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EDITORIAL

Advanced pancreatic cancer - how to choose an adequate treatment option

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Abstract

The prognosis of pancreatic adenocarcinoma is poor, making it one of the leading causes of cancer-related death. The 5-year overall survival rate remains below 5% and little progress is made during the past decade. Only about 10%-20% of patients are eligible for curative-intent surgery and the majority end up having recurring disease even after radical surgery and postoperative adjuvant chemotherapy. Chemotherapy in metastatic disease is palliative at best, aiming at disease and symptom control and prolongation of life. Treatment always causes side effects, the degree of which varies from patient to patient, depending on the patient's general condition, concomitant morbidities as well as on the chosen treatment modality. Why is pancreatic cancer so resistant to treatment? How to best help the patient to reach the set treatment goals?

Key words: Pancreatic cancer; Chemotherapy; Palliative treatment; Prognosis; Side effects

Core tip: The prognosis of metastatic pancreatic adenocarcinoma is poor. Chemotherapy is palliative at best. Some patients benefit from treatment, while some have rapidly progressing treatment-resistant disease. There are several options for single-agent and combined treatment. Some patients may even gain benefit from treatment in second and even further lines and live substantially longer than average. Why is pancreatic cancer so resistant to treatment?

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INTRODUCTION

Why is pancreatic cancer resistant to treatment?

Symptoms of pancreatic adenocarcinoma, including vague upper abdominal or back pain, nausea, fatigue

and weight loss, are associated with more advanced disease. Tumours of the pancreatic head cause icterus, which tends to lead to somewhat earlier diagnosis[1]. There are no effective and sensitive, non-invasive cost-effective methods to screen asymptomatic pancreatic cancer, with the exception of patients who have high-risk precursor lesions, including intraductal papillary mucinous neoplasms, and pancreatic intraepithelial neoplasia[2]. However, among a substantial proportion of patients the diagnosis is inevitably late, making cure unreachable[3-11].

Pancreatic cancer is associated with desmoplastic reaction, *i.e.*, the tumour mass consisting of not only cancer cells but also of an exceptionally high percentage of stromal cells, namely fibroblasts and inflammatory cells, as well as a substantial amount of rigid extracellular matrix[1,12,13]. These factors result in inadequate blood and lymphatic vessels as well as poor vascularisation and hypoxia, leading to poor delivery of chemotherapeutic agents, as focused by Chu *et al*[12] and Feig *et al*[13]. These micro-environmental factors, together with several genetic mutations, among them *KRAS*, and *SMAD4*, *AKT*, *MYC* and *P13K* as well as tumour suppressor genes *TP53* and *PTEN*, support tumour growth and survival, making pancreatic cancer one of the most lethal human malignancies[12-14].

FIRST-LINE CHEMOTHERAPEUTIC OPTIONS

Gemcitabine

Gemcitabine is a nucleoside analogue that blocks DNA replication[1]. Gemcitabine was compared to 5-fluorouracil (5-FU) in a randomized phase Ⅲ trial of 126 patients diagnosed with advanced pancreatic cancer. Treatment efficacy was analyzed using clinical benefit response, consisting of pain evaluation, Karnofsky performance status and weight. Clinical benefit rate and median survival were superior among patients treated with gemcitabine as compared with 5-FU (23.8% *vs* 4.8%, $P = 0.0022$; 5.65 mo *vs* 4.41 mo, respectively)[15]. Thereafter, gemcitabine has been the mainstay of treatment in pancreatic cancer. The general side effects of treatment, including fever, infection and elevation of liver enzymes are usually transient and easily manageable. Hemolytic-uremic syndrome is a rare, serious side effect, which can be fatal[16].

Gemcitabine combinations

Gemcitabine combined with either 5-FU, cisplatin, oxaliplatin, or capecitabine has been studied in several trials, but no statistically significant survival advantage has been shown in pre-nab-paclitaxel-era[17-21]. A randomized phase Ⅲ study reported by Cunningham and colleagues, showed higher response rate and progression-free survival for the combination treatment as well as a trend for superior overall survival. However, in a meta-analysis a survival benefit could be reached[22].

Combination chemotherapy without gemcitabine

The PRODIGE group trial randomized 342 patients with good performance status (Zubrovsky 0/1) diagnosed with metastatic pancreatic cancer to receive either a combination of oxaliplatin, irinotecan, leucovorin, 5-FU bolus and 5-FU continuous infusion (FOLFIRINOX) or single gemcitabine. FOLFIRINOX treatment was associated with a statistically superior overall survival as compared to gemcitabine (11.1 mo *vs* 6.8 mo, HR = 0.47, $P < 0.001$). Combined treatment was, however, associated with a higher incidence of grade 3-4 side effects, including neutropenia, febrile neutropenia, thrombocytopenia, diarrhoea and sensory neuropathy[23]. Hence, treatment-related toxicity has limited the use of FOLFIRINOX in everyday clinical practice in full doses.

Nab-paclitaxel-gemcitabine

Nab-paclitaxel is a nanoparticle albumin-bound chemotherapeutic agent, which has synergistic effects with gemcitabine[24]. MPACT-study randomized 861 patients with metastatic pancreatic cancer to receive nab-paclitaxel plus gemcitabine or gemcitabine alone. This study showed the combination treatment to improve median overall survival (8.5 mo *vs* 6.7 mo, $P = 0.000015$)[25], although the survival difference was more modest than expected on the basis of the previous phase Ⅱ trial (12.2 mo)[24]. The side effects of treatment included fatigue, febrile neutropenia and reversible sensory neuropathy. However, treatment effect in the majority of pre-specified subgroups favoured the combination treatment arm. Moreover, even patients with less favourable disease features, including performance status 2, benefited from treatment[25].

Targeted therapy

The addition of bevacizumab or cetuximab to gem-citabine has not shown improvement in survival among patients with pancreatic cancer[26-30].

Erlotinib is an oral tyrosine kinase inhibitor that blocks the activity of human epidermal growth factor receptor type 1 (HER1/EGFR)[30]. The combination of erlotinib and gemcitabine was compared to gemcitabine alone among 569 patients with advanced pancreatic cancer in a phase Ⅲ trial[31]. Overall survival was significantly longer in the combined treatment arm than gemcitabine alone arm (6.24 mo *vs* 5.91 mo, $P = 0.038$). Patients in the combination arm had higher incidence of skin rash, infection, diarrhoea, stomatitis and interstitial pneumonitis. Patients with grade 2 skin rash benefited from the combined treatment, as compared with those who developed no rash[31]. Erlotinib is the only targeted therapy shown to improve

Table 1 Phase Ⅲ trials of combined treatment showing statistically significant survival benefit in metastatic pancreatic cancer

Ref.	Primary endpoint	Treatment arms	No. of patients	OS (mo)
Moore *et al*[31]	OS	Gemcitabine + erlotinib *vs* gemcitabine	569	6.24 *vs* 5.91 HR = 0.82 CI: 0.69-0.99 *P* = 0.038
Cunningham *et al*[22]	OS	Gemcitabine + capecitabine *vs* gemcitabine	533	7.1 *vs* 6.2 HR = 0.86 CI: 0.72-1.02 *P* = 0.08
			Meta-analysis 935	OS NA HR = 0.86 CI: 0.75-0.98 *P* = 0.02
Conroy *et al*[23]	OS	FOLFIRINOX *vs* gemcitabine	342	11.1 *vs* 6.8 HR = 0.57 CI: 0.45-0.73 *P* < 0.0001
Von Hoff *et al*[25]	OS	Nab-paclitaxel + gemcitabine *vs* gemcitabine + placebo	861	8.5 *vs* 6.7 HR = 0.77 CI: 0.62-0.83 *P* < 0.0001

OS: Overall survival; NA: Not available.

survival so far, albeit the prolongation of life was only 2 wk.

HOW TO CHOOSE? WHAT ABOUT SECOND LINE?

What is comforting enough, we now have choices for treatment. Phase Ⅲ trials showing survival benefit of combined treatment are displayed in Table 1. Gemcitabine-nab-paclitaxel combination and FOLFIRINOX have provided the longest survival benefit in pancreatic cancer. These two treatment modalities have not yet been compared in head-to-head-studies. Both options are valid. Nab-paclitaxel combined to gemcitabine is relatively well tolerated, even though it is associated with increased risk of, *e.g.*, infection and sensory neuropathy. The latter is transient and subsides rapidly after cessation of treatment. However, the original FOLFIRINOX treatment carries an increased risk of side effects and thereby is only suitable for patients with a very good performance status. Hence, when used, it has generally been delivered with reduced doses. Gemcitabine alone or in combination with erlotinib are still options for some patients. All patients are not eligible to combined treatments; some patients have a widely advanced disease and are not candidates for any form of chemotherapy. Whichever treatment is chosen in first-line, its efficacy lasts 4-5 mo at most. Some patients may benefit from second-line treatment and even in subsequent lines. Most often, an oxaliplatin-based regimen is chosen, if not used in first-line, although no data from randomized phase Ⅲ trials are available[32]. All patients should receive treatment for their symptoms and psychological support as needed.

CONCLUSION

The basis for taking care of a patient with a highly malignant incurable disease rests on a good patient-physician interaction. The patient needs to know where he stands, in order to form an opinion how he wants to proceed. Hope is at least as crucial as honesty. It is important for the patient to know what can be done to help him, rather than what cannot. The symptoms can usually be controlled at least to some extent; bile obstruction managed with a stent, and importantly, pain alleviated with the help of medication or special techniques. Even though some patients are not fit for active chemotherapeutic treatment, some do gain benefit from therapy and a few live considerably longer than average. In my opinion, every person has a right to know the basic facts of his disease, have his questions answered (if there is an answer) and have a chance to participate in deciding, how he is going to spend probably the last weeks or months of his life. Especially, the patient needs time to think and discuss with family and friends, before returning to possible treatment options and details or referral to symptomatic care.

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