

Targeting the stroma in pancreatic cancer

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Abstract: The tumor stroma in pancreatic adenocarcinoma is recognized as an integral component in tumorigenesis through its effects on cell signaling, immunosuppression and inhibitory effect on therapeutic agents. Promising preclinical activity has been observed with novel therapeutic agents that target the tumor microenvironment and represent one of many potential treatment strategies of interest in this disease. Herein, we will highlight and review therapeutic novel agents aimed at tumor stroma in pancreas cancer.

Keywords: Microenvironment; pancreatic cancer; stroma; targeted therapies; immunotherapy

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Pancreatic adenocarcinoma remains the fourth leading cause of cancer deaths in the United States, with a 5-year survival of <5% across all stages (1). In 2014, there were approximately 53,070 new cases of pancreatic cancer with only 9% of patients having localized, resectable disease (2). With the vast majority of patients (91%) that present with advanced or metastatic disease at the time of diagnosis, the primary focus for drug development has been in the metastatic setting, with two standardized therapies, FOLFIRINOX and gemcitabine/nab-paclitaxel, for advanced disease (3,4), and the recently first approved treatment for patients with treatment refractory disease (5). Despite these recent advances, patient outcomes remain poor, emphasizing the need for novel therapies for the treatment of pancreas cancer. One approach that has garnered much enthusiasm in pancreatic cancer has been investigating therapeutic agents aimed at targeting the tumor stroma. The stroma functions to enhance tumorigenesis via cell signaling, immunosuppression and inhibiting chemotherapy efficacy. Herein, we will highlight novel biologic therapies aimed at targeting the tumor microenvironment of pancreatic cancer.

Pancreatic cancer tumor microenvironment

Hyaluronic acid (HA)

Pancreatic ductal adenocarcinoma (PDA) is known for its characteristic desmoplastic stroma, a heterogeneous milieu comprised of pancreatic stellate cells, cancer-associated fibroblasts (CAFs), nerves, inflammatory cells and the acellular extracellular matrix (ECM). The ECM is comprised of several glycosaminoglycans (GAG), including HA and is found in small quantities in several organs. HA is a GAG commonly found in the ECM and in several solid tumor malignancies, where high HA content has been observed in several solid tumor malignancies, including PDA. High HA content is observed in upwards of 90% of PDA and portends to advanced disease and poor prognosis (6). HA contributes to the physical barrier that the ECM forms which contributes to treatment resistance in PDA. HA polymers bind and trap water molecules, which transform the tissue architecture into an immobile mechanical barrier that increases interstitial fluid pressure (IFP) and hinders chemotherapy delivery throughout the stroma to neoplastic cells. HA also binds to cell surface

Table 1 Summary of ongoing or completed phase clinical trials investigating novel therapeutic agents in pancreas cancer

Agent	Phase	Primary endpoint	Treatment	Median PFS	Median OS	Comments	Ref./NCT
PEGPH20	II	PFS	AG vs. PAG	5.7 vs. 5.2 months; HR, 0.69; P=0.11	Pending	TE events (25% vs. 42%)	(10)
PEGPH20	II	PFS	AG vs. PAG	9.2 vs. 5.2 months	Pending	TE events similar (PAG 14% vs. AG 10%)	(11)
PEGPH20	II	PFS	FOLFIRINOX ± PEGPH20	Pending	Pending	Halted early due to futility	NCT01959139
APX005M	I/II	Safety, tolerance, PFS	PX005M + gemcitabine /Nab-paclitaxel ± nivolumab	Pending	Pending		NCT03214250
PF-04136309	Ib/II	Safety, tolerance, PFS	PF-04136309 + Gemcitabine /Nab-paclitaxel	Pending	Pending	Treatment naïve	NCT02732938
Ibrutinib	II/III	PFS	Ibrutinib + Gemcitabine /Nab-paclitaxel	Pending	Pending		NCT02436668

AG, gemcitabine/nab-paclitaxel; PAG, PEGPH20 + gemcitabine/nab-paclitaxel; TE, thromboembolic; PFS, progression free survival; OS, overall survival.

receptors (CD44, RHAMM, LYVE-1, HARE, TLR-4), which stimulates downstream signaling pathways associated with tumorigenesis.

Given the role of stromal HA and its association with treatment resistance and tumorigenesis, studies have explored the potential at exploiting HA as a therapeutic target. PEGylated hyaluronidase alfa (PEGPH20; Halozyme Therapeutics) is a pegylated form of recombinant hyaluronidase, which prolongs the circulatory half-life to >20 hours, allowing for the degradation of HA within the tumor microenvironment (7). In mouse models, PEGPH20 reduced intra-tumor IFP to near normal physiologic pressures and showed increased intra-tumor chemotherapy delivery and tumor cell apoptosis (8). The results of phase I trials HALO-109-101 and HALO-109-102 were consistent with preclinical studies, where the administration of PEGPH20 increased plasma HA in conjunction with decreased tumor metabolic activity and increased tumor permeability (9). These results led to the completion of the randomized phase 2 trial, where patients with treatment naïve metastatic PDA were randomized to receive gemcitabine/nab-paclitaxel alone or in combination with PEGPH20 (10,11) (Table 1). Correlative studies included the assessment of baseline tumor HA levels, which were categorized into HA^{low} or HA^{high} based on the H-score. HA levels were assigned an H-score that was calculated

as the sum of the products of the percentage of positive staining areas and the staining intensity (0, 1, 2 or 3) with scores ranging from 0–300. Based on exploratory analyses of the distribution of HA surrounding tumor cells in PDA tumor biopsies, a H score of ≥100 was defined as HA^{high} (12). In stage 1 of the study, 135 patients were randomized in a 1:1 fashion to receive gemcitabine/nab-paclitaxel alone or in combination with PEGPH20. Findings showed similar progression free survival (PFS) between the two treatment arms (5.7 vs. 5.2 months; HR, 0.69; P=0.11) with an increase of thromboembolic events in the PEGPH20 arm (43% vs. 25%) (10). In patients with HA^{high} tumors, a significant improvement in PFS was noted in those that received the combination of chemotherapy + PEGPH20 (9.2 vs. 6.3 months; HR, 0.48) (10). Based on the HA-high cohort results, in stage 2 of the study, 279 patients were randomized to receive in a 2:1 fashion to receive gemcitabine/nab-paclitaxel with PEGPH20 (PAG) or gemcitabine/nab-paclitaxel (AG) (11). Eighty-four (34%) of the 231 patients evaluable for efficacy were identified as having HA^{high} tumors. At the time of the interim analysis, a significant improvement in PFS was seen in patients that received PAG [6.0 vs. 5.3 months; HR, 0.73; 95% confidence interval (CI), 0.53–1.00; P=0.048]. Patients who were identified as HA^{high} showed an improvement in median overall survival (OS) (11.5 vs. 8.5 months; HR,

0.96; 95% CI, 0.57–1.61) and PFS (9.2 *vs.* 5.2 months; HR, 0.51; 95% CI, 0.26–1.00) when treatment with PEGPH20 plus gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel alone. With the initiation of prophylactic enoxaparin in part 2 of the study, similar thromboembolic events were observed between both arms (PAG 14% *vs.* 10% in the AG arm). The most common PEGPH20-related adverse effects were musculoskeletal events (MSE), which included muscle spasms (58%), arthralgia (28%) and myalgia (27%). MSEs were primarily grade 1–2 and were managed through various medical interventions, including rest, muscle relaxants, anti-inflammatory agents including NSAIDs and corticosteroids. Four percent of patients discontinued PEGPH20 treatment due to MSEs (13). These results supported the ongoing HALO 301 study, an international phase 3 trial where patients with treatment naïve metastatic pancreatic adenocarcinoma with HA^{high} tumors are randomized to receive in a 2:1 fashion to receive PEGPH20 in combination with gemcitabine/nab-paclitaxel or in gemcitabine/nab-paclitaxel (ClinicalTrials.gov, NCT02715804). Recently however, the interim analysis of S1313, a randomized phase 1b/2 trial that investigated FOLFIRINOX chemotherapy alone or in combination with PEGPH20, resulted in the study being halted for futility (ClinicalTrials.gov, NCT01959139). The lack of a pre-specified patient population based off a biomarker, patients with HA^{high} tumors, could have contributed to the negative results in the trial. However, the final data has not been presented or published to date. These unexpected results will need further evaluation as to the appropriate sequencing and administration of PEGPH20 with various cytotoxic combinations.

Sonic hedgehog pathway (SHh)

The SHh is a signaling pathway that transmits crucial information to embryonic cells required for cell differentiation and organ development. SHh is overexpressed in PDA tumor cells, where it contributes to the development of the paracrine signaling network that promotes the desmoplasia in the stroma (14,15). Within the stroma, cancer associated fibroblasts have also been identified as having aberrant SHh activation (16).

In preclinical mouse models, the administration of IPI-926, a SHh inhibitor, enhanced delivery of gemcitabine through depletion of stromal tissue and increase in vascular density (17). Despite the interesting preclinical activity, these findings did not translate to an improvement in

patient outcomes across several clinical trials. A phase 2 trial that investigated gemcitabine alone or in combination with IPI-926 in untreated patients with metastatic PDA was halted when the interim analysis showed patients enrolled in the IPI-926 arm experienced an inferior PFS and OS (18). A second randomized phase Ib/II trial in patients with treatment naïve metastatic PDA also failed demonstrate an improvement in PFS, the primary endpoint, in patients that received gemcitabine in combination with vismodegib, another SHh inhibitor (19). Patients randomized to vismodegib experienced a trend towards an improvement in PFS (4.0 *vs.* 2.5 months; HR, 0.81; P=0.30) and OS (6.9 *vs.* 6.1; HR, 1.04; P=0.84). The discordance in findings between the preclinical to clinical studies is unclear. Recent preclinical studies suggest a potential detrimental effect from SHh inhibitors where prolonged exposure to IPI-296 led to a more aggressive phenotype with undifferentiated histology, increased vascularity and tumor proliferation (20). Similar findings were also seen with vismodegib that resulted in tumor progression (21). Thus, it is possible that certain components of the tumor may serve as a protective mechanism in restraining tumor growth. Thus, further work that includes a better understanding of the predictive value of SHh in pancreas cancer is needed. Despite the completion of further studies investigating the combination of more active chemotherapy regimens with SHh inhibitors (22) in PDA, further development of SHh inhibitors in this disease is unlikely.

The immune system and its compartments in the TME

While immunotherapeutic agents have shown promise in the treatment of other solid tumor malignancies, PDA is considered to be a non-immunogenic malignancy, as tumor-infiltrating effector T lymphocytes do not represent a histopathologic hallmark in this disease. The pancreatic tumor microenvironment suppresses the activity of tumor infiltrating lymphocytes that contributes to blunting an anti-tumor immunogenic response (23). Given this, approaches aimed at overcoming T-cell immune checkpoints, with agents including anti-PD1 or anti-CTLA-4 monoclonal antibodies (mAbs), have failed to demonstrate any meaningful clinical activity in this disease (24,25).

Several strategies have attempted to sensitize the immune system against tumor antigens including the utilization of modified vaccines comprised of cancer specific antigens or protein that are overexpressed in PDA. GVAX

is an irradiated whole-cell modified vaccine comprised of two irradiated pancreas cancer cell lines (PANC 6.03 and PANC 10.05) engineered to express granulocyte-macrophage colony-stimulating factor (GM-CSF), which is integral in stimulating the immune system response through the induction of dendritic cell differentiation. The administration of GVAX with 5-Fluorouracil based chemoradiation in the neoadjuvant setting for patients undergoing planned resection for PDA showed an infiltration of intratumoral lymphoid structures in the resected tumor, suggesting a possibility to induce a more immunogenic environment (26). Additional studies that have investigated the immunologic effects of GVAX have confirmed its ability to create an inflammatory reaction by causing an upregulation of PD-L1, suggesting the potential utility of combining this vaccine with immune checkpoint inhibitors (27,28).

Another agent of interest in PDA is CRS-207, a live-attenuated *Listeria monocytogenes* (LM) vaccine genetically modified to express mesothelin, a protein that is often overexpressed in pancreatic cancer. A randomized phase II trial in patients with chemo-refractory metastatic PDA showed a significant improvement in OS when sequential treatment with GVAX/CRS-207 was administered, as compared to GVAX alone (median OS, 6.1 *vs.* 3.9 months; HR, 0.59; *P*=0.02) (29). The similar clinical benefit was not observed in a more recent randomized phase 2 trial. Patients with metastatic treatment refractory PDA were randomized to receive 2 doses of cyclophosphamide (CY)/GVAX + 4 dose of CRS-207 (Arm A), 6 doses of CRS-207 (Arm B) or physician's choice of chemotherapy (Arm C) (30). The combination of CY/GVAX + CRS-207 did not show an improvement in OS over chemotherapy (3.8 *vs.* 5.4 *vs.* 4.6 months, Arms A *vs.* B *vs.* C, respectively). High dropout rates were observed in the chemotherapy arm prior to treatment, likely a result for patient preference to pursue alternative therapies (combination chemotherapy, investigational agents). Thus, while vaccine therapy represents a promising strategy towards allowing transforming PDA into a more immunogenic malignancy, this has not been proven to be effective. The identification of new targets in the TME may facilitate in the development of immunotherapeutic agents in this disease.

CD40

CD40 is a co-stimulatory protein found on antigen presenting cells (APCs) that is required for activation

by CD4⁺ T helper cells. Activated APCs are needed to transform CD8⁺ T cells into cytotoxic effector T cells. Thus, CD40 activating mAbs have the potential to reverse immune suppression by activating CD8⁺ T cells (31). In mouse models, the combination of a CP-8970,893, a fully human CD40 agonist antibody, with gemcitabine induced metabolic responses and tumor shrinkage on assessment by CT and PET-CT imaging (32). Interestingly, the study also demonstrated that the observed anti-tumor activity was induced by CD40 activated macrophages (32). Thus, immunogenic activity against cancer cells is not dependent on T cells but a CD40-dependent mechanism may be an additional approach at targeting the stroma in PDA. In a phase I study, CP-8970,893 was administered in combination with gemcitabine in patients with treatment naïve advanced PDA (33). Of the 22 patients enrolled, 4 patients experienced a partial response, suggesting the potential of CD40 agonists a therapeutic modality in PDA. Treatment was well tolerated with the most common side effect related to cytokine release syndrome, which included fevers, chills and rigors on the day of CP-8970,893 infusion. Currently, an ongoing phase I/II study is investigating the combination of APX005M, a CD40 agonistic mAb in combination with gemcitabine/nab-paclitaxel with or without Nivolumab, an anti-PD-1 antibody (ClinicalTrials.gov, NCT03214250).

CCL2-CCR2

The CCL2-CCR2 signaling axis has garnered interest as a potential therapeutic target in pancreas cancer. Chemokine CCL2 and its cognate receptor CCR2 promote the recruitment of monocytes and tumor-associated macrophages (TAM) in the TME that contributes to the immunosuppressive environment that promotes chemoresistance, metastatic spread and tumor immune evasion. Preclinical studies in pancreas cancer have shown that the production of CCL2 resulted in infiltration of immunosuppressive CCR2⁺ TAMs (34). Patients whose tumors exhibited high CCL2 expression/low CD8 T-cell infiltrate had worse outcomes. In pancreatic cancer mouse models, targeting CCR2 depleted inflammatory monocytes and macrophages, resulting in improved chemotherapy efficacy, enhanced anti-tumor T-cell response while inhibiting tumor cell growth and metastasis (34,35). A recent randomized phase IB trial was completed to evaluate the safety and tolerability from the combination of FOLFIRINOX with PF-04136309, a CCR2 inhibitor

in patients with borderline resectable or locally advanced PDA. A response rate of 48.5% was observed in patients who received the combination in comparison to the pre-specified expected response rate of 25% seen with FOLFIRINOX alone (36). A second randomized phase 1b/2 study investigating the gemcitabine/nab-paclitaxel alone or in combination with PF-04136309 (ClinicalTrials.gov, NCT02732938) has also been completed but the results are still in progress.

Targeting mast cells

The characteristic desmoplastic stroma seen in PDA is comprised of many inflammatory cells, including mast cells, which serve as one of the key components in the TME. Analysis of human PDA samples demonstrated that mast cell infiltration correlated with higher tumor grade and worse survival (37), and high mast cell concentration was associated with lymphatic and microvascular invasion and lymph node metastasis (38). Ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor that has been approved for the treatment of chronic lymphocytic leukemia and mantle cell lymphoma (39), inhibits mast cell degranulation (40). In pancreas cancer mouse models, Ibrutinib diminished tumor-associated inflammation and fibrosis, suggesting that fibrosis seen with pancreas cancer is a mast cell dependent mechanism (41). Additionally, Ibrutinib limited pancreatic cancer growth and demonstrating an anti-tumor effect and improved response to gemcitabine, while enhancing T cell-dependent immune cytotoxicity (41,42). Based on these findings, RESOLVE, a randomized phase 2/3 trial comparing gemcitabine/nab-paclitaxel alone or in combination with Ibrutinib with a primary endpoint of progression survival, is ongoing (ClinicalTrials.gov, NCT02436668).

Conclusion and future directions

Despite recent advances in cancer care and research, pancreas cancer remains very challenging, with standard treatment regimens providing modest gains at a significant cost. Novel treatment strategies that include approaches aimed at targeting the tumor microenvironment and stroma are needed to improved outcomes in this dismal disease. This includes the incorporation of biomarker-driven strategies to identify specific cohort of patients who are likely to derive benefits from various novel therapeutic agents. An increased understanding has spurred further

investigation in both early- and later-phase studies. While the results so far have been disappointing, innovative and “outside of the box” approaches can result in the continued promise in shifting the treatment paradigm in this terrible disease.

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Footnote

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