Editorial

Exploring treatment options for biliary tract cancers: moving beyond the era of gemcitabine and platinum doublet

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Biliary tract cancers (BTCs) refer to invasive adenocarcinomas arising from the bile duct (intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma) and gallbladder (gallbladder cancer). Patients with BTCs typically present at an advanced stage due to a lack of early detection methods and non-specific symptoms; systemic chemotherapy is the cornerstone of treatment for these advanced BTCs. Gemcitabine plus cisplatin (GC) has been the standard treatment since the pivotal ABC-02 randomized phase 3 trial conducted in 2010 (1). Moving beyond the era of GC, several triplet combination regimens have been proposed in recent years (*Table 1*). The combination of nab-paclitaxel (nab-P) and GC showed promising survival outcomes in a phase 2 trial (2), although it eventually failed to meet the primary endpoint of overall survival (OS) in a randomized phase 3 trial (3). Around the same time, TOPAZ-1 (5) demonstrated that the programmed death ligand 1 (PD-L1) inhibitor durvalumab combined with GC significantly improved the median OS [11.5 *vs.* 12.8 months; hazard ratio (HR), 0.80; 95% confidence interval (CI): 0.66–0.97; P=0.021] and median progression-free survival (PFS) (5.7 *vs.* 7.2 months; HR, 0.75; 95% CI: 0.63–0.89; P=0.001), with an objective response rate (ORR) of 26.7%. Moreover, KEYNOTE-966 (6) found that the addition of programmed death-1 (PD-1) inhibitor pembrolizumab also improved median OS (10.9 *vs.* 12.7 months; HR, 0.83; 95% CI: 0.72–0.95; P=0.0034), whereas the median PFS only showed numerical improvements (5.6 *vs.* 6.5 months; HR, 0.86; 95% CI: 0.75–1.00; P=0.023), with an ORR of 29%. Consequently, the combination of PD-1/PD-L1 inhibitors and GC has become the new standard of care for first-line treatment of patients with BTCs, establishing the new era of triplet combinations.

Recently, Zhang *et al*. demonstrated the efficacy of nab-P plus tegafur gimeracil oteracil potassium capsule (S-1) as a first-line treatment for advanced BTCs (7). The doublet nab-P and S-1 is a novel combination that excludes gemcitabine and platinum, which are traditionally the most active agents used against BTCs. S-1 emerged from a Japanese randomized phase 3 trial (FUGA-BT) (8) that revealed the non-inferiority of gemcitabine plus S-1 to GC for treating advanced BTCs in the first-line setting. As for nab-P, it is combined with gemcitabine in the standard frontline regimen for pancreatic cancer, and this combination has been shown to have favorable outcomes in patients with cholangiocarcinoma (9).

In this single-arm phase 2 trial by Zhang *et al*., the primary endpoint was ORR, with the goal of improving ORR from 26% to 40% compared with the conventional GC regimen (1). While this novel combination offered a new treatment option for cisplatin-ineligible patients, the ORR was found to be 27.5%, and therefore the primary

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Table 1 Recent phase II/III trials for first-line systemic chemotherapy in advanced BTCs

Study	Trial setting	Prior systemic treatment	Primary endpoint	BTC subtypes	Study population	ORR (%)	DCR (%)	PFS (m), median	OS (m), median	Trial number
ABC-02 (1) (*NEJM* 2010)	Phase 3 (n=410)	Treatment-naïve	OS	CCA (57.8%); GBC (36.9%); AoV cancer (5.3%)	Gem monotherapy (n=206)	15.50	71.80	5.0	8.1	NCT00262769
					Gem/Cis (n=204)	26.10	81.40	8.0	11.7	
								P<0.001	P<0.001	
Shroff RT *et al.* (2) (*JAMA Oncol* 2019)	Phase 2, single-arm (n=60)	Treatment-naïve: locally advance, 22%; metastatic, 78%	PFS	iCCA (63%); eCCA (15%); GBC (22%)	Gem/Cis/Nab-P (n=60)	45	84	11.8	19.2	NCT02392637
SWOG 1815 (3) (*J Clin Oncol* 2023)	Phase 3 (n=441)	Treatment-naïve: locally advance, 27%; metastatic, 73%	OS	iCCA (67%); eCCA (17%); GBC (16%)	Gem/Cis (n=147)	22	69	6.4	12.7	NCT03768414
					Gem/Cis/Nab-P (n=294)	31	77	8.2	14.0	
								P=0.47	P=0.58	
Oh DY *et al.* (4) (*Lancet Gastroenterol Hepatol* 2022)	Phase 2 (n=124)	Treatment-naïve	ORR	iCCA (53%); eCCA (11%); GBC (24%); AoV cancer (11%)	Gem/Cis → Gem/Cis/Durva/Trem (n=30)	50	97	12.8	15.0	NCT03046862
					Gem/Cis/Durva (n=47)	72	100	11.8	20.2	
					Gem/Cis/Durva/Trem (n=47)	70	98	12.3	18.7	
TOPAZ-1 (5) (*NEJM Evid* 2022)	Phase 3 (n=685)	Treatment-naïve: locally advance, 11.1%; metastatic, 88.9%	OS	iCCA (55.7%); eCCA (19.4%); GBC (24.9%)	Gem/Cis (n=344)	18.70	82.60	5.7	11.5	NCT03875235
					Gem/Cis/Durva (n=341)	26.70	85.30	7.2	12.8	
								P=0.001	P=0.021	
KEYNOTE-966 (6) (*Lancet* 2023)	Phase 3 (n=1,069)	Treatment-naïve	OS	iCCA (60%); eCCA (18%); GBC (22%)	Gem/Cis (n=536)	29	76	5.6	10.9	NCT04003636
					Gem/Cis/Pembro (n=533)	29	75	6.5	12.7	
								P=0.023	P=0.0034	
Zhang W, *et al.* (7) (*HBSN* 2023)	Phase 2, single-arm (n=54)	Treatment-naïve	ORR	iCCA (64.8%); eCCA (11.1%); GBC (24.1%)	Nab-P/S-1 (n=54)	27.50	70.60	6.0	13.2	NCT03830606

BTCs, biliary tract cancers; n, number; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; CCA, cholangiocarcinoma; GBC, gallbladder cancer; AoV, ampulla of Vater; iCCA, intrahepatic cholangiocarcinoma; eCCA, extrahepatic cholangiocarcinoma; Gem, gemcitabine; Cis, cisplatin; Nab-P, nano albumin bound-paclitaxel; Durva, durvalumab; Trem, tremelimumab; Pembro, pembrolizumab; DCR, disease control rate; m, months; S-1, tegafur gimeracil oteracil potassium capsule.

endpoint was not met. The median PFS was 6.0 months (95% CI: 4.2–7.7), and the median OS was 13.2 months (95% CI: 10.3–16.0). When considering primary sites, median PFS was 4.5 months (95% CI: 2.1–6.8) in gallbladder cancer and 6.0 months (95% CI: 3.9–8.0) in cholangiocarcinoma. Thus, the survival outcomes with this combination of nab-P and S-1 were comparable with the traditional GC doublet combination; however, BTC treatment is now shifting to triple combination therapies. Moreover, given that the promising phase 2 results of GC plus nab-P (2) and GC plus durvalumab (4) tended to be diminished in the larger and more heterogeneous population of phase 3 trials (3,5), the survival outcomes of nab-P and S-1 demonstrated in this phase 2 trial are unlikely to meet the expectations of frontline treatments in the era of triple combinations. To establish a new frontline standard of care, median OS needs to exceed 13–14 months and ORR needs to be greater than 30–40% to surpass the survival outcomes of the current

triplet regimen, based on the results of representative BTC trials (*Table 1*). In addition, the opportunity for long-term survival that immune checkpoint inhibitors can offer to a fraction of patients cannot be discounted.

The following factors need to be addressed for the combination of nab-P and S-1 to be recognized as a new standard treatment for BTCs. First, as the authors also noted, assessing the efficacy of a PD-1/PD-L1 inhibitor in combination with the current doublet combination is an interesting avenue for future research. As nab-P does not require pretreatment with corticosteroids, the combination of nab-P and a PD-1/PD-L1 inhibitor has been studied in other solid tumors such as breast cancer (10) and non-small cell lung cancer (11), with promising efficacy and favorable safety. Thus, PD-1/PD-L1 inhibitors are anticipated to have additive or synergistic effects in advanced BTCs. Second, the continuation of nab-P dosing was tolerable in a previous study (9); therefore, uncapping the number of nab-P doses may be considered (a maximum of 6 were allowed in the Zhang *et al.* study), which may ultimately enhance the synergistic effects of nab-P and S-1. Third, considering the comparability of nab-P plus S-1 with GC and the toxicities of platinum, further studies including patients who are expected to achieve more favorable outcomes from the nab-P plus S-1 combination than GC, especially those who are not candidates for PD-1/PD-L1 inhibitors, would be intriguing.

In summary, this study by Zhang *et al.* should be commended for establishing a platinum-free regimen that was comparable with GC, thereby allowing patients who are cisplatin-ineligible to receive treatment for BTCs. However, to supplant the standard treatment for BTC, which has recently been advancing, improving treatment efficacy (e.g., via the addition of PD-1/PD-L1 inhibitors) is necessary.

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Footnote

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