Editorial Commentary

Is modified FOLFIRINOX a standard regimen for 2nd line chemotherapy for pancreatic cancer after gemcitabine plus nab-paclitaxel failure?—insights from the MPACA-3 trial

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Pancreatic cancer is one of the most common cancers globally and is expected to become the second leading cause of cancer-related deaths in the United States by 2030 (1). For unresectable pancreatic cancer, the prognosis remains poor after standard chemotherapy. In a large Phase 3 trial of metastatic pancreatic cancer, when administered as first-line chemotherapy, gemcitabine plus nab-paclitaxel (GnP) showed 8.5 months of median overall survival (OS) and FOLFIRINOX (FFX) showed 11.1 months of OS (2,3). Currently, both regimens are administered as standard first-line chemotherapy for advanced pancreatic cancer (APC). Among APC patients with germline *BRCA* mutations, induction FFX followed by olaparib maintenance is the standard regimen (4).

For the longest time, there was no standard second-line chemotherapy for APC refractory to first-line chemotherapy. Several clinical trials of second-line chemotherapy were conducted when gemcitabine monotherapy was the standard first-line chemotherapy for APC (*Table 1*). In the CONKO-003 trial, the oxaliplatin, folinic acid, and 5-fluorouracil (5-FU; OFF) regimen showed significantly prolonged OS compared to the 5-FU/leucovorin (LV) regimen (median OS: 5.9 versus 3.3 months, P=0.01) (7). However, chemotherapy, except for OFF, failed to show efficacy as second-line therapy, including FOLFOX (5-11,14). As a result, it was not possible to conclude that a regimen containing oxaliplatin was the standard treatment after the failure of gemcitabine-based regimen. In the NAPOLI-1 trial, nano-liposomal irinotecan (nal-IRI)/5-FU/LV showed significantly prolonged OS compared with 5-FU/LV alone (median OS: 6.2 *vs.* 4.2 months; P=0.039), and it became the standard second-line regimen (12).

In the NAPOLI-1 trial, 45% of patients received gemcitabine alone and 55% received gemcitabine-based regimen as prior chemotherapy (12). However, none of the patients received GnP therapy as the first-line treatment in the NAPOLI-1 trial. There are no reports of clinical trials verifying the usefulness of nal-IRI/5-FU/LV after refractory or intolerant GnP therapy. In regard to real world data, Kieler *et al.* reported efficacy and safety of nal-IRI/5-FU/LV after gemcitabine based therapy (15). In this study, 77% of patients received GnP prior to the administration of nal-IRI/5-FU/LV. The median progression-free survival (PFS) of patients who received nal-IRI/5-FU/LV as second-line treatment after gemcitabine-based chemotherapy was 4.49 months. It was significantly better than oxaliplatin plus fluoropyrimidines (PFS: 3.44 months, P=0.007) in a matched cohort. Another retrospective study involving most (approximately 95%) patients who received GnP as pretreatment showed that nal-IRI/5-FU/LV had similar efficacy as the NAPOLI-1 trial (15-17).

On the other hand, sequential use of FFX and GnP is one of the most important strategies for APC in the real world. Matsumoto *et al.* and Sawada *et al.* performed retrospective studies on the efficacy and safety of FFX or modified FFX

Table 1 Randomized studies on second-line chemotherapy for pancreatic cancer

Study	Prior therapy	Regimen	n	Prior GnP	RR	P	PFS (months)	HR, P value	OS (months)	HR, P value
Pelzer *et al.* (2011) (5)	GEM	BSC	23	0%	NE		NE		2.3	HR: 0.45, P=0.008
Phase 3	GEM	OFF	23	0%	NE		NE		4.8	
Ioka *et al.* (2017) (6)	GEM	S-1	60	0%	6.0%	0.03	1.9	HR: 0.77, P=0.18	5.8	HR: 0.75, P=0.13
Phase 2	GEM	S-1 + IRI	67	0%	18.3%		3.5		6.8	
Oettle *et al.* (2014) (7)	GEM	FF	84	0%	NE		2	HR: 0.68, P=0.019	3.3	HR: 0.66, P=0.01
CONKO-03 Phase 3	GEM	OFF	76	0%	NE		2.9		5.9	
Gill *et al.* (2016) (8)	GEM	5-FU/LV	54	0%	8.5%	0.361	2.8	HR: 1.00 P=0.99	10	HR: 1.78, P=0.024
Phase 3	GEM	mFOLFOX6	54	0%	13.2%		3.1		6.1	
Ohkawa *et al.* (2015) (9)	GEM	S-1	135	0%	11.5%	0.04	2.8	HR: 0.84 P=0.18	6.9	HR: 1.03, P=0.82
Phase 2	GEM	SOX	136	0%	20.9%		3		7.4	
Ioka *et al.* (2019) (10)	GEM based	S-1	290	0%	11.5%	0.127	2.8	HR: 0.80, P=0.009	7.9	HR: 0.98, P=0.756
Phase 3	GEM based	S-1/LV	296	0%	20.6%		3.9		7.6	
Hurwitz *et al.* (2015) (11)	GEM	Cape	63	0%	1.0%	0.017	1.5	HR: 0.75 P=0.14	4.3	HR: 0.79, P=0.25
Phase 2	GEM	Cape + ruxolitinib	64	0%	7.8%		1.7		4.5	
Wang-Gillam *et al.* (2016) (12)	GEM based	FU + FA	119	0%	1.0%	<0.0001	1.5	HR: 0.56, P=0.0001	4.2	HR: 0.67 P=0.012
NAPOLI-1 Phase 3	GEM based	nal-IRI/FU/LV	117	0%	16.0%		3.1		6.1	
Go *et al.* (2021) (13)	GEM based	S-1	41	59%	2.0%	0.04	2.2	HR: 0.40, P<0.001	4.9	HR: 0.40, P=0.002
MPACA-3 Phase 3	GEM based	mFFX	39	56%	15.0%		5.2		9.2	

GEM, gemcitabine; nabP, nab-paclitaxel; BSC, best supportive care; OFF, oxaliplatin, folinic acid and fluorouracil; IRI, irinotecan; FF, folinic acid and fluorouracil; LV, leucovorin; cape, capecitabine; nal-IRI, nanoliposomal irinotecan; FU, fluorouracil; FA, folinic acid; FFX, FOLFIRINOX; mFFX, modified FOLFIRINOX; NE, not evaluated; RR, response rate; PFS, progression free survival; OS, overall survival; GnP, gemcitabine plus nab-paclitaxel.

(mFFX) as second-line therapy following GnP (18,19). Matsumoto *et al.* reported a response rate (RR) of 23%, disease control rate (DCR) of 68%, PFS of 5.3 months, and OS of 12.1 months. There was no significant difference between the administration of FFX and mFFX (18). Sawada *et al.* reported an RR of 10.6%, DCR of 56.7%, PFS of 3.9 months, and OS of 7.0 months (19). mFFX has been shown to be effective and favorable in Phase 2 trials of second-line therapy in those who received gemcitabine-based regimens, and it is considered to be one of the standards of care as second-line treatment after GnP refractory or failure (20). Currently, the fluoropyrimidine-based regimen, nal-IRI/5-FU/LV, and mFFX may be therapeutic options after GnP therapy, based on a retrospective study (21). Only one retrospective observational study reported that second-line nal-IRI/5-FU/LV and FOLFIRINOX showed similar effectiveness after progression following first-line gemcitabine-based therapy (20). However, there have been no randomized Phase 3 studies of APC after GnP refractory or failure.

S-1 is an oral fluoropyrimidine agent that consists of tegafur, 5-chloro-2,4-dihydropyrimidine, and potassium oxonate. S-1 is mainly used in East Asia as a second-line chemotherapy for advanced pancreatic cancer that is resistant or intolerant to gemcitabine and has been subjected to several clinical trials (9,14). S-1 is a fluoropyrimidine drug and is considered one of the current standards of care for second-line treatment after GnP refractory. Therefore, a Phase 3 study (MPACA-3) was conducted (13).

MPACA-3 was the first randomized Phase 3 study of mFFX versus S-1 as second-line chemotherapy in gemcitabine-failed APC patients. Almost 60% of patients received GnP therapy as first-line chemotherapy, and the primary endpoint was OS. Although this was a randomized

controlled Phase 3 study, the total number of registered patients was 80, which was extremely small. In this study, the independent Data Safety Monitoring Board (DSMB) led to the premature discontinuation of patient recruitment because of the following: significant differences in the efficacy between the two arms and the expectation of poor patient accrual. In this study, a statistically significant improvement was observed in the mFFX group as compared to those who were administered S-1, such as RR (15% *vs.* 2%; P=0.04), DCR (67% *vs.* 37%, P=0.007), PFS (5.2 *vs.* 2.2 m, P<0.001) and OS (9.2 *vs.* 5.4 m, P=0.002). In addition, there were no significant differences between the groups in regard to health-related quality of life (HRQoL) based on the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) questionnaire.

The MPACA-3 trial was the first Phase 3 trial for second-line cancer treatment comprising first-line GnP-refractory cases. This study showed that Grade 3/4 adverse events were significantly higher in the mFFX group (56% *vs.* 17%, P<0.001). mFFX showed promising effects compared to S-1; although, it was more toxic than S-1, it did not worsen the patient's quality of life. Therefore, mFFX can be considered an option for the treatment of GnP-refractory APC. However, as indicated by the independent DSMB of MPACA-3, nal-IRI/5-FU/LV has become one of the standard therapies for GnP-refractory APC after it was approved. No study has compared the efficacy and safety of nal-IRI/5-FU/LV and mFFX for patients with GnP-refractory APC; therefore, there is no conclusion as to which regimen is more effective.

In conclusion, although the study was discontinued prematurely, mFFX showed potential efficacy against GnP-refractory APC in a randomized Phase 3 study when compared with S-1. However, nal-IRI/5-FU/LV also showed a significant improvement in OS compared with fluoropyrimidine monotherapy. Both nal-IRI/5-FU/LV and mFFX are currently considered as the standard of care for GnP-refractory APC, and a prospective randomized trial comparing the two regimens is needed in the future.

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