Editorial Commentary

Immune checkpoint inhibitors in combination with chemotherapy for patients with biliary tract cancer: what did we learn from TOPAZ-1 and KEYNOTE-966

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Biliary malignancies are rare but fatal diseases with rising incidence worldwide. Patients often present with unresectable or metastatic disease; even when presenting early, the disease has a high recurrence rate with overall poor prognosis (1).

Gemcitabine and cisplatin combination has been established as the standard of care for metastatic disease for more than two decades since the completion of the ABC-02 trial. The trial randomized 401 patients with locally advanced or metastatic disease to receive either gemcitabine alone or in combination with cisplatin. Patients who received the combination had a better overall survival (OS) (11.7 months in the combination arm *vs.* 8.1 months in the single agent gemcitabine arm, P<0.001) compared to those who received gemcitabine alone (2). Since then, several combinations failed to improve the outcome in metastatic biliary cancer. Finding more effective treatment has been challenging especially with the rarity and heterogeneity of the disease, and the poor liver function at presentation.

Recently two large randomized trials evaluated the addition of immune checkpoint inhibitors (ICI) to standard chemotherapy in patients with advanced biliary cancer: In the TOPAZ-1 trial, 685 patients with advanced biliary cancer were randomized to receive gemcitabine and cisplatin with durvalumab, a programmed death cell ligand 1 (PD-L1) inhibitor, or placebo, followed by maintenance durvalumab in the intervention arm. The trial showed statistically significant improvement in OS favoring the addition of durvalumab (12.8 *vs.* 11.5 months, hazard ratio, 0.80; 95% CI: 0.66 to 0.97; P=0.021). An improvement in progression-free survival (PFS) and objective response rate (ORR) was noted as well. Toxicities were similar between the two arms (3).

More recently, the addition of another programmed cell death protein 1 (PD-1) targeted agent, pembrolizumab, to gemcitabine and cisplatin was evaluated in another phase III double blind-placebo control trial: KEYNOTE-966.

A total of 1,069 newly diagnosed biliary cancer patients were randomized to receive either pembrolizumab or placebo in combination with chemotherapy for a total of 8 cycles or best response followed by maintenance gemcitabine plus either placebo or pembrolizumab. At median follow-up of 26 months, the addition of pembrolizumab led to a statistically significant improvement in OS (12.7 *vs.* 10.9 months, hazard ratio =0.83, P=0.0034) and PFS (6.5 *vs.* 5.6 months, P=0.023). Response rate was similar in both arms but with higher duration of response in the intervention arm. Survival benefits were seen across all biliary cancer subgroups, including intra/extra hepatic

cholangiocarcinoma (4). Adding pembrolizumab did not significantly increase toxicity compared to placebo. Health-related quality of life (HRQoL) was maintained with the addition of pembrolizumab (5).

In both trials, the incidences of significant adverse events were similar between the two treatment groups; of interest, In the TOPAZ-1 trial, the rate of immune-mediated adverse events was 12.7% with durvalumab and 4.7% with placebo. Grade 3 or 4 immune-mediated adverse events occurred in 2.4% of patients in the durvalumab group and 1.5% in the placebo group. In the KEYNOTE-966 study, immune-mediated adverse events of any grade occurred in 22% of the experimental arm versus 13% of the control arm. Grade 3 and 4 immune-related adverse event occurred in 7% and 4% respectively.

Both, the TOPAZ-1 and KEYNOTE-966 trials confirm the modest role of adding immune check point inhibition to chemotherapy in the treatment of unresectable and metastatic biliary tumors making it a new standard of care. Benefits were seen irrespective of age, sex, geographic region, tumor location or PD-L1 combined positive score (CPS).

Looking closer, KEYNOTE-966 differs from TOPAZ-1 in that it allowed continuing Gemcitabine alone or in combination with PD-1 inhibitor after eight cycles, so patients were exposed to chemotherapy longer, while in the TOPAZ-1 trial, patients were continued on durvalumab alone in the intervention arm. There were also small differences in the subgroup of patients enrolled in both trials; in the KEYNOTE-966, a larger percentage of patients had intrahepatic bile duct cancers compared with the incidence of the disease in the general population (60%), leading to underrepresentation of patients with extrahepatic and gall bladder tumors. KEYNOTE-966 might be more representative of the global biliary cancer population due in part to the fact that 55% of the cohort were enrolled outside of Asia (versus 45% in TOPAZ-1) and that KEYNOTE-966 required a fresh biopsy that is more feasible in intrahepatic tumors. In KEYNOTE-966, the survival benefits were more pronounced in the patients with intrahepatic tumor, which could be related in part to higher comorbidities in these patients related to biliary obstruction, however, in TOPAZ-1 the benefit was seen in intra- and extrahepatic tumors. Nevertheless, both studies showed modest significant survival benefit of ICIs and similar toxicity profiles.

The lack of predictive biomarkers of therapeutic benefit to ICIs continues to be a real challenge in oncology in general. Given the modest efficacy and the increased financial burden associated with adding immune check point inhibitors to standard treatment, it is important to identify patients who are more likely to respond to treatment. Promising data is emerging on the role of tumor microenvironment, gut microbiome, tumor-infiltrating lymphocytes, neutrophil-lymphocyte ratio and even HLA-I genotypes, however, none has been incorporated in clinical practice as of yet.

Biomarkers known to predict response to ICIs include, among other, CPS score, microsatellite stability (MSI) and possibly tumor mutational burden (TMB). In both trials, benefits of ICIs were seen regardless of PD-1 expression. Evaluating MSI or TMB as predictive markers in the above trials was not feasible as microsatellite instability is rare in biliary cancer (1.5% of patients in the TOPAZ-1 trial) and tumor mutation burden status was not reported in KEYNOTE-966.

With the emergence of new treatment options in the second line including targeting Her-2, and fibroblast growth factor receptors (FGFRs) to name a few; the future question is how to choose and combine all these agents in the first- and second-line treatment. Further studies on the benefit of continuing treatment beyond progression or optimal treatment strategy after resistance to ICI are also needed. Data on the use of ICI in the adjuvant setting are still lacking.

In conclusion, TOPAZ-1 and KEYNOTE-966 are the first phase 3 studies to evaluate first-line chemotherapy/immunotherapy combination in patients with advanced biliary tract cancer. The results showed a modest, yet statistically significant, improvement in OS without increase in toxicity. The addition of immunotherapy to chemotherapy represents a new standard of care first-line treatment for patients with advanced biliary tract cancer. Identifying predictive biomarkers of response is the next step to improved outcome in this disease. Further trials are needed to investigate the possible role of immunotherapy in the adjuvant setting as well.

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