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Management of ductal pancreatic cancer

The oncologists view: systemic treatment options in 2018

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Summary
Background The majority of patients diagnosed with pancreatic cancer have inoperable disease at the time of presentation. For this reason, systemic treatment is the cornerstone of therapy and more options for systemic therapy have now become available than were a decade ago.
Methods In this short review, we will give an overview on the systemic therapeutic landscape in 2018 and briefly discuss the challenging topic of neoadjuvant therapy.
Results However, there are a lot of unsolved questions and an urgent need of more clinical trials and new therapies.
Conclusions In conclusion, despite recent advances, there remains much room for improvement in all aspects of treatment for pancreatic cancer.

Keywords Ductal pancreatic cancer · Pancreas · Chemotherapy · FOLFIRINOX · Nanoliposomal irinotecan

Introduction

Ductal pancreatic cancer currently represents the seventh most common cause of cancer mortality worldwide, accounting for about 4% of cancer-related deaths in males and females [1]. It is more common in the elderly population and rarely diagnosed in people younger than 40 years of age. Unfortunately, less than 20% of patients present with localized, resectable, and hence potentially curable tumors. The overall 5-year survival rate among patients with pancreatic cancer is less than 5% [2, 3]. Based on current projections, pancreatic cancer is expected to be the second leading cause of cancer mortality in the US in the next 15 years [4]. Despite recent progress there remains much room for improvement in all aspects regarding the treatment of pancreatic cancer.

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Adjuvant therapy

At the moment, standard treatment for patients with resectable pancreatic cancer is surgery followed by adjuvant chemotherapy. Because of the poor outcome associated with surgery alone, the role of adjuvant therapy has been extensively evaluated. The aim of systemic therapy is to reduce the risk of distant metastases.

A series of studies has established that 6 months of adjuvant chemotherapy with either infusional gemcitabine or infusional fluorouracil (5-FU) improves overall survival. The ESPAC-3 trial compared gemcitabine versus bolus 5-FU plus folinic acid. Median survival was equivalent, but gemcitabine was less toxic and therefore became standard of care for a long time [5]. In the recently published ESPAC-4 trial, adding capecitabine (oral Fluorouracil) to gemcitabine compared to gemcitabine improved median survival significantly (28.0 versus 25.5 months) [6]. Particularly R0-resected patients showed a marked benefit from combined chemotherapy (mOS 39.5 months). Given the results of ESPAC-4, this is now considered as the new standard of care, especially for the R0-resected group. However, 60% of the patients in this study were R1-resected and show a more confined benefit to a combined therapy with capecitabine and gemcitabine.

Table 1 Selected ongoing neoadjuvant trials for PDAC

Trial	Phase	Treatment	Endpoint
NEOPAC (NCT01521702)	3	Neoadj gem/ox + adj gem in resectable PCa	PFS
NEOPA (NCT01900327)	3	Sequential neoadj CRT followed by surgery vs. surgery in resectable PC	3-year survival
NCT01458717	3	Neoadj CRT vs. surgery in borderline resectable PC	2-year survival
NorPACT-1 (NCT02919787)	2/3	Neoadj vs. adjuvant CT in resectable PA	OS after 1 year
NCT02172976	2/3	Adjuvant gem vs. neoadj/adj FOLFIRINOX in resectable PCa	OS
S1505 (NCT02562716)	2	Periop mFOLFIRINOX vs. gem/nab-paclitaxel in resectable PC	OS
NCT03199144	2	Neoadj gem/nab-paclitaxel combined with radiotherapy in borderline resectable PC	OS after 3a
NCT02305186	1/2	CR +/– pembrolizumab in resectable and borderline PC	Safety/tumor infiltration
PANDAS-PRODIGE 44 (NCT02676349)	2	Neoadj FOLFIRINOX +/– RCT in borderline PC	R0 resection

a years, *CR/CRT* Chemoradiotherapy, *OS* overall survival; *PA/PC* pancreatic cancer, *PFS* progression free survival, *RCT* radiochemotherapy

Table 2 Selected ongoing phase III trials in mPDAC

Study	Mechanism of action of experimental agent	Indication	Specific requirements	Trial number
Gemcitabine/nab-paclitaxel +/– PEGPH20	PEGPH20: recombinant hyaluronidase (stroma target)	1st line metastatic	High intratumoral levels of HA (hyaluronic acid)	NCT02715804
Gemcitabine/nab-paclitaxel +/– BBI608	BBI608: cancer stem cell inhibitor	1st line metastatic	–	NCT02993731
FOLFOX +/– AM0010	AM0010: PEGylated human IL-10	2nd line (after gemcitabine-based treatment)	–	NCT02923921
Glufosfamide vs. 5-FU	Glufosfamide: alkylating agent	2nd line (after gemcitabine-based treatment)	–	NCT01954992
Olaparib vs. placebo	Olaparib: PARP inhibitor	"Maintenance" treatment following response or stabilization on front-line platinum	Germline *BRCA* mutation	NCT02184195 (results expected in February 2019)

5-FU 5-Fuorouracil, *BRCA* breast cancer gene, *A* hyaluronic acid, *IL-10* Interleukin-10, *PARP* Poly-ADP-Ribose-Polymerase

At the recent ASCO Annual Meeting, Conroy T. and colleagues presented the results of the phase III Unicancer GI PRODIGE 24/CCTG PA.6 trial, and in December 2018, the results were published in the *NEJM* [7]. Adjuvant treatment with modified FOLFIRINOX resulted in the longest overall survival yet reported for patients with resected pancreatic cancer [8]. With adjuvant modified FOLFIRINOX (2400 mg per square meter fluorouracil [5-FU], 400 mg per square meter leucovorin, 150 mg per square meter irinotecan, 85 mg per square meter oxaliplatin) every 2 weeks, median overall survival was 54.4 months, compared with 35.0 months with gemcitabine. Similarly, patients with R1-resection margins had a significant benefit when treated with modified FOLFIRINOX. However, modified FOLFIRINOX is more toxic than gemcitabine. Adverse events of grade 3 or 4 occurred in 75.9% of the patients in the modified-FOLFIRINOX group and in 52.9% of those in the gemcitabine group. The toxic effects were reversible, except for oxaliplatin-induced peripheral neurotoxic effect.

Nevertheless, it should now be considered as the new standard for adjuvant therapy for patients who are able to tolerate it (young age und ECOG 0).

We expect this year the results of the APACT trial (gemcitabine/pemetrexed vs. gemcitabine). It will be very interesting to see the results of this study impact on our daily practice.

Neoadjuvant approach

The high rate of positive lymph nodes and surgical resection margins at the time of surgery has prompted investigators to evaluate preoperative chemoradiotherapy approaches. Moreover, real-life data demonstrate that only about 50% of the patients actually receive chemotherapy after resection [9]. In a recently published paper by Weinrich and colleagues, the rate of adjuvant chemotherapy was much higher (98%) but only 50% of the patients completed the therapy (six cycles) [10]. The most common reason for discontinuation was toxicity.

Despite the use of neoadjuvant concepts in this patient population, scientific evidence remains scarce and no common practice has been established yet [11]. On the basis of their effectiveness in patients with metastatic disease (see below), there is growing interest in incorporating multiagent chemotherapy regimens such as the combination of fluorouracil, irinotecan, oxaliplatin, and leucovorin (FOLFIRINOX) and gemcitabine plus albumin-bound paclitaxel particles (nab-paclitaxel) in preoperative regimens. Interestingly, neoadjuvant FOLFIRINOX resulted in about

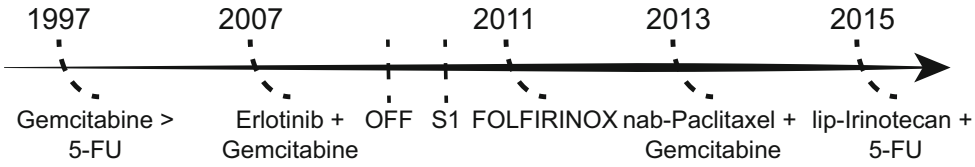

Fig. 1 Key milestones that represent significant advancements in the therapy of PDAC are shown in chronological order. *5-FU* 5-Fluorouracil, *FOLFIRINOX* Oxaliplatin + Irinotecan + 5-Flourouracil, *OFF* Oxaliplatin + 5-Fluorouracil

25% secondary resectability and a median survival of 24.2 months in a recent meta-analysis, making this chemotherapy a valuable tool for locally advanced disease [12].

At this year's ASCO-GI (2019), Unno M. et al. presented a Japanese phase II/III trial in resectable pancreatic cancer patients. One group (180 patients) was resected upfront and received adjuvant chemotherapy with S1, the other group ($n=182$) received neoadjuvant chemotherapy with gemcitabine and S1, followed by surgery and adjuvant chemotherapy. Looking at their primary endpoint (mOS), the group with neoadjuvant therapy showed a mOS of 36.7 months vs. 26.6 months. This hints towards a potentially important role of neoadjuvant therapy in this patient group, but unfortunately the data cannot be easily transferred to other regions, since S1 is exclusively used in the Asian population and comparable studies using different treatment regimens are currently lacking.

At the moment there are ongoing trials to combine chemotherapy with radiotherapy in a neoadjuvant setting; however, firm conclusions cannot be drawn at this stage (Table 1).

Moreover, the use of neoadjuvant/preoperative therapy may result in progression of the disease in a proportion of patients to the point of becoming unresectable (missed window) and might increase the risk of perioperative morbidity and mortality due to side effects of chemotherapy or chemoradiation.

Palliative therapy

As mentioned above, more than half of the patients suffer from metastatic disease at the time of presentation. For these patients, palliative systemic treatment remains the only option in addition to best supportive care.

Fluorouracil-based chemotherapy compared to best supportive care alone improves survival by approximately 3 months [13]. In 1996, a study comparing gemcitabine with fluorouracil in patients with advanced pancreatic cancer showed an improvement in overall survival of roughly 1 month among patients receiving gemcitabine [14].

Over the next 10 years, multiple randomized studies compared single-agent gemcitabine with combination therapy. However, no combination regimen showed an improvement in overall survival.

Recently, two results from clinical phase III trials changed the standard of care from single-agent gemcitabine to combination chemotherapy in the first-line treatment strategy. The intense chemotherapeutic regime with FOLFIRINOX has been shown to be superior to gemcitabine monotherapy in PFS and OS [15]. In the MPACT trial, a combination of gemcitabine and nab-paclitaxel was also superior to single-agent gemcitabine [16].

Unfortunately, there has been no head-to-head comparison between these two regimes in a prospective randomized study. At the moment, there are no predictive biomarkers or patient subpopulations that allow to distinguish between patients who will benefit from one or the other regimen. However, pancreatic cancer associated with a *BRCA2* mutation may be uniquely sensitive to platinum agents [17]. Patients who are known mutant *BRCA* carriers or have a strong family history of cancer suggesting *BRCA* mutation should be considered for FOLFIRINOX. For all other patients, physicians have to decide which first-line therapy should be used on the basis of symptoms and general conditions.

About 40–48% of patients receive a second-line treatment. Most of the trials have focused on fluoropyrimidine-based combinations [18]. Positive results of the NAPOLI-1 trial, an FDA-approved, global randomized phase III study in patients, who had progressed on first-line gemcitabine-based chemotherapy, showed that the combination of nanoliposomal irinotecan with fluorouracil and folinic acid had a higher median overall survival compared to those receiving 5-FU/leucovorin alone (6.1 vs. 4.2 months, HR 0.67, $p=0.012$) [19].

There are still ongoing trials for particular indications as well as for first-line therapy, and hopefully in the future there may be more options for patients requiring first- or second-line treatment (Table 2).

A small proportion of patients may even be suitable for third-line treatment, but scientific evidence and clinical trials are missing.

In conclusion, despite recent advances (Fig. 1), there remains much room for improvement in all aspects of treatment for pancreatic cancer.

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Conflict of interest A. Djanani, A. Schmiderer, L. Niederreiter, M. Niederreiter, and H. Tilg declare that they have no competing interests.

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