Editorial

Determinants of gemcitabine response in pancreatic cancer: are we there?

Orla M. Fitzpatrick[1], Grainne M. O'Kane[1,2]

[1]Department of Medical Oncology, Trinity St. James's Cancer Institute, Dublin, Ireland; [2]Princess Margaret Cancer Centre, Toronto, Canada

Correspondence to: Grainne M. O'Kane, MB, BCh, BAO, MRCPI, MD. Department of Medical Oncology, Trinity St. James's Cancer Institute, James Street, Dublin 8, Dublin, Ireland; Princess Margaret Cancer Centre, Toronto, Canada. Email: gokane@stjames.ie.

Comment on: Piquemal D, Bruno R, Bournet B, *et al.* Performance of a blood-based RNA signature for gemcitabine-based treatment in metastatic pancreatic adenocarcinoma. J Gastrointest Oncol 2023;14:997-1007.

Keywords: Pancreatic cancer; gemcitabine; biomarker; RNA

Submitted Aug 28, 2023. Accepted for publication Sep 08, 2023. Published online Sep 22, 2023.
doi: 10.21037/jgo-2023-04
View this article at: https://dx.doi.org/10.21037/jgo-2023-04

Pancreatic ductal adenocarcinoma (PDAC) is one of the most common causes of cancer mortality in developed countries, but despite its rising prevalence, the prognosis has remained largely static over the past two decades (1). Genomic efforts in PDAC have led to a deep understanding of the mutational and structural landscape, dominated by oncogenic mutations in KRAS mutations in 90% of patients. The latter has been considered undruggable until recently. Renewed efforts have led to several trials evaluating KRAS mutant allele-specific inhibitors, together with pan-RAS inhibitors and vaccine strategies. Nevertheless, resistance to these agents is likely to develop and chemotherapy will ultimately continue to have a role in PDAC management, underscoring the need to identify biomarkers.

The NAPOLI-3 trial has demonstrated superiority of NALIRIFOX over Gemcitabine and nab-Paclitaxel (GnP) (2), representing the first positive trial in PDAC in over 12 years. Disappointingly, however, survival remains less than 1 year, and many physicians will continue to use modified FOLFIRINOX given the substantial differences in cost and the similar survival achieved.

Biomarkers for the aforementioned regimens are lacking aside from germline or somatic alterations in BRCA1/2 or PALB2 (3,4). This is important given concerns regarding the addition of experimental agents to the triplet regimen of mFOLFIRINOX which has meant a reliance on GnP as a backbone (5).

Given a largely immunosuppressive tumour microenvironment and the heterogeneity associated with PDAC, efforts have focussed on tumour subtypes and dissecting the stromal and immune compartments for a more informed approach to trial design (6). Liquid biopsy has seen exponential growth in recent years in other malignancies, and its non-invasive approach has been utilised to identify targetable mutations, provide prognostic information including the identification of minimal residual disease. The ease of acquisition longitudinally can also identify resistance mechanisms while on therapy (7).

Piquemal *et al.* first published on their blood-based RNA signatures for gemcitabine response in advanced PDAC in 2020 (8). Using qualitative real-time PCR to identify 62 genes of interest, prognostic signatures were identified for both overall survival (OS) and progression-free survival (PFS). This information was used to create a unique nine-gene based score (8). This blood-based RNA signature known as the GemciTest, appears to identify those most likely to benefit from a gemcitabine-based treatment (8,9).

In this issue, authors provide clinical validation of the GemciTest in 336 patients with samples acquired prior to the initiation of chemotherapy in treatment-naïve patients (9). The chemotherapy regimens were either gemcitabine-based or fluoropyrimidine-based, specifically gemcitabine monotherapy, GnP, FOLFIRINOX or FOLFOX. The physiological roles of each of the selected genes have previously been described and include the ATP Binding Cassette Subfamily C Member 1 (ABCC1) which is linked

to chemotherapy resistance, due to efflux of treatment from the cells induced by the expression of membrane drug transporters (10). ADP Ribosylation Factor Like GTPase 4C (ARL4C) expression is associated with cell proliferation, drug resistance, and pancreatic stellate cell activation, which further enhance cancer stem cell properties (11). LYN Proto-Oncogene, Src Family Tyrosine Kinase (LYN) and NME/NM23 Nucleoside Diphosphate Kinase 4 (NME4) which contribute to cell proliferation and migration. The remainder of genes examined in this panel included Peptidylprolyl Isomerase B (PPIB), Ubiquitin Conjugating Enzyme E2 H (UBE2H), Aldolase, Fructose-Bisphosphate A (ALDOA), GRB2 Associated Binding Protein 3 (GAB3), and transporters like Solute Carrier Family 35 Member E2B (SLC35E2B).

Piquemal *et al.* have shown that use of their GE test can identify patients with advanced PDAC who may have a clinical response, defined as PFS ≥3.5 months and OS >8.7 months. Patients with advanced PDAC treated with a gemcitabine-based protocol, with a positive GemciTest had both a longer PFS (5.3 *vs.* 2.8 months) and OS (10.4 *vs.* 4.8 months) compared to those with a negative GemciTest. This study has also shown that patients with a positive GemciTest treated with a gemcitabine-based regimen had a similar median PFS (5.6 months for 5FU-based patients *vs.* 5.3 months for gemcitabine-based ones) and OS (10.1 *vs.* 10.4 months) to patients treated with a 5FU-based regimen.

The model developed here is based on prospective observational studies, and is currently awaiting validation from a randomised phase III trial: GEMFOX 233, comparing FOLFOX versus gemcitabine monotherapy in patients unsuitable for FOLFIRINOX (NCT04167007). This may provide additional information on this test, especially if patients who are considered GemciTest positive have similar outcomes on single-agent gemcitabine compared to FOLFOX.

In this regard, the GemciTest is not the first tool developed to assess response to Gemcitabine. The "GemPred" signature, derived from FFPE tissue, was developed to identify patients who would respond to Gemcitabine in the adjuvant setting, and has been validated to predict both OS and PFS (12,13). Notably in a retrospective analysis of PRODIGE-24, patients considered GemPred positive and treated with single-agent gemcitabine had very similar OS to those receiving modified FOLFIRINOX. If validated in prospective studies these gemcitabine signatures may be very powerful in eliminating the toxicity seen with the triplet regimen.

Human equilibrative nucleoside transporter 1 (hENT1) was investigated as a predictive marker of objective response rates and OS in patients receiving GnP in pancreatic cancer (12,13). In a retrospective analysis of the ESPAC-3 trial, hENT1 low patients, using immunohistochemistry, did not derive benefit from adjuvant gemcitabine (14). The COMPASS trial evaluated RNAseq expression data in treatment naïve patients with advanced pancreatic cancer and found hENT1 expression to predictive for GnP (15). Further validation and assessment of these biomarkers, accounting for variation in expression throughout the tumour microenvironment, will provide further answers in determining chemotherapy resistance (16). Each of these studies assessing prognostic and predictive biomarkers, with multi-omic approaches contribute toward better understanding of pathological processes and accelerate the implementation of precision oncology. In this regard the PASS-01 trial (NCT04469556) randomizing patients to mFOLFIRINOX *vs.* GnP with in depth correlative analyses may provide a further platform for biomarkers.

Novel therapeutics in PDAC are desperately needed, Piquemal *et al.* (9) have provided a potential new tool to identify patients with advanced PDAC to predict outcomes with gemcitabine-based protocols and its validation is eagerly awaited.

Acknowledgments

Funding: Dr. Grainne M. O'Kane was funded by the Irish Cancer Society as part of the Irish Cancer Society Trinity St James Cancer Institute Strategic Partnership through the Research Grant (No. TSJCI22OKA).

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Gastrointestinal Oncology*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-2023-04/coif). GMO has received Honoraria/Consulting fees from AstraZeneca, Roche, Servier, MSD, Incyte and Eisai. She has received grant funding from Roche. OMF has no conflicts of interest to report.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. O'Kane GM, Ladak F, Gallinger S. Advances in the management of pancreatic ductal adenocarcinoma. CMAJ 2021;193:E844-51.
2. Wainberg ZA, Melisi D, Macarulla T, et al. NAPOLI-3: A randomized, open-label phase 3 study of liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin (NALIRIFOX) versus nab-paclitaxel + gemcitabine in treatment-naïve patients with metastatic pancreatic ductal adenocarcinoma (mPDAC). J Clin Oncol 2023;41:LBA661.
3. Reiss KA, Mick R, O'Hara MH, et al. Phase II Study of Maintenance Rucaparib in Patients With Platinum-Sensitive Advanced Pancreatic Cancer and a Pathogenic Germline or Somatic Variant in BRCA1, BRCA2, or PALB2. J Clin Oncol 2021;39:2497-505.
4. Golan T, Hammel P, Reni M, et al. Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. N Engl J Med 2019;381:317-27.
5. Ramanathan RK, McDonough SL, Philip PA, et al. Phase IB/II Randomized Study of FOLFIRINOX Plus Pegylated Recombinant Human Hyaluronidase Versus FOLFIRINOX Alone in Patients With Metastatic Pancreatic Adenocarcinoma: SWOG S1313. J Clin Oncol 2019;37:1062-9.
6. Ho WJ, Jaffee EM, Zheng L. The tumour microenvironment in pancreatic cancer - clinical challenges and opportunities. Nat Rev Clin Oncol 2020;17:527-40.
7. Lone SN, Nisar S, Masoodi T, et al. Liquid biopsy: a step closer to transform diagnosis, prognosis and future of cancer treatments. Mol Cancer 2022;21:79.
8. Piquemal D, Noguier F, Pierrat F, et al. Predictive Values of Blood-Based RNA Signatures for the Gemcitabine Response in Advanced Pancreatic Cancer. Cancers (Basel) 2020;12:3204.
9. Piquemal D, Bruno R, Bournet B, et al. Performance of a blood-based RNA signature for gemcitabine-based treatment in metastatic pancreatic adenocarcinoma. J Gastrointest Oncol 2023;14:997-1007.
10. Adamska A, Falasca M. ATP-binding cassette transporters in progression and clinical outcome of pancreatic cancer: What is the way forward? World J Gastroenterol 2018;24:3222-38.
11. Chen X, Zhang Y, Qian W, et al. Arl4c promotes the growth and drug resistance of pancreatic cancer by regulating tumor-stromal interactions. iScience 2021;24:103400.
12. Nicolle R, Gayet O, Duconseil P, et al. A transcriptomic signature to predict adjuvant gemcitabine sensitivity in pancreatic adenocarcinoma. Ann Oncol 2021;32:250-60.
13. Nicolle R Bachet J, Harlé A, et al. 1297P Adjuvant gemcitabine is as efficient as mFOLFIRINOX in patients with GemPred+ tumor signature and resected pancreatic adenocarcinoma (PDAC): An ancillary study of the PRODIGE-24 clinical trial. Ann Oncol 2022;33:S1136.
14. Greenhalf W, Ghaneh P, Neoptolemos JP, et al. Pancreatic cancer hENT1 expression and survival from gemcitabine in patients from the ESPAC-3 trial. J Natl Cancer Inst 2014;106:djt347.
15. Perera S, Jang GH, Wang Y, et al. hENT1 Expression Predicts Response to Gemcitabine and Nab-Paclitaxel in Advanced Pancreatic Ductal Adenocarcinoma. Clin Cancer Res 2022;28:5115-20.
16. Perera S, Jang GH, Grant R, et al. hENT1 as a Predictive Biomarker in PDAC-Response. Clin Cancer Res 2023;29:2945-8.

Cite this article as: Fitzpatrick OM, O'Kane GM. Determinants of gemcitabine response in pancreatic cancer: are we there? J Gastrointest Oncol 2023;14(5):2290-2292. doi: 10.21037/jgo-2023-04

