Mini-Review

Pancreatic Cancer: Progress in Systemic Therapy

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Key Words

Chemotherapy · Pancreas · Pancreatic cancer · Therapy

Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) is a leading cause of cancer-related deaths in the Western world. Due to lack of specific symptoms and no accessible precursor lesions, primary diagnosis is commonly delayed, resulting in the identification of only 15–20% of patients with potentially curable disease. The major limiting factor is an already locally advanced or metastatic disease at the time of diagnosis. Consequently, systemic therapy forms the backbone of treatment strategy for the majority of patients. **Summary:** A deeper understanding of the molecular characteristics of pancreatic cancer has led to the identification of several potential therapeutic targets. A variety of targeted therapies are currently under clinical evaluation as single agents or in combination with chemotherapy for PDAC. This review highlights the current state of chemotherapy in pancreatic cancer and provides an outlook on its future perspectives. **Key Message:** This review focuses on the current chemotherapy regimens for the systemic treatment of PDAC. **Practical Implications:** Various neoadjuvant approaches have been explored, including chemoradiation, chemotherapy followed by chemoradiation or intensified chemotherapy without defining a standard of care so far. The standard of care is gemcitabine or 5-fluorouracil. The oral fluoropyrimidine S-1 may be a promising new agent in this setting. For first-line treatment of metastatic pancreatic cancer, no targeted therapy has yet demonstrated clinical benefit apart from the combination of the tyrosine kinase inhibitor erlotinib plus gemcitabine. Recently, novel chemotherapeutic regimens such as FOLFIRINOX and gemcitabine plus nanoparticle albumin-bound paclitaxel have been introduced. Both combinations have proved to be superior to the standard gemcitabine regimen. For second-line treatment the combination of 5-fluorouracil/leucovorin and oxaliplatin yields improved results compared to best supportive care.

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is still the most lethal cancer in the Western world [1]. Whereas survival times in various other solid tumor entities have constantly improved, only subtle advances were achieved in PDAC over the last decade [2]. Moreover, forecasts predict only a marginal improvement in overall survival (OS) by 2030 when pancreatic cancer shall be the third leading cause of cancer death due to a steady rise in incidence [3].

The only potentially curative approach for PDAC is surgery. Only 15–20% of patients are eligible for surgery at primary diagnosis. The major limiting factor is an already locally advanced or metastatic disease at the time of diagnosis. Consequently, the 5-year OS does not exceed 7% [1, 2]. After surgical resection and adjuvant chemotherapy the OS rate is about 20% [1, 4]. To improve this outcome a neoadjuvant treatment strategy may be helpful, and several small trials have been conducted [5–11]. As yet, there is no established standard of care for the neoadjuvant treatment of resectable, borderline or locally advanced PDAC. Recently the standard of care in the metastatic setting has been improved by the FOLFIRINOX protocol [12], a combination of 5-fluorouracil (5-FU), leucovorin, irinotecan and oxaliplatin that was first examined in colorectal cancer [13, 14] and by the combination of gemcitabine plus nanoparticle albumin-bound paclitaxel (nab-paclitaxel) [15]. Both regimens are superior to the standard of single-agent gemcitabine [12, 15].

Apart from conventional chemotherapies, various targeted therapies including anti-EGFR, anti-VEGF and anti-Her2 antibodies have become the standard of care for certain types of colorectal or gastric cancer [13, 16–19]. However, despite numerous large clinical trials, no targeted therapy has as yet demonstrated clinical benefit in PDAC apart from the tyrosine kinase inhibitor erlotinib in combination with gemcitabine [20].

Our understanding of the molecular biology of PDAC increases steadily. Various novel drugs have emerged for a targeted treatment of PDAC. A major focus in PDAC research is nowadays on the interaction of the tumor with its microenvironment, in particular with its surrounding stroma. The tumor stroma with its cellular components, in particular the so-called pancreatic stellate cells, is thought to provide a pro-tumorigenic microenvironment associated with tumor hypoxia, hypovascularization and epithelial-mesenchymal transition. This, in turn, lowers the concentration of chemotherapeutic agents in the tumor and confers chemoresistance, changes the tumor metabolism and leads to the competitive selection of more aggressive tumor subclones [21]. Another concept addresses the marked heterogeneity of PDAC and the likely existence of cancer stem cells or cancer-initiating cells in at least a subset of these tumors. Cancer-initiating cells are characterized by a high level of resistance to common therapies and may be a key factor for tumor recurrence [22]. Again, the stroma appears to play a supportive role since pancreatic stellate cells have been shown to generate a ‘niche’ for cancer-initiating cells [23].

This review aims at providing an overview on the current and emerging therapeutic strategies in PDAC treatment.

Neoadjuvant Treatment Strategies

Neoadjuvant treatment in PDAC has different aims. It can be a valid tool for downsizing or even downstaging borderline resectable or locally advanced PDACs and thereby enable surgery with curative intent in a subset of patients. It may also be a strategy to reduce the risk of early metastasis, given the fact that a large proportion of PDACs are likely to be metastatic even when they appear clearly resectable as determined by conventional imaging [24].

Various neoadjuvant approaches have been examined for borderline resectable and locally advanced pancreatic cancers, including chemoradiation (CRT), chemotherapy followed by chemotherapy/radiotherapy or intensified chemotherapy. These approaches were largely hampered by the fact that until recently there were few protocols that induced a significant tumor response in a significant number of patients. Only the combination of gemcitabine with oxaliplatin showed a significantly improved response rate compared to gemcitabine alone in a GERCOT trial (26.8 vs. 17.3%, $p = 0.04$), but resectability was not systematically evaluated in these patients. It has become evident that conventional imaging may not be sufficient to assess resectability after neoadjuvant treatment and therefore even patients who exhibit stable disease according to computed tomography or magnetic resonance imaging after neoadjuvant treatment should undergo diagnostic laparotomy to evaluate resectability [25]. Recently, there have been small trials publishing promising data for the use of FOLFIRINOX [26] or gemcitabine plus nab-paclitaxel [10, 27], but these data have to be confirmed in larger, randomized trials.

There have been conflicting data regarding the use of CRT with either gemcitabine or fluoropyrimidines [28] in patients with locally advanced PDAC [29–32]. This is mainly due to the fact that while local recurrence can be controlled by CRT, the majority of patients succumb to distal metastases. Retrospective analyses suggested that a strategy with initial chemotherapy followed by CRT for those patients who had at least stable disease during chemotherapy may help to select those patients who really benefit from the addition of radiotherapy as local treatment. However, when this hypothesis was examined in a prospective trial (the so-called LAP-07 trial), there was no difference in OS of patients with locally advanced PDAC receiving gemcitabine followed by CRT with capecitabine as compared to gemcitabine only treatment [33]. Given these data, CRT in locally advanced PDAC should only be performed within a clinical trial.

Data on combinations of CRT with targeted therapies are still preliminary. A recently published phase II trial reported no benefit for the addition of bevacizumab to a capecitabine-based CRT followed by gemcitabine [34]. Interesting survival rates (1-year OS 66%, 2-year OS 25%) were reported in a single-arm phase II trial using a combination of cetuximab, gemcitabine and oxaliplatin followed by CRT with cetuximab/capecitabine in locally advanced pancreatic cancer, with acceptable toxicity [35]. The above-mentioned LAP-07 trial also examined the use of adding erlotinib to gemcitabine for the treatment of patients with locally advanced PDAC. However, the addition of erlotinib did not confer any benefit [33].

New approaches with the aim of finally defining the role of neoadjuvant therapies in resectable, borderline and locally advanced disease are currently under investigation by many study groups. In particular, there is increasing interest in true neoadjuvant treatment concepts to improve the outcome of patients with clearly resectable disease.

Adjuvant Treatment

PDAC is characterized by its high risk of early metastasis. This fact and the chance of minimal residual disease after resection are the rationale of adjuvant chemotherapy. Three major trials could confirm a survival benefit for adjuvant chemotherapy with gemcitabine or 5-FU after R0/R1 resection compared to surgery alone [36–38]. Based on these and further studies there are general recommendations for adjuvant therapy (table 1, fig. 1). The ESPAC-1 trial compared chemotherapy with 5-FU/leucovorin (CT) versus CRT or observation (O). This trial used a 2×2 factorial design and showed significant differences in favor of CT in median progression-free survival (mPFS) (15.3 months CT vs. 9.4 months O, $p = 0.02$; 10.7 months CRT vs. 15.2 months no CRT, $p = 0.04$) and median OS (mOS) (20.1 months CT

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Fig. 1. Stage-dependent therapeutic decisions in pancreatic cancer. ERL = Erlotinib; GEM = gemcitabine; LAPC = locally advanced pancreatic cancer; mPDAC = metastatic PDAC; NAB = nab-paclitaxel; – = normal; ↑ = bilirubin >1.5 times the upper limit of normal.

Table 1. Adjuvant therapies in PDAC

Trial	Treatment	Patients, n	mPFS, months	p value	mOS, months	p value	2-year OS, %	5-year OS, %	Ref.
EORTC	observation 5-FU/RT	108 110	16.0 17.4	NR	19.0 24.5	0.208	41 51	22 28	72
ESPAC-1	CRT vs. no CRT ¹ CTx vs. no CTx	145/144 147/142	10.7/15.2 15.3/9.4	0.04 0.02	15.9/17.9 20.1/15.5	0.05 0.009	29/41 40/30	10/20 21/8	38
CONKO-001	observation gemcitabine	175 179	6.7 13.4	<0.001	20.2 22.8	0.01	NR	10.4 20.7	37
ESPAC-3	5-FU/LV gemcitabine	551 537	14.1 14.3	0.53	23.0 23.6	0.39	48.1 49.1	NR	36
RTOG 9704	5-FU/RT gemcitabine/RT	230 221	NR	NR	17.1 20.5	0.08	NR	18 22	73
JASPAC-01	S-1 gemcitabine	187 191	23.3 11.2	0.67	46.3 25.9	<0.001	70 53	NR	41

CONKO = Charité Onkologie; CTx = chemotherapy with 5-FU and leucovorin; EORTC = European Organisation for Research and Treatment of Cancer; ESPAC = European Study Group for Pancreatic Cancer; JASPAC = Japan Adjuvant Study Group of Pancreatic Cancer; LV = leucovorin; NR = not reported; Ref. = reference; RT = radiotherapy; RTOG = Radiation Therapy Oncology Group.

¹CRT = 5-FU/leucovorin + radiotherapy.

vs. 15.5 months O, $p = 0.009$; 15.9 months CRT vs. 17.9 months no CRT, $p = 0.05$) as well as 5-year OS rates (21% CT vs. 10% CRT vs. 8% O) [38]. The CONKO-001 compared gemcitabine with best supportive care after R0/R1 resection of PDAC. This trial also showed a significant benefit in favor of chemotherapy with respect to mPFS (13.4 vs. 6.7 months, $p < 0.001$) and mOS (22.8 vs. 20.2 months, $p = 0.01$) as well as 5-year OS rates (20.7 vs. 10.4%) [37]. The ESPAC-3 trial directly compared both regimens (5-FU and gemcitabine) and did not show a significant difference in outcome, but differences in the respective toxicity profiles [36]. Accordingly both substances are recommended equally for adjuvant treatment and can replace each other.

When to Start Adjuvant Treatment?

It is currently unclear when adjuvant chemotherapy should be started after surgery for pancreatic cancer. In other tumor entities such as colorectal cancer, starting as early as possible after surgery has been recommended to obtain the maximum benefit from this treatment [39]. After surgery for pancreatic cancer the start of adjuvant chemotherapy is frequently delayed due to postoperative complications or slow recovery of the patient. A recently published subgroup analysis of the ESPAC-3 trial suggests that the treatment duration (6 months) and the associated dose intensity are more relevant than a very early (within 6 weeks) initiation of treatment after surgery. Indeed, there was no significant difference in OS when chemotherapy was started up to 12 weeks after surgery [40].

Novel Drugs in the Adjuvant Setting

A promising new drug for adjuvant therapy of PDAC may be S-1, an oral fluoropyrimidine. The recently presented data of the JASPAC-01 trial revealed a significantly superior 2-year OS rate for S-1 compared to gemcitabine (70 vs. 53%) [41]. However, the trial is not yet fully published and is limited to an Asian collective and will have to be reproduced in the Caucasian population due to differences in the metabolism of S-1 between Asian and Caucasian patients. Further new concepts examine FOLFIRINOX or nab-paclitaxel/gemcitabine compared with single-agent gemcitabine in the adjuvant setting [42, 43].

Metastatic Pancreatic Cancer

Most patients with pancreatic cancer present with metastatic disease. At this stage systemic chemotherapy is the mainstay of therapy. There is a relationship between the patient's performance status and the therapeutic outcome in first- and second-line therapy of advanced PDAC [44–46]. Chemotherapy should not be applied above an Eastern Cooperative Oncology Group (ECOG) score of 2.

First-Line Therapy

Gemcitabine and the combination of gemcitabine/erlotinib have been the standard of care for quite some time [20, 47]. Erlotinib is a selective, small-molecule inhibitor of the EGFR tyrosine kinase and so far the only approved targeted therapy in PDAC. The addition of erlotinib to gemcitabine improved the mOS of patients in a phase III study by 0.33 months (about 10 days) in the experimental arm, which was statistically significant but of questionable clinical relevance [20]. However, according to an as yet not fully published subgroup analysis, patients who developed skin rash upon erlotinib treatment did benefit from the combination (mOS up to 10.5 months), whereas patients without skin rash had no benefit from additional erlotinib. Consequently, discontinuation of erlotinib is recommended in case no rash appears within the first 8 weeks of treatment with erlotinib. Another EGFR inhibitor, cetuximab, was

also examined and did not show a significant difference in mOS. There is no subgroup analysis for skin rash for that trial [48]. Further trials are required to precisely define the patient population that benefits from a combinational approach, since other EGFR inhibitors like panitumumab (phase II) [49], nimotuzumab (phase II) [50] and matuzumab (phase I) [51] showed promising effects, but have not been tested in a phase III setting.

After a long series of failed phase III trials, the FOLFIRINOX protocol (5-FU/leucovorin/irinotecan/oxaliplatin) substantially improved all outcome parameters in metastatic PDAC compared to gemcitabine alone: response rate (54 vs. 16%, $p < 0.001$), mPFS (6.4 vs. 3.3 months, HR = 0.47) and mOS (11.1 vs. 6.8 months, HR = 0.57). The OS rate at 1 year was 48.4% for FOLFIRINOX and 20.6% for gemcitabine, respectively [12]. FOLFIRINOX is more toxic than gemcitabine. There are significantly more neutropenia and consecutive febrile neutropenia as well as non-hematological adverse effects such as sensory neuropathy. Interestingly, a subgroup analysis of the PRODIGE 4/ACCORD 11 trial revealed an improved quality of life for FOLFIRINOX compared to gemcitabine despite the increased toxicity of this regimen [52].

The second combination regimen that was superior to single-agent gemcitabine is the recently published combination of nab-paclitaxel with gemcitabine. The combination was superior with respect to PFS (5.5 vs. 3.7 months, HR = 0.69) and OS (8.5 vs. 6.7 months, HR = 0.72) [15]. The 1-year OS rate was 35% for the combination and 22% for gemcitabine monotherapy. The trial included only patients with normal bilirubin levels. The combination of gemcitabine and nab-paclitaxel conferred more side effects than gemcitabine, in particular with respect to hematotoxicity and neurotoxicity. However, severe side effects such as febrile neutropenia were less frequent than in the ACCORD trial with FOLFIRINOX. The more favorable toxicity profile makes the combination of nab-paclitaxel and gemcitabine the preferred new chemotherapy backbone for novel combinations. More than 30 trials are currently listed in Clinical Trials that use this backbone together with a novel, mostly targeted therapeutic agent for PDAC.

The combination of nab-paclitaxel with gemcitabine is the only gemcitabine-based combination that significantly increases OS compared to gemcitabine monotherapy. The conjugation of paclitaxel with albumin nanoparticles as a carrier protein may improve its effectiveness by using albumin as a natural carrier for hydrophobic molecules and its active, gp60 receptor-mediated transcytosis across the blood vessel endothelium. Another possible explanation for the efficacy of this combination regimen are synergisms between both substances. In a preclinical mouse model nab-paclitaxel reduced the activity of cytidine deaminase, the key enzyme for inactivation of gemcitabine that is overexpressed in human PDAC [53]. Moreover, nab-paclitaxel interacts with the tumor-surrounding stroma. Preclinical data using human PDAC cell lines and samples show a reduction in stromal density after treatment with nab-paclitaxel/gemcitabine [54, 55]. The reduced stromal density goes along with increased vascularity, which may facilitate gemcitabine delivery and lead to a higher intratumoral gemcitabine concentration [54].

The availability of four different regimens for metastatic PDAC enables us now, for the first time, to tailor the treatment to the individual patient. Patients with metastatic PDAC younger than 75 years, with a good performance status (ECOG score of 0–1) and bilirubin levels ≤ 1.5 times the upper limit of normal qualify for FOLFIRINOX (since these were the inclusion criteria for the study) [12]. According to the data of the MPACT trial, the combination of nab-paclitaxel and gemcitabine is also feasible in patients older than 75 years and with an ECOG score of 0–2, but with normal bilirubin levels. In a subgroup analysis, patients with highly increased CA19-9 levels did particularly benefit from this combination. Patients not fulfilling these criteria are still eligible for gemcitabine or the combination of gemcitabine with erlotinib.

Table 2. Second-line therapies in advanced PDAC

Regimen	Phase	Patients, n	mPFS, months	mOS, months	6-month OS, %	DCR, %	Ref.
FOLFIRINOX	ret.	22	5.4	8.5	n.a.	63	58
FOLFIRINOX	ret.	18	2.8	8.4	44.4	55.6	74
Nab-paclitaxel	II	19	1.7	7.3	58	37	59
FOLFIRI	II	50	3.2	5.0	32	36	75
Capecitabine/docetaxel	II	43	3.7	5.3	n.a.	73	76
Modified FOLFOX	II	30	1.5	3.7	30	17	77
FOLFIRI		31	2.1	4.2	27	23	
OFF	III	46		4.8	n.a.	n.a.	56
Mitomycin/ifosfamide	II	21	1.7	3.7	n.a.	15	78
Capecitabine/oxaliplatin	II	39	2.5	5.8	44	28.6	79
OFF	III	76	2.9	5.9	n.a.	n.a.	57
FF		84	2.0	3.3			
Nal-IRI	II	40	2.4	5.2	42.5	50	62
Nal-IRI/5-FU/LV	III	417	3.1	6.1	n.a.	n.a.	63
5-FU/LV			1.5	4.2			
Gemcitabine/oxaliplatin	II	33	4.2	6	n.a.	61.3	80
Vatalanib	II	67	2	n.a.	29	31	81
5-FU/paclitaxel	II	28	2.5	7.6	n.a.	30	82
FOLFOX	II	44	2.5	7.8	n.a.	40.9	83

DCR = Disease control rate; FF = folinic acid and 5-FU; FOLFIRI = 5-FU, leucovorin and irinotecan; FOLFOX = 5-FU, leucovorin and oxaliplatin; LV = leucovorin; n.a. = not assessed; Ref. = reference; ret. = retrospective.

Second-Line Therapy

For a long time second-line therapy in pancreatic cancer was uncommon. However, recent data showed that the combination of 5-FU/leucovorin and oxaliplatin (OFF) significantly prolongs OS by 2.52 months compared to best supportive care ($p = 0.008$) [56]. This regimen can be recommended for patients with an ECOG score of 0–2 [57]. Second-line therapy with gemcitabine can be beneficial for patients who were previously treated with FOLFIRINOX [12]. There are also data from small prospective or retrospective trials using the FOLFIRINOX protocol [58] or nab-paclitaxel [59] as monotherapy in the second-line setting. Table 2 gives an overview on various second-line trials in metastatic PDAC. In summary, the data demonstrate a mPFS of 3 months and a mOS of up to 6 months for second-line treatments. This shows that patients with advanced pancreatic cancer eligible to receive second-line treatment substantially benefit from such therapy.

Improved conjugation systems may also offer a chance to improve the efficacy of chemotherapeutics for second-line treatment. The formulation of nanoliposomal irinotecan (nal-IRI) yielded increased intratumoral levels of CPT-11 and its active metabolite SN-38 compared to standard irinotecan in a mouse xenograft of human colon carcinoma and pancreatic cancer [60, 61]. The preclinical data could be somewhat confirmed by a phase II and III study of

nal-IRI in advanced gemcitabine-refractory PDAC [62, 63]. After failure of first-line therapy with gemcitabine, nal-IRI treatment achieved a mPFS of 2.4 months and a mOS of 5.2 months, with a disease control rate of 50% in the phase II trial [62]. These data were confirmed by the so far not fully published NAPOLI-1 trial (phase III) [63]. Here the combination of nal-IRI with 5-FU/leucovorin significantly improved mPFS (3.1 vs. 1.5 months, HR = 0.56) and mOS (6.1 vs. 4.2 months, HR = 0.67) compared to 5-FU/leucovorin. Nal-IRI as a single agent was not significantly superior to 5-FU/leucovorin. However, the combination of nal-IRI with 5-FU/leucovorin has side effects such as fatigue and diarrhea that need to be considered in this setting, see figure 1.

Even at the early stages of tumor development, local and systemic inflammation is present in PDAC [64, 65]. Given the role of JAK/STAT signaling in this setting, the combination of the JAK1/2 inhibitor ruxolitinib with capecitabine was recently compared to capecitabine plus placebo in a phase II trial in the second-line setting [66]. Within the randomized population, mPFS (HR = 0.75) and mOS (HR = 0.79) favored ruxolitinib over placebo. Interestingly, the subgroup with elevated CRP levels (>13 mg/l) significantly benefited from the addition of ruxolitinib compared to capecitabine monotherapy (3- and 6-month OS rates 48 and 42% vs. 29 and 11%) [66].

Immunotherapy for PDAC?

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) is a pivotal immune-inhibitory molecule [67]. In a mouse model of two non-immunogenic murine tumor models, the combination of a CTLA-4 inhibitor and gemcitabine was tested. The combination exhibited tumor regression and long-term protective immunity, indicating a synergistic effect in the treatment of cancer [68]. In a first clinical trial, monotherapy with the CTLA-4 inhibitor ipilimumab failed to show a significant benefit in locally advanced or metastatic PDAC [69].

Another approach for specific targeting of participating tumor-associated antigens are vaccination strategies. In a recent phase II trial a vaccine of devitalized allogeneic pancreatic cancer cells transfected with GM-CSF (GVAX) was combined with mesothelin-expressing live-attenuated *Listeria monocytogenes* (CRS-207) for additive stimulation of the innate and adaptive immunity and compared to GVAX alone [70]. Prior to GVAX patients received low-dose cyclophosphamide as an immune modulator for inhibition of regulatory T cells. The trial was conducted in a patient collective with metastatic PDAC and at least one prior chemotherapy regimen. An interim analysis of 90 patients revealed a significantly improved OS for the combination of GVAX plus CRS-207 in contrast to GVAX alone (mOS 6.1 vs. 3.9 months, HR = 0.54) [70]. A phase IIb trial (ECLIPSE) is currently examining this concept in patients with pretreated metastatic PDAC [71].

Conclusion

FOLFIRINOX and nab-paclitaxel/gemcitabine have improved the standard of care for patients with metastatic PDAC. These combinations may also improve the treatment of PDAC in the neoadjuvant and adjuvant setting. Nab-paclitaxel plus gemcitabine is a novel backbone for the development of further therapeutic regimens in locally advanced and metastatic PDAC.

Since PDAC is a heterogeneous and genetically highly complex disease, the molecular characterization of a given tumor represents an important cornerstone for the development of future therapies. To overcome the difficulties associated with intratumoral heterogeneity

of PDAC, various targets in different pathways have to be considered. However, the first experiences with such multi-targeting strategies resulted in increased toxicity as a limiting factor. A major challenge is also the establishment of biomarkers in the tumor and/or in blood (liquid biopsies) for response prediction, response evaluation and molecular monitoring of the tumor under or after therapy.

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