Review Article

Systemic therapy for metastatic pancreatic cancer

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Pancreatic cancer (PC) is a complex and highly lethal malignancy. Surgery currently remains the only curative modality, although this cancer typically presents at advanced incurable stages. This obviates the use of definitive therapies and underscores the need for better systemic therapies. Unfortunately, limited progress has been made over the past decades with regard to effective treatment. Despite many clinical trials using combinations of various promising agents, there was no real improvement in outcomes until recently. Many of the molecular interactions involved were previously unrecognized and new approaches are now being investigated as a deeper understanding of the pathogenesis evolves. Newer therapies seeking to exploit known oncogenic pathways are being explored, along with alternate delivery mechanisms using conventional cytotoxic drugs.

Keywords: Pancreatic cancer (PC); systemic therapy; immunotherapy

Submitted Sep 25, 2015. Accepted for publication Dec 03, 2015.
doi: 10.3978/j.issn.2218-676X.2015.12.03
View this article at: http://dx.doi.org/10.3978/j.issn.2218-676X.2015.12.03

Pancreatic cancer (PC) remains the fourth leading cause of cancer-related death in the U.S, with a median 1 year survival of 20% and 5 year survival of 5%. In 2015, the American Cancer Society estimates there will be 48,960 new cases, with 40,560 deaths (1). Incidence has increased from 1999 to 2008, in part due to the obesity epidemic and associated diabetes amongst other factors in an aging population. PC is predicted to become the 2nd leading cause of death by 2030 (2). Despite tremendous efforts in understanding the molecular and genetics of PC, improvements in clinical outcomes have been slow to materialize. Only 2% of PC patients are alive 5 years after diagnosis, underscoring the need for more effective therapies.

Gemcitabine (Gem) has been the standard of care since 1997 for first line treatment of patients with metastatic pancreatic cancer (mPC). Gemcitabine was evaluated in a small trial in which patients were randomized to either gemcitabine *vs.* bolus 5-fluorouracil. Median survival (5.65 *vs.* 4.41 months, P=0.0025) and one-year survival (18% *vs.* 2%) were superior with gemcitabine. In addition, clinical benefit response, a novel endpoint defined as at least a 4 week sustained improvement in pain scores, Karnofsky performance status, and weight, was also assessed and favored gemcitabine, 22% *vs.* 5% (3). Based on this data, gemcitabine gained FDA approval and remained the standard despite over 39 subsequent phase III trials being conducted. These studies directly compared new drugs to gemcitabine, added both conventional or newly formulated cytotoxic agents or added well conceived biologic agents to a gemcitabine backbone. Unfortunately, despite tremendous effort by investigators and patients, no regimen demonstrated improved survival over gemcitabine monotherapy.

Progress was finally achieved when gemcitabine was combined with erlotinib, the oral tyrosine kinase inhibitor targeting the epidermal growth factor receptor. In a phase III double blind, placebo controlled trial, 569 patients with

advanced or metastatic pancreatic adenocarcinoma were randomized to either erlotinib plus gemcitabine or gemcitabine alone. The erlotinib and gemcitabine combination achieved a median overall survival (OS) of 6.24 months compared to 5.91 months (P=0.038) with gemcitabine alone (4). One-year survival was also improved with erlotinib-gemcitabine (23% *vs.* 17%; P=0.023). There was suggestion that survival increased correlated with development of the EGFR inhibition specific toxicity, acneiform rash, as 10.5 months survival was seen with grade 2+ rash *vs.* 5 months with grades 0-1. Ultimately, the regimen was not well received and was criticized for providing a marginal clinical benefit, 2-week improvement in survival, despite being statistically significant. Nonetheless, erlotinib received FDA approval in 2005 but the regimen is not commonly used due to the development of more active, meaningful combinations.

Advances in the treatment of PC began to be observed with the presentation of the ACCORD 11 trial which evaluated the FOLFIRINOX regimen (5). The trial was a randomized, phase III, multicenter trial comparing gemcitabine monotherapy to FOLFIRINOX (oxaliplatin, irinotecan, leucovorin, fluorouracil) in which 342 patients with untreated metastatic pancreatic adenocarcinoma were enrolled. Patient selection for this study was stringent-age was limited to 75 years and below and only ECOG of 0-1 patients were included. In addition, patients with elevated bilirubins were excluded due to potential for increased irinotecan-induced toxicities and subsequently the proportion of patients with biliary stents was low (14.3%). The primary endpoint of OS demonstrated a dramatic improvement in the FOLFIRINOX group compared to the gemcitabine group (11.1 *vs.* 6.8 months; P<0.001). Median progression free survival (PFS) also favored the FOLFIRINOX group *vs.* the gemcitabine group (6.4 *vs.* 3.3 months; P<0.001). The objective response rate (ORR) was 31.6% in the FOLFIRINOX group *vs.* 9.4% in the gemcitabine group (P<0.001). The FOLFIRINOX group did experience significantly more grade 3-4 toxicities including neutropenia (46%), fatigue (24%), diarrhea (13%), thrombocytopenia and sensory neuropathy (both 9%). In addition, 5.4% of patients experienced febrile neutropenia and 43% required growth factor support. Despite the increased toxicity, QOL and Global Health Status assessments favored FOLFIRINOX over gemcitabine. The concerns regarding toxicities have led to the development of modified versions (mFOLFIRINOX) of the regimen which vary from institution to institution. One group used 75% of the 5-fluorouracil (5-FU) and irinotecan doses, administered with prophylactic pegfilgrastim in a single institution prospective phase II trial and showed improved tolerability with similar ORR and PFS (6). FOLFIRINOX has subsequently become a standard of care in a select subset of patients.

Another first line treatment option for patients with mPC is gemcitabine combined with nab-paclitaxel (nab-P; Abraxane). Preclinical work supports nab-P being uniquely tailored for PC due to its ability that disrupts the desmoplastic stroma that surrounds and shields pancreas cancer cells. Eloquent work in mouse models demonstrates increased stromal breakdown and tumoricidal activity when nab-P is combined with gemcitabine chemotherapy (7). In addition, nab-P has been shown to decrease the activity of cytidine deaminase, a critical enzyme that inactivates gemcitabine, resulting in additive effects with the combination. The regimen was first tested in a phase I/II trial in which previously untreated metastatic patients (n=67) were assigned to nab-P at 100, 125, and 150 mg/m^2 with standard gemcitabine. The maximum tolerated dose was defined as 125 mg/m^2 and at this dose, the ORR was 48%, OS 12.2 months, and one year survival 48%.

These encouraging results led to a randomized, international phase III trial (MPACT) of 861 previously untreated patients who were randomized to either gemcitabine alone or gemcitabine plus nab-P (8). Eligibility was notable for no age limitations, Karnofsy Performance Score (KPS) ≥70 and normal bilirubin. The primary endpoint of the study was OS and superiority of nab-P/gemcitabine (8.7 *vs.* 6.6 months; P<0.0001) was demonstrated. Gemcitabine and nab-P also achieved improved median PFS (5.5 *vs.* 3.7 months, P<0.0001) and ORR (23% *vs.* 7%, P<0.001) compared with gemcitabine. The most common grade 3 or higher adverse events attributed to the nab-P were neutropenia, fatigue, and neuropathy. However, in the nab-P/gemcitabine arm, neuropathy of grade 3 or higher improved to grade 1 or lower if nab-P was held over a median of 29 days. Prespecified subgroup analyses also demonstrated improved OS with the regimen in patients with poor prognostic factors including neutrophil to lymphocyte ratio (NLR) >5 and elevated CA 19-9s. Based on the MPACT trial, nab-P and gemcitabine are approved by the FDA for first line treatment of mPC patients.

With the establishment of two standards of care for the treatment of mPC patients, there is debate of which regimen is the most practical and clinically useful. To

address this, the patient selection and eligibility of the ACCORD 11 and MPACT trials need to be considered. The French trial limited accrual by age, performance status and was conducted only at academic centers. Conversely, MPACT did not restrict age (10% of patients were 75 or older) and included ECOG PS 2 (8%) patients. The trial was conducted globally with the majority of patients, 55%, being treated in the US, with most (66%) being treated at community as opposed to academic centers. In terms of clinical outcomes, FOLFIRINOX has a longer median survival although patients with similar performance status (ECOG 0) in the MPACT trial achieved a better survival of 12.6 months. Response rates with the 2 regimens are identical when the same methodology, investigator assessed and not central review, is used 29% in MPACT *vs.* 31% in ACCORD 11. In addition, toxicity with FOLFIRINOX is substantial and 43% *vs.* 26% required growth factor support. This, and the potential for hospitalization, results in the under-appreciated increased costs with FOLFIRINOX. Finally, the comment is made that the single agent gemcitabine control arms in both trials showed similar outcomes although this may be more reflective of the maximal benefit with gemcitabine alone as was also seen in a multitude of negative phase III trials. Regardless of the ongoing debate, two standards of care for the treatment of PCs have been established and represent progress in the treatment of this disease.

In general, FOLFIRINOX is recommended as first line treatment in good performance status, younger (<60 years old) patients whereas nab-P/gemcitabine is also appropriate for these patients in addition to older individuals and patients with PS 2. With both regimens, the bilirubin levels need to be <1.5 upper limit of normal.

Second line therapy

Advances in the second line treatment of metastatic cancer patients have also been achieved. The National Comprehensive Cancer Network (NCCN) guidelines are for patient to be treated with the alternative based regimen from their first line chemotherapy for example, gemcitabine based in the 2nd line if first line 5-FU based regimens were used. In general, either 5-FU alone or combined with oxaliplatin has been the most commonly used 2nd line regimens. This is partly based on the phase III German CONKO-003 trial (9) that compared a weekly infusional 5-FU/leucovorin to the same regimen with biweekly oxaliplatin (OFF). Patients on the OFF arm experienced an OS of 5.9 months compared to patients on the control arm, 3.3 months (HR=0.66, P=0.010) The Canadian PANCREOX trial (10) challenged these findings as modified FOLFOX led to only a 6.1-month OS compared to a 9.9-month survival in the 5-FU based control arm (P=0.02). Imbalances in 3rd line treatments (25% *vs.* 7%) and toxicity (11% *vs.* 63%) favoring the control arm may have contributed to the study results.

MM-398 (Onivyde) is irinotecan, approximately 80,000 molecules, encapsulated in a nanoparticle, liposome drug delivery system. In preclinical studies, this formulation improves pharmacokinetics and tumor biodistribution of both irinotecan and its active metabolite, SN-38, compared with free irinotecan. This leads to increased efficacy as observed in an orthotopic PC mouse model with less exposure to non-target organs and associated toxicities. MM398 was studied in a randomized phase III trial (NAPOLI-1) in 417 gemcitabine-refractory metastatic cancer patients (11). This 2nd line trial randomized patients to either MM-398 alone, MM-398 + 5-FU/LV, or the control arm of 5-FU/LV, with OS as the primary endpoint. Patients on the MM-398 + 5-FU/LV arms achieved a median OS benefit of 6.1 *vs.* 4.2 months for the 5-FU/LV control arm (HR 0.68, P=0.014). There was no statistical benefit for the single agent MM-398 arm compared to control. MM-398 is approved by the FDA for treatment of patients with advanced PC who was previously treated with gemcitabine-based chemotherapy.

With MM-398 now available, sequencing of treatments for PC can be considered. If patients receive a gemcitabine-based regimen in the first-line setting, it is practical to use MM-398 as 2nd line treatment. This is especially true for patients receiving nab-P or oxaliplatin in whom neuropathy and thrombocytopenia are common adverse events leading to treatment discontinuation. The MM398/5-FU/LV regimen is not associated with these specific side effects. If patients receive upfront FOLFIRINOX, a gemcitabine-based combination such as gemcitabine/nab-P can be considered but this places MM-398 to a later line of treatment and fewer patients would be eligible for treatment with the agent. Whichever approach is favored, the need to strategize which regimen to use in the first-line to facilitate treatment in the second line is a new and welcomed consideration in the treatment of advanced PC.

Another interesting approach in the treatment of mPC is to reduce Inflammatory-mediated cytokine signaling which underlies the evolution of many cancers, including mPC. These patients typically have elevated CRP levels and other

clinical signs of systemic inflammation including cancer cachexia. Ruloxitinib, a JAK1/JAK2 inhibitor currently approved for treatment of myelofibrosis, has documented activity in JAK-STAT pathways thought to promote this proinflammatory cytokine release. The phase II RECAP study randomized 127 patients to capecitabine plus ruloxitinib or placebo in the second line setting, with OS as the primary endpoint (12). A pre-planned subset analysis was included evaluating patients based on CRP levels. Although this was a negative study overall, patients with CRP >13 mg/L did show a statistically significant OS improvement with 42% *vs.* 11% alive at 6 months (P=0.005). Grade 3/4 adverse event incidence was 75% with ruloxitinib combination *vs.* 82% in placebo arm. Currently, the JANUS 1 and JANUS 2 phase III trials are evaluating second-line ruloxitinb in mPC patients with systemic inflammation as defined by modified Glasgow Prognostic Scores of 1 and 2.

Future directions

With the improvements in treatments for mPC being achieved, concentrated focus on genetic and molecular targets continues. Newer therapies seeking to exploit known oncogenic pathways and the tumor microenvironment are being explored. Several promising approaches are discussed below.

High hyaluronan (HA) levels have been observed in PC, and are felt to hinder chemotherapy perfusion due to increasing interstitial stromal pressures within the tumor. Pegylated recombinant human hyaluronidase (PEG-PH20) lowers this resistance by reducing HA. In a phase II randomized trial, untreated mPC patients were assigned to either PEG-PH20 and Gem/nab-P *vs.* Gem/nab-P (13). Tumors with high HA had a better ORR with the 3-drug combination than with Gem/nab-P (52% *vs.* 24%, P=0.038). Median duration of response was 8.1 *vs.* 3.7 months. PFS also favored the high HA group with PEG-PH20 (0.2 *vs.* 4.2 months, P=0.03). There was a concerning increase in thromboembolic events (TEs), with 42% *vs.* 25% of study patients having at least 1 event, and 4% of PEG-PH20 patients discontinuing due to TE. The protocol was temporarily placed on hold and amended to exclude high TE risk patients and to add enoxaparin prophylaxis, which led to a reduction in TE events. A global phase III, randomized, double-blind placebo-controlled study is planned.

Evofosfamide (TH-302) is a prodrug activated to release the potent DNA alkylating agent bromo-isophosphoramide mustard only in hypoxic conditions. Upon activation, the drug also diffuses into surrounding oxygenated areas of the tumor killing nearby cancer cells via a "bystander effect". Because of its preferential activating in hypoxic areas, evofosfamide is well suited for PC where hypoxia regions are commonly found in the tumor microenvironment. Evofosfamide was evaluated in a randomized phase II trial with 214 advanced PC patients randomized to one of three treatment arms: single-agent gemcitabine, gemcitabine and TH-302 at a dose of 240 mg/m^2 or at a dose of 340 mg/m^2 (14). The two combination regimens demonstrated longer PFS than with gemcitabine alone (5.6 *vs.* 3.6 months; HR=0.61; 95% CI, 0.43–0.87) and in the metastatic patient cohort, the PFS benefit with TH-302 was 5.1 *vs.* 3.4 months. Response rates were also improved 26% at the 340 mg/m^2 dose, 17% at the lower TH-302 dose and 12% with gemcitabine alone (P=0.04). Median OS was 9.2 and 8.7 months at the high and low TH-302 doses, respectively, *vs.* 6.9 months with gemcitabine. The differences were not statistically significant although crossover (38%) was allowed. Toxicities included dose dependent grade 3/4 thrombocytopenia (30%, 55%), neutropenia (34%, 43%), as well as rash (2%) and grade 1-2 stomatitis but overall the combinations were well tolerated. The results of a global phase 3 trial comparing gemcitabine-TH-302 at 340 mg/m^2 *vs.* gemcitabine is to be reported in the near future.

It has long been postulated that heparins have some anti-neoplastic effect through modulation of tumor growth and metastasis (15). Cancer patients on heparin-based therapy may have better overall outcomes which is not completely attributable to anticoagulation effects. Additionally, PC is one of the most thrombogenic malignancies. Unfortunately, the clinical utility of heparin as therapy for cancer has been limited by its anticoagulant effect. A novel agent, necuparanib (M402) was developed from unfractionated heparin with the intent of attenuating anticoagulation but preserving desired antineoplastic properties, allowing it to be given in higher doses. This drug is being evaluated in a phase II, double blinded, proof-of-concept clinical trial as first line therapy in mPC, in combination with Gem/nab-P *vs.* Gem/nab-P alone. Necuparanib was granted Orphan Drug Designation by the FDA in 2014.

Immunotherapy, specifically immune checkpoint inhibition, is an exciting area of interest in PC, given its success in other solid malignancies. Interesting data in non-colorectal microsatellite unstable patients has recently been presented with pembrolizumab and reveals high response rates and preliminarily, improvements in survival (16).

PARP inhibition is another area of research, based on the fact that up to 8% of PC harbors *BRCA* mutations (up to 17% familial PC kindreds have *BRCA*-2 mutations). Drugs such as olaparib and velaparib are currently under investigation.

Conclusions

Metastatic PC remains a highly lethal disease with poor prognosis as patients typically present at advanced, unresectable stages. Since gemcitabine was approved in 1997, advances in systemic therapy were not achieved until FOLFIRINOX was presented in 2011 and nab-paclitaxel was approved in 2013. Both regimens extend OS with FOLFIRINOX reaching 11 months but with significant toxicities. Many of the patients typically encountered in everyday clinical practice are not eligible for this approach. Gem/nab-P is a reasonable alternative, although with its own unique side effects. In subsets of patients, survival over 12 months is observed and rivals outcomes with FOLFIRINOX. With the approval of MM-398, there is now an option that improves survival for patients in the second-line setting. These regimens now create the previously unheard of need to consider sequencing when beginning to treat a patient with first-line chemotherapy. In the second-line setting, fluoropyrimidine-based regimens are options in patients treated with nab-P, and gem/nab-P can be given to frontline FOLFIRINOX-treated patients. Several clinical trials have shown promising results with novel therapies exploiting oncogenic pathways or disrupting the tumor microenvironment. Strategies focusing on immunotherapy and specific genetic syndromes, although still in early stages of development, hold promise for the future. In conclusion, PC remains a complex disease, and despite progress in systemic therapy being made, further work remains to be done.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Cancer Research* for the series "Pancreatic Cancer". The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.3978/j.issn.2218-676X.2015.12.03). The series "Pancreatic Cancer" was commissioned by the editorial office without any funding or sponsorship. GPK served as the unpaid Guest Editor of the series. The authors have no other conflicts of interest to declare.

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.

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Cite this article as: Zaiden R, Zhou L, Kim GP. Systemic therapy for metastatic pancreatic cancer. Transl Cancer Res 2015;4(6):653-658. doi: 10.3978/j.issn.2218-676X.2015.12.03

