may provide more favorable outcomes, as highlighted by TOPAZ-1 and KEYNOTE-966.[2,3]

This study evaluated patients by PD-L1 status and included 45.2% of patients who tested positive for PD-L1 and 28.6% who tested negative (26.2% missing). Patients with PD-L1–positive tumors had a higher ORR of 5.3% and DCR of 36.8%. No responses were observed in patients who were negative for PD-L1 expression. Although an interesting finding, previous studies have shown that PD-L1 positivity is usually low in BTCs, and responses to treatment were achieved regardless of PD-L1 status.[2,3] There have been previous attempts to identify additional predictive biomarkers including viral status, tumor mutational burden, and driver mutations; however, no specific biomarker of response has been reliably identified.

Toripalimab has been evaluated in combination with several agents, with improved response rates, suggesting a synergistic benefit of immunotherapy. For example, there is an ongoing phase III study evaluating toripalimab plus lenvatinib in combination with chemotherapy. Early results are promising, with an ORR of 80%, mPFS of 10.2 months, and an impressive mOS of 22.5 months.[12] Based on the available data, a combination approach will likely yield better outcomes than single-agent immunotherapy, given the interplay of BTCs and their tumor microenvironment.

In summary, patients with advanced-stage BTCs have an unmet need for additional therapies to improve survival outcomes. The phase I open-label study by Naing et al[8] provides valuable insight into the safety and early efficacy of the anti–PD-1 inhibitor toripalimab as monotherapy in patients with advanced-stage BTC whose disease had progressed despite first-line chemotherapy. Although toripalimab was well tolerated, its effectiveness as a single agent was modest. However, early data exploring combination strategies seem promising. Future directions include investigating new biomarkers that may predict response to therapy and exploring novel combination strategies on how toripalimab can be optimally integrated into the treatment landscape of patients with advanced BTC.

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