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Updated role of chemotherapy and immunotherapy in biliary tract cancer

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Lecture : Biliary tract cancer (BTC) has immunogenic features. Immune checkpoint inhibitors are being tested in BTC. Monotherapies of these immune checkpoint inhibitors have shown modest efficacy in general in BTC. The combination of dual immune checkpoint inhibitors, combination with cytotoxic chemotherapy, combination with antiangiogenic agents, combination with multi-target TKIs are being tested.
Now, we have the first success of immunotherapy in biliary tract cancer in TOPAZ-1 study (NCT03875235). TOPAZ-1 is the multicenter, double-blind, placebo-controlled, global phase III study. Patients previously untreated for unresectable locally advanced, recurrent, or metastatic BTC were randomized 1:1 to receive durvalumab (1500 mg every 3 weeks [Q3W]) or placebo + GemCis (Gem 1000 mg/m2 and Cis 25 mg/m2 on Days 1 and 8 Q3W) for up to 8 cycles, followed by durvalumab (1500 mg Q4W) or placebo until disease progression or unacceptable toxicity. The primary objective was to assess overall survival (OS). Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and safety. A total of 685 patients were randomized to durvalumab + GemCis (n = 341) or placebo + GemCis (n = 344). The primary objective was met: durvalumab + GemCis significantly improved OS vs placebo + GemCis (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.66–0.97; p = 0.021). PFS was also significantly improved with durvalumab vs placebo (HR, 0.75; 95% CI, 0.64–0.89; p = 0.001). ORR was 26.7% with durvalumab and 18.7% with placebo. Adverse events profile showed very similar frequency between 2 arms. Grade 3/4 treatment-related adverse events (TRAEs) occurred in 62.7% of patients receiving durvalumab and 64.9% of patients receiving placebo. NCCN guideline adopted Durvalumab+GemCis as preferred regimen, category 1, as 1st-line treatment. Globally, multiple regulatory authorities including US FDA, S. Korea have approved durvalumab in BTC. Based on this first success of immunotherapy in BTC, many studies using diverse immunotherapies will be anticipated.
In case of targeted therapies, FGFR inhibitors and IDH1 inhibitor have shown efficacy in FGFR fusion (+) patients, and IDH1 mutation (+) patients, respectively. From the tissue-agnostic approach, NTRK fusion is also proven-target in biliary tract cancer, too.

Keywords: biliary tract cancer, immunotherapy, TOPAZ-1

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