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Precision medicine in pancreatic cancer: treating every patient as an exception

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Abstract

Patients with pancreatic cancer have not benefited from recent improvements in overall survival brought about by precision medicine in other malignancies. This failure is not due to a dearth of precision-medicine research in pancreatic ductal adenocarcinoma (PDAC), the main type of pancreatic cancer. In fact, the stalled progress in precision therapies for this type of cancer is due to the absence of agents that are able to target the common genetic alterations in PDAC. Several studies have attempted to phenotypically stratify PDAC at the transcriptional level. However, the value of such classifications will only be revealed through prospective studies and, crucially, only after development of new treatment options for this disease. Therefore, it is essential to learn from breakthrough discoveries in other cancer types that could benefit subpopulations of patients with PDAC and convert them from ordinary to exceptional responders. Identifying these exceptional patients will help to bring PDAC in line with other cancer types in terms of availability of precision therapies. Thus, the true challenge to precision medicine for PDAC might be the poor

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Contributors

LZ developed the concept. Both authors collected and analysed the data (literature review) and wrote the manuscript.

Declaration of interests

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consensus on which genetic and phenotypic alterations across the spectrum of this disease are actionable; not the absence of actionable variables themselves. To reach consensus, knowledge and tools must be developed and disseminated for individuals who provide pancreatic cancer care, to enable the real-time identification of exceptional patients, more precise subgroup classifications, and effective disease management strategies; all informed by immediate feedback from clinical outcome data.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a cancer of the pancreas with a dismal outcome. In 2018, an estimated 55 440 new cases of PDAC and 44 330 deaths caused by this cancer occurred in the USA.[1] Over the last 10 years, 5-year survival has improved marginally from 5% to 8%.[1] This improvement, albeit small, suggests that recent advances in treatments for PDAC did affect the long-term outcomes for some patients. This improvement can be attributed to the use of adjuvant and combination therapy, and the development of neoadjuvant strategies; it is unlikely to be due to an improvement in surgical techniques.[2] Current treatment strategies aim to improve outcomes for the general patient population with PDAC; however, most patients receive only marginal benefits. The results of the CONKO-001 study,[3] which compared surgical resection alone with resection followed by adjuvant chemotherapy, strongly underscore this point. This study[3] showed that with surgery alone, 10-year survival was 7·7% for patients with resectable PDAC; the addition of chemotherapy conferred 10-year survival of 12·2%. More patients with resectable tumours would benefit from additive chemotherapeutics but they would also need to have an excellent performance status to tolerate the regimen.[4] Even though their PDACs were resectable, most patients in CONKO-001 were not cured by either surgery or surgery followed by adjuvant chemotherapy. Therefore, a one-size-fits-all approach is probably incapable of fundamentally improving PDAC outcomes. A more precise and patient-specific approach to the management of PDAC is required.[1]

Is precision medicine practice for pancreatic cancer imminent?

After gemcitabine became a standard-of-care chemotherapy agent in the 1990s, thousands of patients with PDAC were enrolled in randomised, phase 3 clinical trials to try to identify a second synergistic chemotherapy agent or targeted agent alongside gemcitabine.[5] Unfortunately, none of these clinical trials had positive results except the NCIC CTG PA.3 study,[6] which showed that combining gemcitabine with erlotinib, an EGFR tyrosine kinase inhibitor, prolonged median overall survival by 10 days compared with gemcitabine alone in patients with metastatic pancreatic cancer. The positive result of this clinical trial did not generate new enthusiasm for practising precision medicine for patients with pancreatic cancer. Promoted as a molecularly targeted therapy, erlotinib is rarely used in pancreatic cancer treatment because the 10-day increment of survival cannot justify daily prescription. The subsequent successes in showing the superiority of FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin), a triple chemotherapeutic combination, and the doublet combination of gemcitabine and protein-bound paclitaxel, over gemcitabine alone further diverted attention from the precision-medicine approach in pancreatic cancer.[7,8]

How can precision medicine be developed for pancreatic cancer?

The non-existence of precision-medicine therapies for PDAC is not due to insufficient research or knowledge about the molecular underpinnings of the disease. In fact, the description of the genetics and transcriptomics of PDAC has revealed a lot of information that is, unfortunately, resistant to clinical translation. The main reason for this resistance is the absence of targeted therapies for the genetic alterations common to most PDACs. Studies[9–13] of whole-genome sequencing and whole-exome sequencing of PDACs consistently showed mutations in four genes: *KRAS*, *TP53*, *CDKN2A*, and *SMAD4*. None of these four genes was shown to be targetable in clinical trials. However, more recently, small molecules that irreversibly bind to the mutant $KRAS^{Gly12Cys}$, subverting the native nucleotide preference to favour GDP over GTP and impairing binding to RAF, have been discovered.[14–16] These small molecules are under clinical investigation in all solid tumours with $KRAS^{Gly12Cys}$. However, the $KRAS^{Gly12Cys}$ mutation occurs in only 3% of PDACs, compared with 14% of non-small-cell lung cancers. While waiting for the report on the clinical efficacy of $KRAS^{Gly12Cys}$ inhibitors, targeted agents for common types of KRAS mutations need to be developed. Because cancer genotyping was inadequate to guide the treatments for PDAC, several studies have attempted to phenotype the disease through stratification at the transcriptional level.[17] Collisson and colleagues[18] stratified PDACs into three subtypes: classical, quasimesenchymal, and exocrine-like, according to clinical outcome and therapeutic response. Moffitt and colleagues[19] did a similar stratification by subtyping PDACs into epithelial, basal-like, and classical. Bailey and colleagues[11] stratified PDACs into four molecular subtypes according to their molecular signatures: squamous, progenitor, immunogenic, and ADEX (aberrantly differentiated endocrine exocrine). A more recent study[20] stratified PDACs into hypoxia high and hypoxia low subtypes by integrating the analysis of genomic signatures and transcriptional signatures. Despite the innovations in these transcriptome-based approaches, the challenge remains in how to use all these stratification systems in clinical management of PDAC when potentially corresponding treatment strategies are unavailable or unknown. For example, PDACs rarely respond to contemporary or experimental immunotherapeutics, calling into question the predictive value of the immunosubtyping of PDAC. Furthermore, the study that defined the immunogenic subtype could have encountered the issue of the contamination of neoplastic samples with surrounding normal pancreatic and lymphoid tissues.[11,17]

So far, molecular subtyping of PDACs has a prognostic value for patients who received certain types of chemotherapy, whereas its predictive value for selecting patients prospectively for certain types of chemotherapy remains to be established. The classification of basal-like and classical subtypes is considered to be a consensus among multiple published studies of molecular stratification systems, and the two subtypes are consistently associated with poor prognosis and good prognosis, respectively.[21] However, none of the molecular stratification systems is readily used to triage patients for specific treatment options. In addition, physicians would not limit the use of chemotherapy to the classical subtype of PDAC that is associated with better outcome following FOLFIRINOX treatment, when there are only two approved combination chemotherapy regimens with benefits for advanced PDAC.[21] The value of molecular stratification will not be uncovered until

the subtypes are validated by prospective studies and, more importantly, only after new treatment options are available for PDAC.

Additionally, molecular stratification based on cancer genomics and transcriptomics might be insufficient for PDAC. Information on cancer epigenomics and proteomics could reveal more potential targets and disclose the molecular determinants of response and resistance to specific treatments.[22,23] Moreover, the stromal element plays a pivotal role in determining the biology of each PDAC and its response to chemotherapy and immunotherapy. Thus, understanding the interaction between tumour and stroma in PDAC is probably required to uncover the molecular identity of each individual patient.[24,25] A comprehensive study of the stroma is prerequisite for the understanding of this tumour–stroma interaction, because every PDAC has multiple immune defects due to the physiochemical properties of the stromal barrier, as evidenced by a paucity of high-quality T cells and the infiltration of immunosuppressive cells in the tumour microenvironment.[26] Recently, Neuzillet and colleagues[27] showed that human PDAC-derived cancer-associated fibroblasts display a high level of intertumour and intratumour heterogeneity and at least four subtypes based on transcriptomic analysis. Biffi and colleagues[28] and our research group[29] had similar and independent findings showing the intertumour and intratumour heterogeneity of the regulatory signalling in the stroma and thus showing the potential underlying mechanism for the heterogeneity of cancer-associated fibroblasts at the transcriptome level. Moreover, all groups found that cancer-associated fibroblasts are programmed by neoplastic cells at the epigenetic or transcriptional level and are subsequently phenotypically reprogrammed,[25,30] suggesting that the heterogeneity of neoplastic cells can also influence the heterogeneity of stromal cells. Taken together, these studies highlight the importance of profiling both the tumour and the tumour's microenvironment for the molecular stratification of PDACs.

Exceptional patients hold the key for precision medicine

Patients with pancreatic cancer have not benefited from improved overall survival brought about by precision medicine. This absence of improvement is often attributed to the so-called bad biology of all pancreatic cancers, which has contributed to the hesitancy to adopt a precision-medicine management approach for patients with PDAC. Fortunately, the medical community is increasingly aware that every PDAC has a different genotype and phenotype; that not all patients with PDAC are destined for poor prognosis. The set of core mutations that are common to all PDACs should neither define nor limit the potential for precision therapies for pancreatic cancer; the opportunities that do exist are at the omics periphery. For example, our data from testing consecutive, surgically resected PDACs show that less than 1% of these carcinomas are mismatch repair (MMR) deficient (unpublished). However, this small population of patients displays an approximately 60% radiographic response to immune checkpoint blockade, and often demonstrates a durable response.[31] Translating breakthroughs from outside the field of pancreatic cancer can therefore convert ordinary patients with PDAC (from here onwards referred to as ordinary patients), who have the poor outcomes that are anticipated for the majority of patients with PDAC, into exceptional responders (from here onwards referred to as exceptional patients), who have substantially better outcomes than the majority of patients with PDAC.

The rarity of PDACs that are deficient in MMR necessitates identification of other potentially exceptional patient subgroups. Detection of patients with actionable alterations in homologous DNA repair (HDR) pathways is a promising development. Hereditary deficiency in HDR genes, including *BRCA1*, *BRCA2*, and *PALB2*, is associated with approximately 5–8% of PDACs.[32–34] However, a prospective study showed that pathogenic germline alterations in 24 different genes, including *BRCA1*, *BRCA2*, *ATM*, *PALB2*, and multiple additional genes associated with the DNA damage response and repair (DDR) pathway (table), were detected in more than 19·8% of patients with exocrine pancreatic neoplasms.[35] Pathogenic somatic mutations in the HDR genes, including *BRCA1*, *BRCA2*, *PALB2*, and *ATM*, occur in 10–15% of PDACs.[37] According to testing of consecutive, surgically resectable PDACs at our institution, the prevalence of genetic alterations in DDR genes is approximately 30% when variants with unknown significance are included (unpublished). Knowledge of HDR and DDR defects would not be meaningful without effective therapies. Inhibitors of poly(ADP-ribose) polymerase (PARP), which repairs single-strand DNA breaks, are effectively used to treat cancers that carry mutations in *BRCA1*, *BRCA2*, or both, and cancers that are DDR deficient.[38]

PARP inhibitors have also been tested in clinical trials of PDACs with HDR gene mutations.[39] However, the synergistic toxicity of PARP inhibitors and chemotherapy has posed a challenge for combined administration.[40] It is still inconclusive whether tumours with a somatic HDR gene alteration are less sensitive to a PARP inhibitor than are tumours with a germline alteration. Different HDR gene alterations are expected to affect the HDR machinery differently, leading to different sensitivities to PARP inhibitors. However, different somatic alterations within the same HDR genes might also affect the HDR machinery differently. Such a heterogeneity has posed a challenge in confirming the effectiveness of PARP inhibitors in PDACs. In a phase 2 trial of patients with previously treated PDAC associated with germline *BRCA* mutations, no confirmed response to veliparib was observed, although four (25%) patients had stable disease for 4 months or longer.[41] Although the effectiveness of single-agent PARP inhibitor in progressive PDAC remains to be established,[41,42] the role of PARP inhibitors in maintenance therapy for patients with metastatic PDAC with germline *BRCA* mutations, whose disease has not progressed on first-line platinum-based chemotherapy, is supported by the results of the POLO-1 clinical trial (NCT02184195).[43] Nevertheless, it is well recognised that PDACs with HDR gene mutations are more sensitive to chemotherapy, particularly platinum-based analogues, compared with PDACs without HDR gene mutations.[34,44] Among patients with these PDACs, some showed complete response, durable response, or both, to chemotherapy, and therefore constitute another subgroup of exceptional patients.[34] The identification of exceptional patients, including those subgroups with HDR, DDR, or MMR alterations, highlights the importance of real-time clinical genomic assays. As can be expected in oncology, not all patients carrying DDR gene mutations respond significantly to chemotherapy. Research into the differences between chemosensitive and chemoresistant PDACs could uncover the targetable resistance mechanism or mechanisms specific to DDR-deficient PDACs. Therefore, molecular profiling might be more productive when exceptional patients are identified.

Molecular profiling can also reveal exceptional patients in the context of immunotherapy. Balachandran and colleagues[45] analysed the differences in the neoantigen repertoire between short-term and long-term survivors, revealing that neoantigens in exceptionally long-term survivors harbour epitopes with higher immunogenicity, including epitopes with high similarity to known pathogen-derived epitopes. This finding suggests that neoantigen-based therapies could be used to treat patients with pancreatic cancer on the basis of knowledge of these patients' genetic, transcriptomic, and immunogenic alterations.

Challenges and opportunities in precision medicine for pancreatic cancer

The challenge for the precision medicine approach in PDAC might not be an absence of actionable genes. In the Know Your Tumor study,[36] involving 640 patients with PDAC, mutations or genetic alterations in DNA repair genes and cell-cycle genes were considered to be actionable and were observed in more than 25% of patients. Among these patients, those who received matched therapy, albeit only 17 of 640 patients, had a significantly longer median progression-free survival than did the 18 patients who received unmatched therapy. It should be noted that these 18 patients were not randomly assigned to the no-treatment group and their inferior outcome might have been determined by other factors, such as performance status, which excluded them from receiving matched therapy. In addition, patients in the no-treatment group might have had rapidly progressing tumours while waiting for the results of the molecular profile. Nevertheless, this prospective study showed the possibility of identifying actionable genetic alterations and subsequently matching identified patients to targeted therapies, although the benefit of matched therapy remains to be confirmed. In the setting of routine practice, the benefit of identifying the actionable mutations and alterations was not supported. At Memorial Sloan Kettering Cancer Center (New York, NY, USA), 336 patients with PDAC had their tumours profiled through the MSK-IMPACT pipeline, an in-house next-generation sequencing panel comprising 410 genes at the time of study.[37] Similarly, archival analysis found that 10·1% of patients had potentially actionable genetic alterations based on clinical evidence (panel).[36,37] However, among the 225 patients who would need therapy options, only three patients received matched therapy, and these three patients either had no response to the treatment, or their responsiveness was unknown.[37]

The two studies[36,37] suggest that the main challenge lies in either the scarcity of matched therapies available to the patients, or the provider's insufficient knowledge of how to act on the genetic alterations. Only approximately 2% of the patients in these two studies received matched therapies, whereas 10–20% of patients had genetic alterations that are potentially actionable.[36,37] Therefore, until matched therapies are more accessible to patients with genetic alterations that are potentially actionable, full evaluation of the benefit of matched therapies is not possible. Additionally, the definition of potentially actionable genetic alterations differs between investigators (panel). A consensus on this definition is warranted and should be used to guide future study designs. Whether a list of actionable genetic alterations should include those supported by preclinical evidence would also require further discussion. Such an effort has been initiated by the European Society for Medical Oncology (ESMO) Translational Research and Precision Medicine Working Group to establish the ESMO Scale for Clinical Actionability of Molecular Targets to rank genetic alterations as

targets for cancer precision medicine.[46] A similar framework specific for PDAC might also be warranted.

Moreover, the current actionable genetic alterations are defined mostly according to whether there are targeted therapies that are genetically matched. However, some genetic alterations lead to a phenotypic change that matches to a certain type of therapy that does not target the genetic alteration directly. In the case of MMR-deficient tumours, the hypermutated phenotype is targeted by immune checkpoint blockade and not by any agent targeted to the MMR pathway itself. Another example is that HDR gene mutations lead to a so-called BRCAness phenotype, characterised by high sensitivity to platinum-based chemotherapy.[47] However, not all genetic alterations leading to the BRCAness phenotype are discerned or of known importance. Although the omics approach permits a more precise patient stratification at the molecular level, it remains challenging to use a complex molecular signature to define a phenotypic alteration because the detail of such an alteration often varies between patients. Nevertheless, such a challenge is an argument for the necessity of profiling as many individual patients as possible to understand the variations. It is also difficult to compare the omics between patient cohorts across different cancer types. By contrast, it is very possible to identify similarities among individual patients across different cancer types, considering microsatellite instability and BRCAness phenotypes as examples. It is important to remember that such similarities could often be as rare as microsatellite instability in pancreatic cancer. Therefore, a precision approach at the level of the individual patient will help to repurpose drugs in pancreatic cancer and identify more exceptional patients. Thus, there are potential opportunities to eventually treat every patient as an exceptional responder.

Other challenges that are often faced in precision medicine include tissue availability and low tumour cellularity. Biopsy specimens occasionally do not contain enough material, and the quality and volume of the specimens can vary because of different biopsy techniques. The tumour cellularity is also determined by the abundance of the stroma. For resected PDACs with abundant stroma, if tumour samples are not enriched by appropriate dissection, the quality of the molecular profiling of the tumour is substantially compromised. Moreover, biopsy specimens that are affected by the biopsy sites within the same or different tumours, or in primary tumours versus metastases, might demonstrate spatially different molecular profiling results. If a tumour biopsy is inadequate for analysis of genetic alteration, a liquid biopsy with sequencing of circulating tumour DNA[48] could serve as an alternative approach. However, the variation between tumour and liquid biopsy samples should be considered. A consensus guideline for specimen acquisition and processing will need to be established.

The fundamental challenge is how to have feedback from outcome data immediately available to improve the knowledge and skill in precision medicine. A real-time collection of clinical data is warranted. Although the patient-derived xenograft model[49] and the organoid system[50] still do not accurately resemble human PDACs in vivo, they could help to obtain proxy outcome data sooner than the availability of actual patient outcome data by testing drug sensitivity and predicting the resistance mechanism ex vivo.

To overcome the challenges and maximise the opportunities of practising precision medicine for pancreatic cancer, we propose the development of an innovative system. First, to sequence the tumour of every patient with PDAC clinically at the time of diagnosis, allowing enough time to navigate and plan matched therapies. Second, to expand the sequencing coverage from targeted gene panels to the whole exome and transcriptome to identify rare mutations and molecular signatures that offer a better chance of matching to therapies being developed for other cancer types. Third, to have a consensus on potentially actionable alterations, including both genetic alterations and phenotypic alterations, to guide the clinical studies of precision medicine. Lastly, to develop and disseminate knowledge and tools for individuals who provide pancreatic cancer care. This will enable the management of patients in real-time, and will lead to increasingly precise definitions of subgroups by having feedback from outcome data immediately available to inform these definitions.

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Panel: Potentially actionable genes in pancreatic cancer

Detected by Lowery and colleagues[37]

*Level 2b**: *ERBB2* (amplification), *CDK4*, *BRCA1, BRCA2*, *BRAF*, *ROS1/ALK1/NTRK3* fusions, and *IDH1*

Level 3b†: *AKT1*, *ERBB2* (mutation), *FGFR1*, *FGFR2*, and *PIK3CA*

Detected by Pishvaian and colleagues[36]

AKT1, *AKT2*, *STK11*, *TSC1, TSC2*, *BRAF*, *CDK4, CDK6*, *FGFR1, FGFR2, FGFR4*, *ALK/ROS1/NTRK1/NTRK2/NTRK3/RET* fusions, *MLH1/PMS2/MSH2/MSH6*, *ERBB2*, *IDH1*, *MET*, *BRCA1, BRCA2*, *ATM*, *PALB2*, *FANCA/FANCC/FANCG*, *CHEK1,* and *CHEK2*

Only genes with alterations detected in the studies are listed. *Level 2b is defined as a Food and Drug Administration (FDA)-approved biomarker in another cancer indication, but not FDA or National Comprehensive Cancer Network-compendium listed for pancreatic adenocarcinoma (therapies targeting *NTRK3* fusion and *IDH1* mutation were FDA approved before the cited study was published). †Level 3b includes alterations for which clinical evidence links the biomarker to drug response in patients but use of the biomarker is not currently a standard-of-care in any cancer type.

Search strategy and selection criteria

We searched PubMed using the keywords “pancreatic cancer”, “precision medicine”, “PARP”, “BRCA”, “molecular profiling”, “molecular classification”, and “stroma heterogeneity” for articles published between Jan 1, 2000 and Jan 1, 2019. Language was restricted to English, no other exclusion or inclusion criteria were used.

Table:

Prospective analyses of the prevalence of alterations of HDR genes in pancreatic cancer

	Type of alterations	HDR genes	Number of patients	Prevalence
Lowery et al (2018)[35]	Germline	*BRCA1, BRCA2, CHEK2, ATM, RAD50, RECQL4, BLM, BRAD1, RAD51D, PALB2*	615	12%
Pishvaian et al (2018)[36]	Somatic	*BRCA1, BRCA2, PALB2, ATM, FANCA, FANCC*	640	14.9%
Johns Hopkins Hospital (unpublished)	Somatic	*BRCA1, BRCA2, ATM, CHECK2, PALB2, FANCA, FANCD2, ATR*	175	8.5 (36% *)

HDR=homologous DNA repair.

* Including all genetic alterations with significance to be determined.