

Pancreatic cancer

OPTIONS FOR SECOND-LINE TREATMENT

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TRIAL SUMMARY: Clinical practice in British Columbia

Tsang ES, Wong H, Wang Y, et al. Outcomes and characteristics of patients receiving second-line therapy for advanced pancreatic cancer. Canadian Association of Medical Oncology Annual Meeting. April 26, 2018, Toronto. Abstract 05.

There are limited randomized controlled trials available to guide the selection of second-line chemotherapy in advanced pancreatic cancer (APC). This study sought to identify patient and prior treatment characteristics that might help predict outcomes of second-line chemotherapy in this context. Records were reviewed for patients with APC who received ≥ 1 cycle of first-line chemotherapy between January 1, 2012, and December 31, 2015, across 6 centres in British Columbia. Baseline characteristics and survival outcomes were summarized.

Results: Of 676 APC patients, 31% had locally advanced APC and 69% had metastatic pancreatic cancer; 164 (24%) received second-line chemotherapy. Patients who received second-line chemotherapy were younger (median 63.7 years vs 67.4 years; $p=0.01$), had a lower Eastern Collaborative Oncology Group (ECOG) performance status (77% ECOG 0–1 vs 51%; $p<0.001$) and higher carbohydrate antigen 19-9 (median 1034 vs 829; $p=0.01$), compared to patients who received only first-line chemotherapy. There were no differences in rates of second-line chemotherapy between patients with locally advanced and metastatic disease (28% vs 23%; $p=0.18$). On logistic regression, only first-line FOLFIRINOX (5-FU, oxaliplatin, irinotecan, leucovorin; odds ratio [OR] 5.90; $p<0.001$) was associated

with second-line chemotherapy. Median duration of second-line chemotherapy was 3 cycles (range 1–30).

Median overall survival (OS) from diagnosis was 16 months. Median OS from start of second-line chemotherapy was longest with second-line gemcitabine/nab-paclitaxel (GEMABR) compared to fluoropyrimidine (FP) or gemcitabine alone (GEM) (7.9 vs 5.1 vs 4.3 months; $p=0.008$). On multivariate analysis, longer OS after initiation of second-line chemotherapy was associated with GEMABR (vs. single agent; hazard ratio [HR]=0.49), lower ECOG (Eastern Cooperative Oncology Group) performance status (HR=0.67), locally advanced disease (HR=0.58), and lower carbohydrate antigen (HR=0.38).

In this population-based cohort, patients treated with second-line chemotherapy were younger, with better ECOG performance status, and similar rates of locally advanced and metastatic pancreatic cancer. First-line FOLFIRINOX was the strongest predictor of receiving second-line chemotherapy, and GEMABR was associated with superior OS after initiation of second-line chemotherapy.

TABLE 1. Regimens used in patients who received second-line chemotherapy (n=164)

	First-line chemotherapy	Second-line chemotherapy
FOLFIRINOX*	109 (67%)	4 (2%)
Gemcitabine (GEM)	31 (19%)	74 (45%)
Gemcitabine/nab-paclitaxel (GEMABR)	23 (14%)	33 (20%)
Fluoropyrimidine (FP)	1 (0.6%)	44 (27%)
Other	0	9 (6%)

*5-FU, oxaliplatin, irinotecan, leucovorin


COMMENTARY: In Canada, pancreatic ductal adenocarcinoma is the 12th leading diagnosis of cancer and 4th leading cause of cancer death.¹ The median 5-year survival rate for pancreatic ductal adenocarcinoma is 7%.¹ By 2030, in the US, it is predicted that pancreatic cancer will become the 2nd leading cause of death.² Approximately 80%–85% of patients present at an advanced stage, when surgical intervention is not an option.³ The last 10 years have seen advances in first-line systemic treatment for metastatic and advanced pancreatic cancer. Two phase 3 trials using multi-agent chemotherapy such as FOLFIRINOX and GEMABR demonstrated better OS when compared to single-agent gemcitabine.^{4,5} The choice of first-line treatment for metastatic disease should be based on the patient’s performance

status, comorbidity profile and goals of care.⁶

There are limited data on second-line treatment, especially in the setting of first-line combination chemotherapy such as FOLFIRINOX and GEMABR. Previous second-line studies such as CONKO-003⁶ and NAPOLI⁷ examined second-line treatments following first-line single-agent gemcitabine and may not apply to most clinical situations.⁸ American Society for Clinical Oncology (ASCO) guidelines recommend GEMABR or single-agent gemcitabine as second-line management after combination first-line treatment with FOLFIRINOX.⁸ After first-line treatment with GEMABR, ASCO recommends either FOLFIRINOX, or other 5-FU base regimens, or single-agent 5-FU.⁸ ASCO recommendations are based on low-quality evidence.⁶ ASCO also

recommends that decision-making in the second-line setting be based on the patient's performance status, goals of care and comorbidities.⁶

Tsang et al's study provides information about clinical practice in a Canadian setting. It showed that FOLFIRINOX as first-line treatment was a strong predictor for receiving second-line treatment. The most common second-line treatment given was single-agent gemcitabine (45%), followed by combination GEMABR (20%). This may be reflective of provincial funding options at the time of the study. Then, as today, only single-agent gemcitabine is funded following first-line FOLFIRINOX in British Columbia (and Ontario).^{9,10} Some patients may have been able to access second-line GEMABR through private health insurance.

Single-agent gemcitabine as second-line treatment may have been chosen due to toxicity from previous treatment, specifically peripheral neuropathy induced by oxaliplatin. It is unclear from this study what portion of patients did not receive second-line combination treatment due to peripheral neuropathy or other toxicities. This retrospective study found that second-line GEMABR was associated with longer OS. Future prospective studies are needed to evaluate the benefits of GEMABR following FOLFIRINOX compared to single-agent gemcitabine. There are currently several clinical trials underway on second-line treatment following first-line combination chemotherapy for metastatic and advanced pancreatic cancer. These will help guide clinical management and direct funding decisions provincially. In the meantime, the present study contributes invaluable information about clinical practice in the era of combination first-line systemic treatment. Future studies will be necessary to help improve patient outcomes and prolong survival in this devastating disease. 

gastrointestinal#Advanced. Accessed May 4, 2018.

10. Cancer Care Ontario. Drug Formulary: GEMCNPAC(W) - Provider Monograph Available at: <https://www.cancercareontario.ca/en/drugformulary/regimens/46791>. Accessed May 4, 2018.

References

1. Canadian Cancer Statistics 2017. Toronto, ON: Canadian Cancer Society; 2017. Available at: cancer.ca/Canadian-CancerStatistics-2017-EN.pdf. Accessed May 1.
2. Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res* 2014;74(11):2913–21.
3. Allen PJ, Kuk D, Castillo CF, et al. Multi-institutional Validation Study of the American Joint Commission on Cancer (8th Edition). Changes for T and N staging in patients with pancreatic adenocarcinoma. *Ann Surg* 2017;265(1):185.
4. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011;364:1817–1825.
5. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nabpaclitaxel plus gemcitabine. *N Engl J Med* 2013;369:1691–170.
6. Oettle H, Riess H, Stieler JM, et al. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. *J Clin Oncol* 2014; 32(23):2423–9.
7. Wang-Gillam A, Li CP, Bodoky G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomized, open-label, phase 3 trial. *Lancet* 2016;387(10018):545–57.
8. Sohal DPS, Mangu PB, Khorana AA, et al. Metastatic pancreatic cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2016;34:2784–2796.
9. BCCancer. *Gastrointestinal Chemotherapy Protocol*. Available at: <http://www.bccancer.bc.ca/health-professionals/clinical-resources/chemotherapy-protocols/>