Investigating the "Real-World" Clinical Impact of Treatment Sequencing in Advanced Pancreatic Cancer Outcomes: a PURPLE Translational Registry Analysis

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Introduction

- Pancreatic ductal adenocarcinoma (PDAC) is the fourth most common cause of cancer-related deaths in Australia, with a dismal median overall survival (OS) of less than 12 months for advanced disease.(1)
- Gemcitabine monotherapy is an option for advanced PDAC in patients with poorer performance status or significant comorbidity profile but combination regimens with significant toxicities are now standard-of-care given superior survival outcomes (**Figure. 1.**).(2)
- First-line chemotherapy combinations have not been compared in head-to-head trials in advanced PDAC.
- Data on optimum treatment sequencing is lacking.

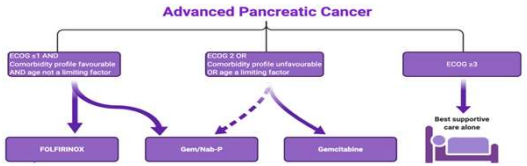
Aims

- To assess whether first-then-second-line treatment sequence wither either FOLFIRINOX or Gem/Nab-P as first-line palliative chemotherapy impacts survival outcomes.

Methodology

- Data was extracted and analysed from the multi-institutional PURPLE (Pancreatic cancer - Understanding Routine Practice and Lifting End results) registry for consecutive patients with locally-advanced, recurrent, or metastatic PDAC, who received palliative chemotherapy between 2016 and May 2020.
- Patients were excluded if they had palliative radiotherapy or had incomplete treatment data preventing survival calculations or treatment group assignment.
- Clinicopathological characteristics were compared using the Chi-square method or Mann-Whitney U test as appropriate for patients treated with first-line FOLFIRINOX and Gem/Nab-P.
- Survival estimates were calculated using the Kaplan-Meier method with log rank tests for survival comparisons. Cox proportional hazards regression was used to obtain hazard ratios.

Figure 1. First-line standard-of-care palliative treatment options for advanced pancreatic cancer according to European, American, and National Comprehensive Cancer Network guidelines with adaptation from Lambert et al.(2)



ECOG = Eastern Cooperative Oncology Group performance status, which is a scale from 0 to 5 of increasing disability, 0 being no disability, 5 being dead. **FOLFIRINOX** = folinic acid, 5-fluorouracil, irinotecan, oxaliplatin. **Gem/Nab-P** = Gemcitabine plus Nab-Paclitaxel.

Table 1. Comparison of clinico-pathological characteristics of first-line palliative Gem/Nab-P- versus FOLFIRINOX-treated patients.

Clinico-pathological characteristic	Gem/Nab-P (n=376)	FOLFIRINOX (n=73)	P value
Age at diagnosis, median years (IQR)	67 (60-83)	59 (54-65)	<0.001*
Male sex n (%)	198 (52.7)	44 (60.3)	0.47
ECOG performance status at first presentation n (%)			0.17
≤1	336 (89.4)	72 (98.6)	(0.01)
2	31 (8.2)	1 (1.4)	(0.04)
3	7 (1.9)	0	
4	1 (0.3)	0	
Obstructive jaundice at first presentation n (%)	96 (25.5)	17 (23.3)	0.69
Charlson Comorbidity Index score at first presentation n (%)			0.002
0	210 (55.9)	56 (76.7)	(0.001)
1	96 (25.5)	15 (20.5)	
≥2	69 (18.4)	2 (2.7)	(0.001)
Primary pancreatic tumour location n (%)			0.90
Unknown	14 (3.7)	3 (4.1)	
Body	80 (21.3)	14 (19.2)	
Head	209 (55.6)	40 (54.8)	
Tail	70 (18.6)	16 (21.9)	
Whole organ	3 (0.8)	0	
Stage at first presentation n (%)			0.77
Resectable	58 (15.4)	9 (12.3)	
Locally-advanced/borderline-resectable	109 (29.0)	23 (31.5)	
Metastatic	209 (55.6)	41 (56.2)	
Number of metastatic sites at onset of advanced disease n (%)			0.97
0	113 (30.1)	24 (32.9)	
1	154 (41.0)	29 (39.7)	
2	81 (21.5)	15 (20.5)	
≥3	28 (7.4)	5 (6.8)	
Metastatic site at onset of advanced disease n (%)			
Liver	188 (50.0)	33 (45.2)	0.45
Lung	59 (15.7)	11 (15.1)	0.89
Peritoneum or malignant ascites	39 (10.4)	7 (9.6)	0.84
Bone	7 (1.9)	2 (2.7)	0.62
Lymph nodes	70 (18.6)	11 (15.1)	0.47
Other	12 (3.2)	5 (6.8)	0.13
Prior treatment n (%)			
Neoadjuvant chemotherapy	17 (4.5)	2 (2.7)	0.49
Surgical resection of primary tumour	47 (12.5)	10 (13.7)	0.78
Adjuvant chemotherapy	45 (12.0)	9 (12.3)	0.93
Biliary stent	111 (29.5)	23 (31.5)	0.73
1st-line palliative treatment duration, median months (IQR)	4.0 (2.2-5.9)	3.2 (1.7-5.9)	0.30*
Received 2nd-line chemotherapy n (%)	140 (37.2)	32 (43.8)	0.29
Received 3rd-line chemotherapy n (%)	43 (11.4)	8 (11.0)	0.91

Results

Figure 2a. Impact of first-line palliative chemotherapy regimen on overall survival (OS) in advanced pancreatic cancer

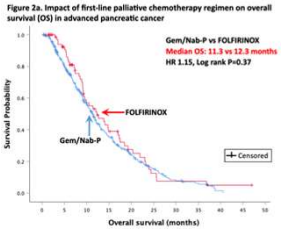


Figure 2b. Impact of first-line palliative chemotherapy regimen on progression-free survival (PFS) in advanced pancreatic cancer

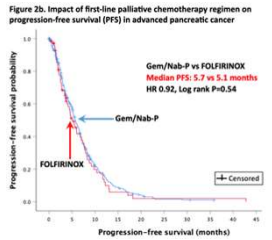


Figure 3a. Impact of treatment sequence on overall survival (OS) in advanced pancreatic cancer

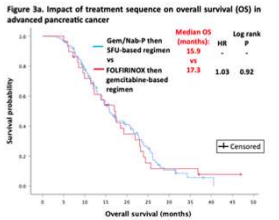
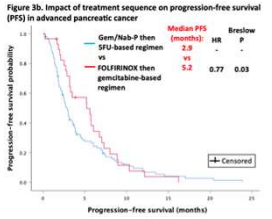


Figure 3b. Impact of treatment sequence on progression-free survival (PFS) in advanced pancreatic cancer



- We identified 615 patients who received palliative chemotherapy and no radiotherapy, including 197 (32%) with locally-advanced disease, 98 (16%) with post-resection recurrence, and 320 (52%) with de novo metastatic disease.
- Patients receiving first-line Gem/Nab-P (n=376) were older (median 67 vs 59 years, P<0.001), had a higher Charlson Comorbidity Index (P=0.002), and poorer performance status (ECOG≤1, P=0.01; ECOG 2, P=0.04) compared to the FOLFIRINOX (n=73) group (**Table 1.**).
- Second-line therapy included Gem/Nab-P (n=19), Gem/Capecitabine (n=4), Gem/Cisplatin (n=1) and gemcitabine alone (n=5) in 29 patients receiving first-line FOLFIRINOX (SEQ1); and FOLFIRINOX (n=14), FOLFIRI (n=48), FOLFOX (n=34), experimental 5-fluorouracil (5FU) combination (n=2), and 5FU alone (n=3) in 101 patients receiving first-line Gem/Nab-P (SEQ2).
- **Efficacy of first-line treatment options**: Median overall survival (OS) (12.3 vs 11.3 months P=0.37; **Figure 2a.**), progression-free survival (PFS) (5.7 vs 5.1 months P=0.54; **Figure 2b.**), and RECIST objective response rates (21.8% vs 20.5% P=0.98) were not significantly different with FOLFIRINOX (n=73) vs Gem/Nab-P (n=376), respectively, but better outcomes were observed with both regimens compared to gemcitabine alone (n=75, median OS 7.3 months, P=0.03 for FOLFIRINOX and P=0.04 for Gem/Nab-P).
- **Efficacy of first-then-second line treatment sequences**: Median OS did not differ significantly between Gem/Nab-P then 5FU-based (n=101) and FOLFIRINOX then gemcitabine-based (n=29) treatment sequences (15.9 vs 17.3 months P=0.91, respectively; **Figure 3a.**); however, median PFS was significantly longer with the latter sequence (2.9 vs 5.2 months P=0.03, respectively; **Figure 3b.**)
- Locally-advanced PDAC patients treated with
- Gem/Nab-P then 5FU-based sequences had significantly longer median OS than those receiving FOLFIRINOX then gemcitabine-based sequences (22.5 vs 13.8 months P=0.01, respectively).
- The converse association for PFS was observed in metastatic PDAC patients, in whom FOLFIRINOX then gemcitabine-based sequences were superior to Gem/Nab-P then 5FU-based sequences (median PFS 5.6 vs 2.3 months, P=0.03).

Conclusions

- There was no significant difference in OS between first-then-second-line treatment sequences with either FOLFIRINOX or Gem/Nab-P as the first-line regimen, despite patients receiving FOLFIRINOX being younger, and having better performance status and less comorbidity.
- Differences observed between locally-advanced disease and metastatic PDAC require further exploration.
- Head-to-head randomised clinical trials are needed to make firm conclusions regarding the optimal initial treatment and sequence of regimens for each patient subset.

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