Advanced pancreatic cancer - how to choose an adequate treatment option

Eija A Korkeila

Eija A Korkeila, Department of Oncology, Turku University Hospital and University of Turku, 20521 Turku, Finland

Author contributions: Korkeila EA wrote this manuscript.

Conflict-of-interest statement: The author Eija A Korkeila has received a fee for serving as a speaker and an advisory board member for Abbott and Roche.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Correspondence to: Eija A Korkeila, MD, PhD, Specialist in Oncology and Radiotherapy, Department of Oncology, Turku University Hospital and University of Turku, Hämeentie 11 PB 52, 20521 Turku, Finland. eija.korkeila@tyks.fi
Telephone: +358-2-3130000
Fax: +358-2-3132850

Received: January 31, 2015
Peer-review started: February 1, 2015
First decision: April 13, 2015
Revised: May 26, 2015
Accepted: August 25, 2015
Article in press: August 25, 2015
Published online: October 14, 2015

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

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

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?

Korkeila EA. Advanced pancreatic cancer - how to choose an adequate treatment option. World J Gastroenterol 2015; 21(38): 10709-10713 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i38/10709.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i38.10709

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\textsuperscript{[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\textsuperscript{[2]}. However, among a substantial proportion of patients the diagnosis is inevitably late, making cure unreachable\textsuperscript{[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\textsuperscript{[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 \textit{et al}\textsuperscript{[2]} and Feig \textit{et al}\textsuperscript{[13]}. These micro-environmental factors, together with several genetic mutations, among them \textit{KRAS}, and \textit{SMAD4}, \textit{AKT}, \textit{MYC} and \textit{P13K} as well as tumour suppressor genes \textit{TP53} and \textit{PTEN}, support tumour growth and survival, making pancreatic cancer one of the most lethal human malignancies\textsuperscript{[12-14]}.

### FIRST-LINE CHEMOTHERAPEUTIC OPTIONS

**Gemcitabine**

Gemcitabine is a nucleoside analogue that blocks DNA replication\textsuperscript{[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 compared to 5-FU (23.8\% vs 4.8\%, \textit{P} = 0.0022; 5.65 mo vs 4.41 mo, respectively)\textsuperscript{[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\textsuperscript{[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\textsuperscript{[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\textsuperscript{[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, \textit{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\textsuperscript{[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\textsuperscript{[24]}. MPACT-study randomized 342 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, \textit{P} = 0.000015)\textsuperscript{[25]}, although the survival difference was more modest than expected on the basis of the previous phase II trial (12.2 mo)\textsuperscript{[26]}. 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\textsuperscript{[26]}.  

**Targeted therapy**

The addition of bevacizumab or cetuximab to gemcitabine has not shown improvement in survival among patients with pancreatic cancer\textsuperscript{[26-30]}.  

Erlotinib is an oral tyrosine kinase inhibitor that blocks the activity of human epidermal growth factor receptor type 1 (HER1/EGFR)\textsuperscript{[30]}. The combination of erlotinib and gemcitabine was compared to gemcitabine alone among 569 patients with advanced pancreatic cancer in a phase II trial\textsuperscript{[31]}. Overall survival was significantly longer in the combined treatment arm than gemcitabine alone arm (6.24 mo vs 5.91 mo, \textit{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\textsuperscript{[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[29] | 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[31] | OS | Gemcitabine + capcitabine vs gemcitabine | 333 | 7.1 vs 6.2 HR = 0.86 CI: 0.72-1.02 P = 0.08 |
| Conroy et al[25] | OS | FOLFIRINOX vs gemcitabine | 342 | 11.1 vs 9.8 HR = 0.57 CI: 0.45-0.73 P < 0.0001 |
| Von Hoff et al[35] | OS | Nab-paclitaxel + gemcitabine vs gemcitabine vs placebo | 861 | 8.5 vs 6.7 HR = 0.77 CI: 0.60-0.93 P < 0.0001 |

Meta-analysis 935 OS NA HR = 0.86 CI: 0.75-0.98 P = 0.02

OS: Overall survival; NA: Not available.

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.

REFERENCES

1. Hidalgo M. Pancreatic cancer. N Engl J Med 2010; 362: 1605-1617 [PMID: 20427809 DOI: 10.1056/NEJMoa0901557]
2. Greer JB, Brand RE. Screening for pancreatic cancer: current evidence and future directions. Gastroenterol Hepatol (N Y) 2007; 3: 929-938 [PMID: 21960811]
3. Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. N Engl J Med 2014; 371: 1039-1049 [PMID: 25207767 DOI: 10.1056/NEJMra140198]
4. Harbaran D, Saied A, Kocher HM. Analysis of mortality rates for pancreatic cancer across the world. HPB (Oxford) 2008; 10: 58-62 [PMID: 18695761 DOI: 10.1080/13651820701883148]
5. Finnish Cancer Registry. 26.1.2015 Available from: URL: www.cancer.fi/syoparekisteri/en/statistics/newest-survival-ratios/
6. Chao YJ, Sy ED, Hsu HP, Shan YS. Predictors for resectability and survival in locally advanced pancreatic cancer after gemcitabine-based neoadjuvant therapy. BMC Surg 2014; 14: 72 [PMID: 25258022 DOI: 10.1186/1471-2482-14-72]
7. Shaib Y, Davila J, Naumann C, El-Serag H. The impact of curative intent surgery on the survival of pancreatic cancer patients: a U.S. Population-based study. Am J Gastroenterol 2007; 102: 1377-1382 [PMID: 17403071]
8. Zuckerman DS, Ryan DP. Adjuvant therapy for pancreatic cancer: a review. Cancer 2008; 112: 243-249 [PMID: 18050292 DOI: 10.1002/cncr.23174]
9. Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Widelski K, Schramm H, Falke J, Zuelke C, Burkart C, Guthberlet K, Kettner E, Schmalenberg H, Weigang-Koehler K, Bechtow WS, Niedergethmann M, Schmidt-Wolf I, Roll L, Doerken B, Riess H. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA 2007; 297: 267-277 [PMID: 17227978]
Oettle H, Neuhaus P, Hochhaus A, Hartmann JG, Gellert K, Ridwelski K, Niedergerthmann Z, Zülke C, Fahikel J, Arming MB, Sinn M, Hinke A, Riess H. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer in a CONKO-001 randomized trial. JAMA 2013; 310: 1473-1481. [PMID: 24104372 DOI: 10.1001/jama.2013.279201]

Neoptolomenos JP, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, Padbury R, Moore MJ, Gallinger S, Mariette C, Wente MN, Izibicki JR, Friess H, Lerch MM, Dervenis C, Olah A, Butturini G, Doi R, Lind PA, Smith D, Valle JW, Palmer DH, Buckels JA, Thompson M, McKnight CJ, Rawcliffe CL, Büchler MW. Adjuvant chemotherapy with fluorouracil plus folinic acid versus gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA 2010; 304: 1073-1081. [PMID: 20823433 DOI: 10.1001/jama.2010.1275]

Chu GC, Kimmelman AC, Hezel AF, DePinho RA. Stromal biology of pancreatic cancer. J Cell Biochem 2007; 101: 887-907 [PMID: 17266048 DOI: 10.1002/jcb.21209]

Feig C, Gopinathan A, Neese A, Chan DS, Cook N, Tuveson D, Herrmann R, Renschler MF. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. JAMA 2011; 305: 1817-1825 [PMID: 21561347 DOI: 10.1056/NEJMoa1011923]

Von Hoff DD, Ramanathan RK, Borad MJ, Laheru DA, Smith LS, Wood TE, Korn RL, Desai N, Tieu V, Gielasz JL, Zhang H, Soon-Shiong P, Shi T, Rajeshkumar NV, Maitra A, Hidalgo M. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase II/III trial. J Clin Oncol 2011; 29: 4548-4554. [PMID: 21969517 DOI: 10.1200/JCO.2011.36.5742]

Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Hainaut P, Rixe O, Fournier MC, Fichet-Calvet E, Chau I, Stocken DD, Valle JW, Smith D, Rajeshkumar NV, Maitra A, Dang CV. Conceptual biology of pancreatic cancer.
Korkeila EA. Advanced pancreatic cancer

Oncol 2007; 25: 1960-1966 [PMID: 17452677 DOI: 10.1200/JCO.2006.07.9525]

Seufferlein T, Bachet JB, Van Cutsem E, Rougier P. Pancreatic adenocarcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012; 23 Suppl 7: viii33-viii40 [PMID: 22997452 DOI: 10.1093/annonc/mds224]

P- Reviewer: Delitala AP, Mizuno N, Plaza MA, Yip-Schneider MT
S- Editor: Ji FF
L- Editor: A
E- Editor: Liu XM
