Novel approaches to pancreatic cancer

With a five-year overall survival of less than 5%, there is an urgent need to explore new treatment paradigms for pancreatic cancer, including targeting stroma cells, cancer stem cells and metabolic pathways. **Ignacio Garrido-Laguna** and **Manuel Hidalgo** outline the current standard of care and review promising novel treatments.

This is an abridged version of I Garrido-Laguna and M Hidalgo (2015) Pancreatic cancer: from state-of-the-art treatments to promising novel therapies. ***Nat Rev Clin Oncol*** *12:319–334. It was edited by Janet Fricker and is published with permission* ©*2015 Nature Publishing Group.*
doi:10.1038/nrclinonc.2015.53

nature REVIEWS CLINICAL ONCOLOGY

Surgery is still the only curative treatment for pancreatic cancer; however, therapeutic strategies based on initial resection have not substantially improved the survival of patients with resectable disease over the past 25 years. Presently, more than 80% of patients suffer disease relapse after resection.

The state of the art

Resectable disease

More effective chemotherapy backbones are currently being tested in the adjuvant setting (nab-paclitaxel plus gemcitabine, APACT trial) and FOLFIRINOX (PRODIGE study).

Neoadjuvant therapy

Potential advantages for neoadjuvant therapy include increasing negative margin (R0) resection rates, improving surgical selection, earlier treatment of micrometastatic disease, and enhancing chemoradiotherapy delivery.

Single-institution studies suggest neoadjuvant treatment increases the rate of R0 resections. Such findings contrast with a retrospective analysis of resections of pancreatic ductal adenocarcinoma between 1992 and 2011, which showed no R0 margin differences between upfront resection and neoadjuvant treatment (*World J Surg* 2014, 38:1184–95).

Meta-analyses have consistently failed to demonstrate neoadjuvant survival advantages. A lack of consensus over which tumours are borderline resectable influenced results.

Predictive biomarkers of response to gemcitabine or 5-fluorouracil (5-FU) are urgently needed.

Unresectable disease

The ECOG 4201 trial demonstrated a modest improvement in survival

for chemoradiotherapy compared to gemcitabine, but with increased toxicity (*JCO* 2011, 29:4105–12). The FFCD/ SFRO study, however, suggested detrimental overall survival for chemoradiotherapy versus gemcitabine therapy (*Ann Oncol* 2008, 19:1592–99).

The rationale for the detrimental effects of chemoradiotherapy comes from a study showing enhanced invasiveness for cancer cells co-cultured with irradiated fibroblasts due to activation of MET and MAPK signalling pathways (*Cancer Res* 2004, 64:3215–22).

The SCALOP trial demonstrated that capecitabine is superior to gemcitabine as a radiosensitiser (*Lancet Oncol* 2013, 14:317–326).

Clinical trials are needed to validate biomarkers to identify patients less likely to benefit from chemoradiotherapy. The RTOG 1201 trial is currently testing nab-paclitaxel plus gemcitabine followed by chemoradiation. This study stratifies patients according to *SMAD4* status. The hypothesis is that patients with preserved *SMAD4* may benefit from intensification of local therapy.

Advances in metastatic disease

Over the past decade, single-agent gemcitabine has been the standard of care in metastatic pancreatic ductal adenocarcinoma, with multiple trials failing to show that adding targeted therapies improves survival.

Two positive trials have been reported in advanced-stage pancreatic cancer. The PRODIGE-III trial showed better survival (HR 0.57) with FOLFIRINOX over gemcitabine (*NEJM* 2011, 364:1817–25), while the MPACT study showed nab-paclitaxel plus gemcitabine delivered better survival (HR 0.72) than gemcitabine (*NEJM* 2013, 369:1691–1703).

Novel treatment opportunities

Given the poor clinical outcomes for pancreatic ductal adenocarcinoma, novel strategies are needed.

Drugs targeting pancreatic cancer cells

Cytotoxic agents. To tackle the desmoplastic response in pancreatic ductal adenocarcinoma, where dense fibrous tissue grows around tumours, novel formulations of classic cytotoxic agents are currently under development.

MM-398, a nanoliposomal formulation of irinotecan, was recently approved by the US FDA, in combination with 5-FU, for patients with metastatic pancreatic cancer refractory to gemcitabine. The NAPOLI-1 study showed a modest improvement in survival (8 weeks) with the combination compared to 5-FU alone (*Ann Oncol* 2014, 25:ii105–ii117). It is unclear whether MM-398 will provide any benefit to patients who have received first-line therapy with nab-paclitaxel and gemcitabine, as such patients were not included in the study.

TH-302, a releasing DNA-alkylating agent activated under hypoxic conditions, recently failed to provide any added survival benefit to gemcitabine in the MAESTRO trial (Van Cutsem et al. Abstract #193 ASCO GI 2016).

The 'synthetic lethality' strategy holds some promise in patients with aberrations in DNA-repair pathways. A basket study tested olaparib in patients with germline *BRCA1/2* mutations in *BRCA*-associated cancers. The response rate in patients with pancreatic cancer (n=23) was 21%.

RAS pathway inhibitors. Activating *KRAS* mutations are found in more than 90% of pancreatic ductal adenocarcinomas. Inhibition of oncogenic RAS signalling might be achieved by multiple mechanisms including blocking RAS protein transport to the cell membrane, and inhibiting oncogenic RAS activity directly or indirectly through targeting downstream pathway components.

Owing to the complexity of directly targeting *KRAS*, efforts have focused on downstream components of the RAS pathway, such as MEK. Unfortunately, clinical trials with MEK inhibitors (trametinib or pimasertib) have provided disappointing results. Inhibition of ERK has shown promising activity in preclinical models. A phase 1b study will be testing BVD-523 (an ERK inhibitor) in combination with nab-paclitaxel and gemcitabine (NCT02608229) in patients with advanced pancreatic cancer.

Janus kinase inhibitors. High throughput gene-expression analysis showed enrichment of the JAK–STAT pathway in pancreatic cancer (*Pancreas* 2014, 43:198–211). A randomised phase II study failed to show survival benefit when ruxolitinib (a JAK inhibitor) was added to capecitabine. In a small subset of patients with markers of systemic inflammation, a modest improvement in survival was identified. Two phase III trials evaluating capecitabine plus ruxolitinib in second-line advanced stage pancreatic ductal adenocarcinoma are ongoing.

Drugs targeting tumour metabolism. To survive hostile desmoplastic microenvironments, cancer cells reprogramme metabolic pathways to metabolise 10 times more glucose than normal. In addition, cancer cells process glucose through high rates of glycolysis and anaerobic conversion of pyruvate to lactate (Warburg effect). Nutrient deprivation

also activates autophagy, enabling cancer cells to utilise internal fuel sources. Hydroxyl-chloroquine, an autophagy inhibitor approved for malaria, is being evaluated in a neoadjuvant setting and advanced-stage disease in combination with nab-paclitaxel plus gemcitabine.

PI3K–mTOR pathway inhibitors. Mutations in *PIK3CA*, encoding part of the PI3K subunit, have rarely been reported in pancreatic ductal adenocarcinoma. While two phase II trials failed to demonstrate therapeutic activity for rapalogues targeting mTOR (the downstream effector of PI3K–AKT signalling), a case report in a patient with *STK11*-positive pancreatic cancer showed a response to everolimus. In future, next-generation DNA sequencing could identify patients most likely to respond to mTOR inhibitors.

Drugs targeting stromal compartments

A growing body of evidence suggests that crosstalk between malignant epithelial cells and surrounding stroma results in cancer cell proliferation, survival and resistance.

Hedgehog inhibitors. A phase II trial did not observe progression-free survival benefits when the SMO inhibitor vismodegib was added to gemcitabine in patients with chemonaïve metastatic pancreatic cancer. Vismodegib is currently being evaluated in combination with nab-paclitaxel and gemcitabine. The clinical failure of HH pathway inhibitors in pancreatic cancer may be better understood in light of preclinical evidence suggesting pathway inhibition releases tumour restraining influences of the stroma.

Enhancing drug delivery using hyaluronidase. Hyaluronic acid, a glycosaminoglycan extracellular matrix component, is enriched in the hypovascular stroma of pancreatic ductal adenocarcinoma. Degradation of hyaluronic acid might overcome physical barriers, enhancing drug delivery. In a phase II study, the addition of PEGPH20 (a recombinant human hyaluronidase) to nab-paclitaxel and gemcitabine resulted in increased response rate and progression-free survival in *post-hoc* analysis (Hingorani et al Abstract #4006 ASCO 2015).

Drugs targeting cancer stem cells

The concept of cancer stem cells driving tumour growth remains controversial. Expression of cancer stem cell markers in pancreatic ductal adenocarcinoma specimens was associated with shorter survival. In patient-derived xenograft models, treatment with drugs targeting cancer stem cells increased survival. However, as cancer stem cells frequently represent less than 1% of total tumour cells, drugs targeting cancer stem cells are unlikely to result in objective responses. Nevertheless, in advanced-stage pancreatic ductal adenocarcinoma, several drugs inhibiting signalling pathways associated with cancer stem cells are being tested in combination with chemotherapy.

Immunotherapy

Pancreatic cancers are characterised by immune-suppressive microenvironments believed to be orchestrated by multiple cell types recruited to the tumour, including cancer-associated fibroblasts, myeloid-derived suppressor cells, and tumour infiltrating lymphocytes. Disrupting immunosuppressive networks might provide new treatment opportunities.

Monoclonal antibody immunotherapies. Cancer cells evade natural immune responses by modulating T-cell signalling and inducing immune tolerance. While monoclonal antibodies targeting the checkpoint inhibitor PD-1 and its ligand PD-L1 have proved effective in non-small-cell lung cancer and melanoma, responses have not been observed in pancreatic cancer. Furthermore, ipilimumab, an anti-CTLA4 monoclonal antibody, failed to show significant activity in advanced-stage pancreatic ductal adenocarcinoma.

A different approach is through activation of CD40, a member of the tumour necrosis factor receptor superfamily present in tumour-associated macrophages. Gemcitabine combined with a CD40 agonist promoted accumulation of tumouricidal macrophages, leading to stromal collapse and tumour regression.

Cancer vaccines. GVAX pancreas is an allogeneic whole-cell vaccine generated from pancreatic cancer cell lines that have been modified to express granulocyte-macrophage colony-stimulating factor (GM-CSF). GM-CSF induces chemotaxis of dendritic cells to the injection site, which phagocytose tumour cells and subsequently present tumour antigens to T cells, eliciting an immune response against the tumour.

A phase II trial in metastatic pancreatic cancer reported a two-month improvement in overall survival for GVAX–cyclophosphamide and CRS-207 (an attenuated *Listeria monocytogenes* strain given as a boost vaccine) compared with GVAX–cyclophosphamide alone. In a different study, increased expression of PD-1/PD-L1 was noted following resection in patients treated with GVAX. Such studies suggest there may be roles for combining GVAX and immune-checkpoint inhibitors.

Chimeric antigen receptor T cells. A first-in-man study examining the safety of genetically modified T cells engineered to express chimeric antigen receptors recognising tumour antigens (CAR T cells) led to anaphylaxis and

Take home message from the authors

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"Even in the early stages, pancreatic ductal adenocarcinoma is a systemic disease. This is supported by *in vivo* models as well as clinical data showing that up to 60% of patients relapse within six months of resection. Better systemic treatments are needed in adjuvant settings, as well as different treatment strategies allowing early treatment of systemic disease (neoadjuvant therapy). For patients with locally advanced unresectable disease, where the role of chemoradiation is controversial, more effective induction chemotherapy backbones must be tested. For patients with more advanced disease, targeting different tumour compartments, such as the stroma, seems critical. The growing field of immunotherapy could open new treatment opportunities in this lethal disease.

Clinical implications

We would like to see an increasing number of neoadjuvant trials to elucidate the role of early systemic treatment. At a time when the value of care is critical for the sustainability of health care systems across the world, we need to consider whether drugs that provide modest survival benefits (days for erlotinib and weeks for MM-398) deliver any added value to patient care at current costs.

Future studies

In the adjuvant setting it will be interesting to follow up the results of the APACT and PRODIGE studies to discover whether more effective chemotherapy backbones impact on survival in patients with resectable disease. We also need to identify biomarkers to assist treatment decisions. It is also critical to elucidate whether patients with grade 2 ECOG performance status (Karnofsky score 70) benefit from nab-paclitaxel plus gemcitabine. The MPACT study did not find a survival benefit in this subgroup, and there is a potential for harm with gemcitabine doublets in frail patients.

For patients with advanced disease, early results from immunotherapy clinical trials enrolling pancreatic cancer patients were disappointing. The stroma in this disease is predominantly immunosuppressive leading to exclusion of CD8+ effector T lymphocytes. Overall this leads to a tumour phenotype characterised by immune system ignorance. Work in preclinical models shows that, even when only premalignant lesions (PanIN) are identified, the immune response is impaired. Treatment strategies that increase T-cell infiltration of tumour sites have shown promising results in preclinical models and are currently undergoing clinical testing in early-phase clinical trials. In addition, recent preclinical work demonstrates that loss of PTF1A, a regulator of acinar differentiation, is needed to facilitate oncogenic acinar to ductal reprogramming by KRAS. One could envision that the use of preclinical models such as Ptf1a cKO; $KRAS^{G12D}$ may facilitate the identification of neoepitopes as new targets to develop immunotherapies in this disease.

Lastly, use of next-generation sequencing and liquid biopsies need to be further investigated in this disease."

cardiac arrest in one patient, although clinical activity was seen in a patient with pancreatic ductal adenocarcinoma. A phase I study is evaluating meso-CAR T-cell therapy in advanced-stage pancreatic cancer.

Indoleamine-2, 3-dioxygenase inhibitors. Expression of the tryptophan-catabolising enzyme indoleamine-2, 3-dioxygenase (IDO) is associated with poor outcomes, with expression increased in metastases. Tryptophan metabolites are toxic to T cells and contribute to an immunosuppressive microenvironment by increasing regulatory T cell numbers. An ongoing phase Ib trial is testing the IDO inhibitor indoximod combined with nab-paclitaxel plus gemcitabine in advanced pancreatic ductal adenocarcinoma. Preliminary results from this study showed delayed and durable responses (Bahary et al. Abstract #452 ASCO GI 2016).