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REVIEW ARTICLE

Precision medicine in the treatment of pancreatic ductal adenocarcinoma

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Abstract

Pancreatic cancer has a poor prognosis. Current therapies for pancreatic cancer have limited effects. In the past decade, precision medicine has shown great potential for clinical applications. In this review, different strategies for applying precision medicine to the treatment of pancreatic cancer are described.

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Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related death in the United States, with 5-year survival of less than 5% despite advances in treatment [1]. 1 Without treatment, the overall median survival is only 6–9 months, and surgical resection offers the only chance of a cure. However, of the estimated 44,030 new cases diagnosed in the United States in 2011, only 15% of patients present with resectable disease, whereas 40% present with locally advanced unresectable disease, and 45% present with metastatic disease [2]. Even with adjuvant therapies, the prognosis remains dismal because PDAC is highly resistant to chemotherapy and radiation therapy. Human cancer genome studies have unveiled the mutational landscape of PDAC, which is quite heterogeneous in the mutational profiles of individual PDACs [3]. Conventional clinical trial designs have mostly failed to demonstrate a high efficacy in lowering recurrent risk following surgical resection in unselected patients, thus there is an increasing demand for selection of therapies for individual patients according to their individual mutation profiles.

Contemporary therapies

Patients with PDAC might be offered one or more of the following treatments: surgery, chemotherapy, or radiation therapy. Surgery offers the only chance of a cure, even when PDAC is diagnosed at an early stage. However, at the time of diagnosis, only 20% of patients have resectable PDAC. The phase III CONKO-1 study has established a role for adjuvant chemotherapy following curative resection, with 6 monthly cycles of gemcitabine [4]. Nevertheless, as many as 80% of patients in the CONKO-1 study did not survive beyond 5 years, even though they received gemcitabine adjuvant therapy following curative surgery. Moreover, when adjuvant therapy with gemcitabine was compared with 5-FU, in an ESPAC-3 study using mainly European patients, no difference in efficacy was found [5]. However S1, an oral prodrug of 5-FU, was shown to double survival time compared to gemcitabine in a phase III JASPAC 01 and GEST study for resected pancreatic cancer in Japan and unresectable advanced pancreatic cancer in Japan and Taiwan, respectively [6–7]. For advanced, unresectable PDAC or metastatic PDAC, chemotherapy

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is palliative. Combination chemotherapy regimens such as FOLFIRINOX and nab-paclitaxel/gemcitabine were found to be superior to gemcitabine alone in improving the survival time of patients with metastatic PDAC in recently completed phase III clinical trials [8]. Although it is intriguing to examine the efficacy of these combination therapies in the adjuvant setting, the severe toxicities associated with these combinations would be of concern if administered to an unselected patient population. Whether addition of radiation therapy to adjuvant therapy provides an added benefit remains to be seen, but a phase III study is underway. Given the known resistance of PDAC to radiation, we would favor a more selective approach, administering radiation therapy only to patients who are likely to benefit. Moreover, concerning the high incidence of recurrence following surgical resection of PDACs, appropriate selection of patients who would benefit from neoadjuvant therapy may further increase the benefits of surgery for resectable or borderline resectable PDAC patients [9]. Therefore, the limitations of contemporary therapies for PDAC have increased the demand to apply precision medicine to the management of PDAC.

Basis for precision medicine

Precision medicine is defined as administration of the right treatment at the right dose at the right time. With the rapid progress in the fields of biotechnology, genetics, and molecular biology, it has become possible for clinicians to utilize precision medicine techniques to tailor the management of many medical conditions.

New PDAC classification based on genomics and transcriptomics

The mutational landscape of pancreatic neoplasms has begun to be integrated with patient's clinical outcomes. The Vogelstein group conducted the first whole-genome sequencing of PDACs [10]. In this study, 69 gene sets were found to be genetically altered in the majority of the 24 PDACs examined. Thirty-one of these sets could be further grouped into 12 core signaling pathways that were each altered in 67–100% of the 24 PDACs. The core pathways included those involving KRAS signaling and regulation of the G1/S cell cycle transition, in which a single, frequently altered gene was predominant; those involving TGF-β signaling, in which a few altered genes were predominant; and those involving integrin signaling, regulation of invasion, hemophilic cell adhesion, and small guanine triphosphatase–dependent signaling, in which many different genes were altered. On average, each PDAC contains 63 genetic alterations, the majority of which are point mutations, and the pathway components altered in each individual tumor vary widely. Which core pathways and regulatory processes are altered becomes evident only when the coding regions of the genome are analyzed in depth.

Waddell *et al* [3] performed whole-genome sequencing and copy number variation analysis, including analysis for widespread and complex patterns of chromosomal rearrangement, in 100 PDACs. Chromosomal rearrangements leading to gene disruption were prevalent, affecting genes known to be important in pancreatic cancer (*TP53*, *SMAD4*, *CDKN2A*, *ARID1A*, and *ROBO2*) and new candidate drivers of pancreatic carcinogenesis (*KDM6A* and *PREX2*). A significant proportion harbored focal amplifications, many of which contained druggable oncogenes (*ERBB2*, *MET*, *FGFR1*, *CDK6*, *PIK3R3*, and *PIK3CA*), but at low prevalence in individual patients. Genomic instability co-segregated with inactivation of DNA maintenance genes (*BRCA1*, *BRCA2*, or *PALB2*) and a mutational signature of DNA damage repair deficiency. Based on structural variation profiles, PDACs were classified into four subtypes based on predominant genetic alterations with different clinical outcomes, including stable, locally rearranged, scattered, and unstable. The 'stable' subtype contains ≤ 50 structural variation events and often exhibits widespread aneuploidy, suggesting the presence of defects in cell cycle regulation. The 'locally rearranged' subtype contains a copy number gain that harbors known oncogenes. Known oncogenes include common focal amplifications in *KRAS*, *SOX9*, and *GATA6* and potential therapeutic targets such as *ERBB2*, *MET*, *CDK6*, *PIK3CA*, and *PIK3R3*. The remaining genetic alterations in the 'locally rearranged' subtype involve complex genomic events such as breakage–fusion–bridges or chromothripsis, which is linked to *TP53* mutations in medullobastoma and acute myeloid leukemia. The scattered class exhibit a moderate level of non-random chromosomal damage and 50–200 structural variation events. The 'unstable' subtype has defects in maintaining DNA integrity and could be sensitive to DNA-damaging agents. A platinum-containing combination therapy is emerging as a treatment option for advanced PDAC. Defining biomarkers of platinum responsiveness would significantly alter current treatment approaches to PDAC and improve overall outcomes. The researchers defined biomarkers, based on a combination of changes in gene structure, genetic mutations, and mutation features, that characterize the effectiveness of this treatment method. In a series of 8 patients who received platinum-based chemotherapy, of the 5 patients with unstable genomes and/or a high *BRCA* mutational signature burden, 2 had exceptional responses (defined as complete radiological resolution of disease and normalization of CA19.9 levels), and 2 had robust partial responses based on RECIST 1.1 criteria. None of the 3 patients without an 'unstable' genome showed a response. These results support the efficacy of individual tumor therapy.

Bailey *et al* [11] performed an integrated genomic and RNA sequencing analysis of 456 PDACs and classified PDACs into four subtypes: squamous, pancreatic progenitor, aberrantly differentiated endocrine exocrine, and immunogenic PDACs. The 'squamous' subtype is characterized by four core gene signatures, including inflammation, hypoxia response, metabolic reprogramming, TGF-β signaling. These gene signatures are independent poor prognostic factors. They are also highly expressed in tumors of breast, bladder, lung, and head and neck cancers, suggesting that treatments for these other types of cancer could be applied to PDAC. The 'progenitor' subtype is primarily defined by the expression of transcriptional networks containing the transcription factors *PDX1, MNX1, HNF4G, HNF4A, HNF1B, HNF1A, FOXA2, FOXA3*, and *HES1*. These transcription factors are pivotal for determination of the cell fate of pancreatic endoderm towards a pancreatic lineage. The 'aberrantly differentiated endocrine exocrine' (ADEX) subtype is characterized by the upregulation of transcription factors such as *NR5A2, MIST1*, and *RBPJL*, whose downstream targets are important for acinar cell differentiation and regeneration following the occurrence of pancreatitis, and genes associated with endocrine differentiation and MODY (including *INS, NEUROD1, NKX2-2*, and *MAFA*). Importantly, several patient-derived pancreatic cancer cell lines were enriched with gene programs associated with the ADEX subtype. Moreover, these cell lines expressed multiple genes associated with terminally differentiated pancreatic tissues, including *AMY2B, PRSS1, PRSS3, CEL*, and *INS*. In addition, the methylation pattern of the ADEX-type tumors was distinct from that of healthy pancreas tissue, and clustered with that of other pancreatic cancers. The 'immunogenic' subtype shares many of the characteristics of the pancreatic progenitor subtype, but is associated with evidence of abundant immune infiltrates. The 'immunogenic' subtype is also associated with immune gene signatures including B cell signaling, antigen presentation, and CD4+ T cell, CD8+ T cell, and Toll-like receptor signaling pathways. Enrichment analysis identified upregulated expression of genes associated with nine different immune cell types and/or phenotypes. It is intriguing to consider that the 'immunogenic' subtype may be more sensitive to immunotherapy. These four different subtypes of PDACs have different prognoses. The 'squamous' subtype has a median survival time of 13.3 months; the 'progenitor' subtype, 23.7 months, the 'aberrantly differentiated endocrine exocrine' subtype, 25.6 months; and the 'immunogenic' subtype, 30.0 months [11].

Tumor assessment for precision medicine

To guide the practice of precision medicine, it is essential to obtain tumor specimens; however, tumor biopsy often requires invasive procedures and may not be feasible. Recently, circulating tumor cells (CTCs), circulating cell-free DNA (cfDNA), and exosomes, which can be detected in blood obtained through a minimally invasive 'liquid biopsy,' have been shown to potentially represent the molecular landscape of a patient's overall tumor burden and to permit monitoring of the clonal evolution of individual PDACs during the course of treatment and disease progression.

CTCs

CTCs can be found in most patients with PDAC of any stage [12]. Study of CTCs may also help in understanding the biology of metastases, characterizing tumor genetic alterations, and predicting the prognosis for PDAC. Yu *et al* [13] identified Wnt2 as a candidate gene enriched in CTCs through single molecular RNA sequencing in a genetically engineered mouse PDAC model. Non-canonical Wnt signaling pathways have been suggested to contribute to the metastatic potential of human PDAC. The effectiveness of Tak1 inhibition in suppressing this pathway has identified a novel, potential drug target for metastasis suppression. Kulemann *et al* [14] reported that patients with KRAS-mutated CTCs had better survival than patients with KRAS wild-type CTCs following surgical treatment of PDACs (19.4 vs 7.4 months). Poruk *et al* [15] assessed CTCs with epithelial and mesenchymal phenotypes and found that CTCs expressing vimentin, a mesenchymal marker, were associated with a high risk of recurrence following surgical resection of PDACs.

cfDNA

cfDNA is a cancer-derived material that is enriched in tumors and that likely originates from CTCs; it holds promise for directly detecting and monitoring the molecular characteristics of tumors. The presence of cfDNA has been reported to be associated with distant organ metastasis, and mutations in potential therapeutic target genes have been detected in 29.2% of cfDNA samples collected from a retrospective cohort of patients [16].

Exosomes

Exosomes, lipid bilayer–enclosed extracellular vesicles that contain tumor cell materials, can avoid degradation in blood. Kahlert *et al* [17] found that exosomes from PDAC patients contain genomic DNA, RNA, and proteins, as well as mutations in KRAS and p53 in the genomic DNA. It has been reported that the level of glypican-1(+) circulating exosomes is correlated with the tumor burden and the survival of pre- and post-surgical patients with PDAC [18].

Strategies for precision medicine

Precision medicine shows excellent potential for treatment of PDACs, and various strategies are being tested in clinical trials (Fig. 1).

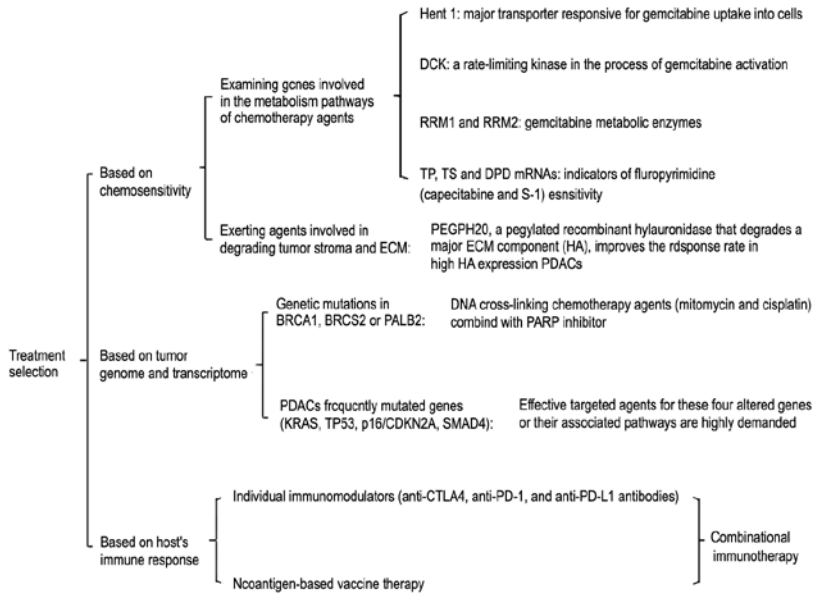

Fig. 1 Strategies for precision medicine in the treatment of PDACs. Different strategies for applying precision medicine to the treatment of PDACs. Hent 1, human equilibrative nucleoside transporter-1; DCK, Deoxycytidine kinase; RRM1 and RRM2, ribonucleoside reductases M1 and M2; TP, thymidine phosphorylase; TS, thymidylate synthase; DPD, dihydropyrimidine dehydrogenase; HA, hylauronic acid; PARP, poly ADP-ribose polymerase; CTLA-4, cytotoxic T lymphocyte antigen-4; PD-1, programmed cell death protein-1; PD-L1, the ligand of PD-1

Treatment selection based on chemosensitivity

The first strategy for selection of chemotherapy for individual patients involves examining genes that are involved in the metabolism of chemotherapeutic agents. Human equilibrative nucleoside transporter-1 (hENT1) is the major transporter responsible for uptake of gemcitabine into cells. A retrospective study including 27 patients with PDAC who underwent resection and treatment with adjuvant gemcitabine therapy revealed that high expression of hENT1 in PDAC is associated with longer survival in patients who received adjuvant gemcitabine monotherapy [19]. Similar results were also reported in other studies [20–21]. Deoxycytidine kinase (DCK) plays an important role in the process of gemcitabine activation and is a rate-limiting kinase in gemcitabine metabolism [22]. Expression of DCK at the gene and protein levels is closely associated with gemcitabine sensitivity in patients with PDAC, and high levels are associated with increased survival [23–25]. The ribonucleotide reductases M1 and M2 are also gemcitabine metabolic enzymes, and decreased levels are associated with gemcitabine resistance and a worse prognosis [26–28]. Recently, the orally administered fluoropyrimidine prodrugs, capecitabine and S-1, have been used for treatment of PDAC. One study showed that expression levels of thymidine phosphorylase, thymidylate synthase, and dihydropyrimidine dehydrogenase mRNA are indicators of fluropyrimidine sensitivity [29].

Tumor stroma and extracellular matrix (ECM) are associated with PDAC aggressiveness and chemotherapy resistance. Members of the lysyl oxidase protein family, which mediate collagen cross-linking and promote ECM stiffening, have been proposed as novel targets for improving chemosensitivity [30]. PEGPH20, a pegylated recombinant hylauronidase that degrades a major ECM component, hylauronic acid (HA), is already on the horizon of clinical development. ECM with high HA expression has been shown to have high hydrostatic pressure that compresses intratumoral blood vessels. By degrading HA, PEGPH20 reopens blood vessels and thus facilitates delivery of chemotherapeutic drugs [31]. A randomized phase 2 study of gemcitabine and Nab-paclitaxel, with or without PEGPH20, showed that the subgroup of patients whose PDACs have high HA expression had a significantly higher response rate to gemcitabine and Nab-paclitaxel combined with PEGPH20 than to gemcitabine and Nab-paclitaxel without PEGPH20 [32]. A phase 3 study of gemcitabine and Nab-paclitaxel, with or without PEGPH20, for treatment of patients with high HA expression has recently been initiated [33].

Treatment selection based on tumor genome and transcriptome

The *BRCA1, BRCA2*, and *PALB2* genes are inactivated in approximately 10% of familiar pancreatic cancers. Their protein products contribute to repair of DNA cross-linking damage and double-strand breaks. Studies have suggested that PDACs with genetically inactivated *BRCA1, BRCA2*, or *PALB2* are significantly more susceptible to DNA cross-linking agents, such as mitomycin and cisplatin. However, tumor cells harboring DNA repair defects due to mutations in *BRCA1, BRCA2*, or *PALB2* can survive with damaged DNA. Inhibition of poly ADP-ribose polymerase (PARP) would inhibit repair of the damaged DNA by the alternative DNA repair machinery,

preventing survival of the tumor cells. Therefore, genetic mutations in *BRCA1, BRCA2*, or *PALB2* have been used to select patients with PDAC for treatment with PARP inhibitors in clinical trials [34–35]. DNA repair defects also commonly occur in sporadic PDACs. Tumor genome- and transcriptome-based subtyping of PDACs may show promise to select patients for DNA cross-linking chemotherapy agents and PARP inhibitor treatments.

The landscape of the PDAC genome is notable for containing four frequently mutated genes (*KRAS, TP53, p16/CDKN2A*, and *SMAD4*). Ideally, driver mutations in these four genes would be used to select the best treatment options for patients. However, effective targeted agents are not available for any of these four altered genes. Therefore, therapeutic agents that target these four altered genes or their associated pathways are in high demand and may be key to the success of precision medicine in PDACs.

Treatment selection based on host immune response

Advances in immunotherapy have facilitated breakthroughs in the treatment of many cancer diseases. Cytotoxic T lymphocyte antigen-4 (CTLA-4) provides an inhibitory signal in the early phase of T-cell activation. The first immune checkpoint inhibitor to be approved is ipilimumab, a fully humanized IgG1 monoclonal antibody that inhibits CTLA-4. Programmed cell death protein-1 (PD-1) and its ligand, the ligand of PD-1 (PD-L1), function in the exhaustion of activated T cells, which can be blocked by therapeutic antibodies such as nivolumab and pembrolizumab, which are now United States Food and Drug Administration-approved. Although T-cell checkpoint inhibitors, including anti-CTLA4, anti-PD-1, and anti-PD-L1 antibodies, have shown substantial clinical benefits for treatment of other cancers, such as melanoma, non-small cell lung cancers, and renal cell carcinoma, their application in PDAC as single agents has shown limited efficacy [36]. Nevertheless, Lutz *et al* [37] showed that vaccine therapy can induce PD-1 and PD-L1 signaling and thus prime PDACs for anti-PD-1/PD-L1 antibody therapies. Soares *et al* [38–39] demonstrated that vaccine therapy can enhance the antitumor activity of anti-PD-1 or PD-L1 antibodies in a preclinical model of PDAC. Based on the rationale established by this preclinical study, multiple clinical trials have been initiated to test the combination of vaccines and anti-PD-1 antibodies in all four stages of PDACs. However, Lutz *et al* [37] highlighted the significant heterogeneity of the intratumoral immune response to vaccine therapy in different patients with PDAC. Thus, assessment of the intratumoral response to vaccine therapy has helped to reveal the immune regulatory signals that should be targeted by different immune modulating agents in individual patients. Moreover, a neoantigen-based vaccine therapy, designed based on whole-exome sequencing of mutated genes, will facilitate further tailoring of vaccine therapies for individual patients [36].

Summary

In the last decade, precision medicine has shown considerable potential for clinical applications, largely owing to advancements in cancer genome research and in our understanding of the tumor microenvironment and the host immune response. However, before we are able to apply precision medicine to our routine practice for managing PDACs, more large-scale prospective clinical studies are warranted, to provide support for precision medicine approaches and to establish guidelines for application of precision medicine.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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