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Palliative systemic treatment of patients with pancreatic cancer — should reimbursement of nab-paclitaxel change the current management paradigm?

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Oncology in Clinical Practice
 2017, Vol. 13, No. 1, 8–13
 DOI: 10.5603/OCP.2017.0002
 Translation: dr n. med. Dariusz Stencel
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 ISSN 2450–1654

ABSTRACT

Pancreatic cancer is associated with poor prognosis. In the majority of patients the disease is diagnosed at an inoperable stage, so palliative chemotherapy is the only possible management. In a highly clinically and biochemically selected subpopulation two chemotherapy multi-drug schemes: FOLFIRINOX regimen and combination of nab-paclitaxel with gemcitabine, are more effective than gemcitabine alone, being the current standard of treatment. As there is a lack of direct comparison between doublet and triplet chemotherapies and the prognosis of patients enrolled to ACCORD 11 and MPACT clinical trials is similar, an attempt at indirect analysis was undertaken. It seems that chemotherapy with the use of FOLFIRINOX regimen prolongs overall survival significantly more and mainly has a beneficial impact on quality of life. In the authors' opinion, the possibilities of using chemotherapy containing nab-paclitaxel and gemcitabine are quite limited. In patients with worse performance status monotherapy with gemcitabine or best supportive care should remain a standard of management.

Key words: FOLFIRINOX, nab-paclitaxel, pancreatic cancer

Oncol Clin Pract 2017; 13, 1: 8–13

Introduction

Pancreatic cancer is a malignant neoplasm of extremely poor prognosis as compared with other — more prevalent — malignancies. The number of reported new cases in Poland is about 3500 annually, which accounts for 2.2% of total cancer incidence. The number of deaths is estimated to be approximately 4700 (5% of deaths due to cancer diseases) [1].

The diagnosis of pancreatic adenocarcinoma is usually late due to long asymptomatic or minimally symptomatic course of disease. Consequently, in majority of patients systemic cytotoxic treatment is the only therapeutic option that is able to influence prognosis. Postoperative chemotherapy is indicated for all patients after

surgical procedure, both microscopically radical and non-radical (R1). However, this management applies to less than 20% of patients with diagnosis of pancreatic cancer. In 30–40% of patients, pancreatic malignancy is diagnosed as locally advanced disease, when surgical treatment is impossible. In some patients the resectability could be reassessed after systemic treatment (the role of preoperative irradiation is still unclear), however the rest of patients receive only palliative chemotherapy. In 40–50% of patients, pancreatic cancer is diagnosed at an the metastatic stage and systemic treatment is the only therapeutic modality.

Palliative systemic treatment in patients with pancreatic cancer is discussed in the following sections of the presented article.

Palliative chemotherapy in patients with pancreatic cancer

In 1997 the results of a clinical trial that compared efficacy of palliative gemcitabine chemotherapy with fluorouracil-based systemic treatment in patients with advanced pancreatic cancer were published. They indicated higher activity of the first one cytotoxic drug. Median overall survival (mOS) in patients treated with gemcitabine reached 5.6 months, however in fluorouracil arm it was 4.4 months ($p = 0.0025$). Despite small (5.4%) objective response rate (ORR), chemotherapy with gemcitabine contributed to better pain control in up to a quarter of patients. The treatment was well tolerated; haematological toxicity was mainly observed [2]. Over the next few years gemcitabine monotherapy was the only standard option of palliative treatment. This therapy is still a valuable choice in patients with worse performance status (ECOG 2), with moderately increased serum bilirubin concentration, e.g. > 1.5 upper limit of normal (ULN), with significant concomitant diseases, or in patients unwilling to accept the risk of toxicity.

A combination of gemcitabine with a second cytotoxic drug (e.g. cisplatin, capecitabine) did not influence OS despite observed increase in the median progression-free survival (mPFS) and ORR, but it was associated with intensified toxicity [3, 4]. Some retrospective analyses suggest that platinum-based chemotherapy results in a greater advantage in patients with mutations in *BRCA1* or *BRCA2* genes [5].

Between 2007 and 2013 the results of 3 phase III clinical trials were published, that indicated the OS benefits from multi-drug chemotherapy in patients with advanced pancreatic cancer as compared to single-agent gemcitabine — the standard option at that time.

In the first study gemcitabine was combined with erlotinib in 569 patients with unresectable, locally advanced or metastatic pancreatic cancer. A small but statistically significant difference in OS was noticed in favour of patients treated with erlotinib and gemcitabine; median OS was increased by 2 weeks (6.24 vs. 5.91 months, HR 0.82; 95% CI: 0.69–0.99; $p = 0.038$); median PFS was also increased (3.75 vs. 3.55 months, HR 0.77; 95% CI: 0.64–0.92; $p = 0.004$). However, objective response rates (8.6% vs. 8%) as well as disease control rates (57.5% vs. 49.2%; $p = 0.07$) were comparable in both treatment arms. Combined therapy was associated with increased toxicity. Rash, diarrhoea, infections and stomatitis were more frequently observed, but they didn't influence the quality of life (QoL) of treated patients [6].

In a second — French academic study (PRODIGE 4), the efficacy of multi-drug chemotherapy with the FOLFIRINOX regimen was assessed in 342 patients with metastatic pancreatic cancer. Median OS was increased by more than 4 months (11.1 vs. 6.8 months) and relative risk of death was decreased by 43% (HR 0.57; 95% CI: 0.45–0.73; $p < 0.001$). The beneficial effects

were also observed for PFS (median: 6.4 vs. 3.3 months; HR 0.47; 95% CI: 0.37–0.59; $p < 0.001$) and ORR (32% vs. 9%; $p < 0.001$) [7].

In the third MPACT study, conducted in the largest population (861 patients), gemcitabine was combined with nab-paclitaxel (nanoparticle complexes of paclitaxel with albumin). As compared to gemcitabine monotherapy, the median OS was increased by nearly 2 months (8.5 vs. 6.7 months) and risk of death was decreased by 28% (HR 0.72; 95% CI: 0.62–0.83; $p < 0.001$). mPFS was also increased (5.5 vs. 3.7 months respectively, HR 0.69; 95% CI: 0.58–0.82; $p < 0.001$), similarly ORR (23% vs. 7%; $p < 0.001$) [8].

FOLFIRINOX regimen

Patients included in the study

The ACCORD 11 (PRODIGE 4) study enrolled patients with stage IV pancreatic cancer, not older than 75 years, with performance status of 0–1 according to ECOG (Eastern Cooperative Oncology Group) score. Exclusion criteria, among others, included serum bilirubin concentration higher than 1.5 x ULN and creatinine concentration equal to or higher than 120 $\mu\text{mol/L}$ (1.36 mg/dL).

Adverse reactions and quality of life

Multi-drug chemotherapy was associated with higher G3–G4 toxicity — more frequently observed reactions included neutropenia (46% vs. 21%; $p < 0.001$), febrile neutropenia (5% vs. 1%; $p = 0.03$), thrombocytopenia (9% vs. 4%; $p = 0.04$), diarrhoea (13% vs. 2%; $p < 0.001$) and sensitive neuropathy (9% vs. 0%; $p < 0.001$).

According to the study protocol, routine primary prophylaxis of febrile neutropenia with filgrastim was not allowed, except for the patients with other important factors that increase the risk of febrile neutropenia. Additionally, in patients with neutropenia of at least grade 2 during multi-drug chemotherapy, it was recommended to continue the chemotherapy in a reduced dose (after recovery of neutrophil count to normal range). However, G-CSF was used in 43% of patients that received multi-drug regimen, compared to 5% of patients treated with gemcitabine alone. Although higher toxicity, chemotherapy according to the FOLFIRINOX regimen had a positive impact on QoL, by decreasing relative risk of its deterioration by 63% (HR 0.47; 95% CI: 0.3–0.7; $p < 0.001$); after 6 months, significant deterioration of QoL was detected in 66% of patients who received gemcitabine alone vs. 31% in those who were treated by the multi-drug regimen [7]. Table 1 summarises the recommendations of the study authors and ASCO (American Society of Clinical Oncology) experts regard-

Table 1. Recommendations of study authors and ASCO experts regarding management of toxicities resulting from FOLFIRINOX chemotherapy

Adverse events	Recommendations of study authors	ASCO recommendations
Neutropenia/FN	Decrease irinotecan dose (150 mg/m ²) and give up injections of FU and folinic acid, then decrease oxaliplatin dose (65 mg/m ²)	Give up injections of FU and infusion of folinic acid + additionally decrease oxaliplatin and irinotecan dose by 20%
Thrombocytopenia	Decrease oxaliplatin dose (60 mg/m ²), decrease FU dose (injection and infusion by 25%), then decrease irinotecan dose (150 mg/m ²)	
Diarrhoea	Decrease irinotecan dose (150 mg/m ²) and give up injections of FU and folinic acid	Decrease irinotecan and FU dose
Mucositis/"hand-foot" syndrome	Decrease FU dose (injection and infusion, by 25%)	
Neuropathy	Decrease oxaliplatin dose	Decrease oxaliplatin dose
Hyperbilirubinemia	Decrease dose or give up irinotecan and/or decrease oxaliplatin and/or FU dose	
Nausea or vomiting	Decrease irinotecan dose (150 mg/m ²) or decrease oxaliplatin dose (60 mg/m ²), or decrease FU dose (injection and infusion, by 25%)	Give up injections of FU and infusion of folinic acid + additionally decrease oxaliplatin and irinotecan dose by 20%
Primary prophylaxis of FN	Not recommended	Not recommended
Secondary prophylaxis of FN	Consider after FN episode or in case of recurrent neutropaenia grade 3 or 4, despite dose reduction	Dose modifications; G-CSF is not recommended

FN — febrile neutropenia; FU — fluorouracil; G-CSF — granulocyte colony stimulating factor

ing management of toxicities related to FOLFIRINOX chemotherapy [7, 9]. Of note, whilst primary prophylaxis of febrile neutropenia is not recommended, modification of the doses of cytotoxic drugs should be primarily considered in case of neutropenia.

Gemcitabine with nab-paclitaxel

Patients included in the study

The MPACT study, that assessed the combination of gemcitabine with nab-paclitaxel compared to gemcitabine alone, enrolled patients without age limitation (however, patients aged over 75 years accounted for only 10% of the study population), with a performance status of at least 70 according to the Karnofsky Performance Scale (KPS) (KPS 70 was found in 7% of patients only). The biochemical criterion regarding the permissible bilirubin level was more stringent than in the ACCORD11 study — patients with level higher than ULN were excluded from the trial. The creatinine level was required to be within normal range or the calculated value of creatinine clearance should amount to at least 60 mL/min/1.73 m².

Adverse reactions and quality of life

The clinical benefit from doublet chemotherapy was counterbalanced by its higher toxicity. More

frequently observed adverse reactions (grade 3/4) included: leukopenia (31% vs. 16%), neutropenia (38% vs. 27%), fatigue (17% vs. 7%), peripheral neuropathy (17% vs. 1%), sepsis (5% vs. 2%) and pneumonia (4% vs. 1%). The risk of febrile neutropenia was 3% vs. 1%, respectively; GCS-F was administered in 26% vs. 15% of patients, respectively. In the MPACT study QoL was not assessed [8].

Table 2 summarises the recommendations of management of treatment-related toxicity that were made by study authors and ASCO experts.

What to choose: FOLFIRINOX or nab-paclitaxel with gemcitabine?

One of the criteria of the Ministry of Health (MoH) drug program of treatment of pancreatic cancer, recently initiated in Poland, indicates that combination of nab-paclitaxel and gemcitabine could be used entirely in patients ineligible for chemotherapy according the FOLFIRINOX regimen. Why such a provision was implemented, and which group of patients could be affected in practice?

There was no clinical study that directly compared the results of FOLFIRINOX-based treatment with a combination of nab-paclitaxel and gemcitabine, so an attempt to indirectly compare those data is warranted.

Table 2. Recommendations of study authors and ASCO experts regarding management of toxicities resulting from chemotherapy with nab-paclitaxel and gemcitabine

Adverse events	Recommendations of study authors	ASCO recommendations
Haematological toxicities:		Decrease nab-paclitaxel and gemcitabine dose by 20%
— on day 1 of cycle	Treatment interruption for 1 week	
— on day 8 of cycle	Omission or decrease of nab-paclitaxel and gemcitabine dose by 20%	
— on day 15 of cycle	Depending on complete blood count, omission of dose or consideration of treatment continuation (optionally with G-CSF)	
FN	Decrease nab-paclitaxel and gemcitabine dose by 20%	Profilaxis with G-CSF is not recommended
— recurrent FN	Decrease nab-paclitaxel dose by 20% and gemcitabine dose by 40%	
Neuropathy	Omission and then decrease nab-paclitaxel dose by 20%	Decrease nab-paclitaxel dose by 20%
Nausea or vomiting	Continuation with 100% of doses to grade 3 (inclusive); in grade 4 treatment discontinuation	Decrease nab-paclitaxel and gemcitabine dose by 20%
Others grade 3 (except nausea/vomiting):		Change dosing scheme, e.g.
— on day 1 of each cycle	Decrease nab-paclitaxel and gemcitabine dose by 20%	— day 1 and 15 every 28 days or
— on the next days of cycle	Omission of nab-paclitaxel and/or gemcitabine dose and then decrease nab-paclitaxel and/or gemcitabine dose by 20%	— day 1 and 15 every 21 days

FN — febrile neutropenia; G-CSF — granulocyte colony stimulating factor

The ACCORD 11 and MPACT studies included quite similar populations; however, biological inclusion criteria in the study with nab-paclitaxel were a little more rigorous. Only 8% of patients enrolled in the MPACT study (nominally 65 patients, half of them received gemcitabine alone) had a KPS of 70 (63 patients) or 60 (2 patients), whereas the remaining 92% of patients had KPS score of 80–100 (which corresponds to ECOG PS 0–1). Although overall survival subgroup analysis was performed depending on performance status (HR 0.61 for KPS 70–80; HR 0.75 for KPS 90–100), there is a lack of separate analysis considering the subgroup of patients with a KPS score of 70 [8]. Median of age of patients participating in both trials was 61 and 63 years, respectively, ranging between 25–76 and 27–88 years, respectively. Nearly the same results achieved in control groups suggest that both trials recruited patients with similar prognosis (Table 3).

The proportions of patients receiving second-line treatment were also similar: 48% in the ACCORD trial and 40% in the MPACT trial. In both studies the frequencies of second line-treatment were practically independent of whether either multi-drug chemotherapy

Table 3. Indirect comparison of results of treatment in control groups (gemcitabine alone) in the ACCORD 11 [7] and MPACT [8] studies

	ACCORD 11	MPACT
mOS (months)	6.8	6.7
mPFS (months)	3.3	3.7
ORR (%)	9	7
6-month OS (%)	58	55
12-month OS (%)	21	22
18-month OS (%)	6	9

mPFS — median progression-free survival; mOS — median overall survival; ORR — objective response rate

or gemcitabine alone was used (ACCORD: 47% and 50%, respectively; MPACT: 38 and 42%, respectively).

The data presented in the article suggest that indirectly better treatment results were nominally achieved in the group of patients treated with FOLFIRINOX regimen (Table 4).

It should be underlined that, despite more frequent adverse events, FOLFIRINOX chemotherapy had

Table 4. Indirect comparison of results of treatment in patients treated with multi-drug chemotherapy in the ACCORD 11 (FOLFIRINOX) [7] and MPACT (nab-paclitaxel with gemcitabine) [8] studies

	ACCORD 11	MPACT
mOS (months)	11.1	8.5
mPFS (months)	6.4	5.5
ORR (%)	32	23
6-month OS (%)	76	67
12-month OS (%)	49	35
18-month OS (%)	19	16

mPFS — median progression-free survival; mOS — median overall survival; ORR — objective response rate

Table 5. Indirect comparison of treatment toxicities in patients treated with multi-drug chemotherapy in the ACCORD 11 (FOLFIRINOX) [7] and MPACT (nab-paclitaxel with gemcitabine) [8] studies

Adverse events grade 3 and 4	ACCORD 11 (%)	MPACT (%)
Neutropenia	46	38
Febrile neutropenia	5	3
Thrombocytopenia	9	13
Diarrhoea	13	6
Sensitive neuropathy	9	17
Fatigue	24	17

a positive impact on patients' QoL [7]. Quality of life was not analysed in the MPACT study, which gives no right to assume with a high degree of certainty, that combined therapy of nab-paclitaxel and gemcitabine does not deteriorate QoL. Table 5 presents an indirect comparison of toxicities of the chemotherapy regimens.

It is worth mentioning, that in the opinion of many agencies (e.g. NICE) the cost-effectiveness of FOLFIRINOX is better than of the combination of nab-paclitaxel and gemcitabine.

Which patients have contraindications to FOLFIRINOX chemotherapy but are eligible for a combination of nab-paclitaxel and gemcitabine?

It seems that the patients with KPS 70 could be natural candidates for combination chemotherapy with nab-paclitaxel and gemcitabine. The situation is found only in some patients with ECOG performance status of 2. It should also be emphasized that in the MPACT study this group of patients accounted for less than 10% of participants. It is not clear whether doublet chemotherapy was more

efficient in those patients as compared to gemcitabine alone, or whether treatment-related toxicity was more intense than in patients with better performance status.

Patients with relative contraindications to oxaliplatin, irinotecan, or infusions of fluorouracil could also be good candidates for such therapy. The most obvious example could be the patients with chronic diarrhoea or active, but not severe, coronary artery disease (CAD). Benign liver injury could also be considered as an indication to dose reduction or even contraindication to irinotecan, but according to the inclusion criteria in the MoH drug program it has no practical importance. Contrary to this, elderly patients (e.g. over 75 years of age) could hardly be considered as good candidates, due to the lack of reliable data regarding the efficacy of doublet or multi-drug chemotherapy in this age group.

Summary

Palliative chemotherapy in patients with pancreatic cancer significantly prolongs OS. For many years monotherapy with fluorouracil was a standard of care, but since 1997 chemotherapy with gemcitabine became a new first-line option, which enables to reach a median of OS slightly over 6 months. During the last 6 years the list of active therapeutic options included subsequent cytotoxic drugs, that, in multi-drug regimens, improved the prognosis of patients. FOLFIRINOX chemotherapy as well the combination of gemcitabine with nab-paclitaxel were compared with gemcitabine alone in phase III clinical trials. Taking into consideration the higher toxicity related to multi-drug therapy, both schemes were evaluated in limited populations, including patients with good performance status, without serious concomitant diseases and without significant hyperbilirubinaemia. Although the efficacy of FOLFIRINOX was not directly compared to the combination of nab-paclitaxel and gemcitabine, indirect comparison, partially justified by similar populations included to both studies, suggests greater benefit from triplet chemotherapy (greater mOS, ORR, and 6- and 12-month survival rates). Moreover, chemotherapy according to the FOLFIRINOX regimen significantly improved QoL of patients with metastatic pancreatic cancer. Quality of life parameters were not evaluated in the study with nab-paclitaxel.

In conclusion, it is quite difficult to precisely determine the place of combined chemotherapy with gemcitabine and nab-paclitaxel in the treatment of patients with metastatic pancreatic cancer. Such a therapy could be justified in patients who closely meet the definition of KPS of 70; however, there are no data regarding the efficacy and safety of doublet chemotherapy exclusively in this subgroup, and for the majority of patients with ECOG performance status 2, monotherapy with gemcitabine would be a safer option.

In patients clinically and biochemically eligible for systematic treatment based on multi-drug chemotherapy it seems that the FOLFIRINOX regimen is a better option, unless there are existing contraindications to the treatment with oxaliplatin, irinotecan, and fluorouracil. Taking this into consideration, it is surprising and ethically difficult to accept the clinical trial designs with administration of nab-paclitaxel and gemcitabine in the control group although in patients without contraindications to FOLFIRINOX chemotherapy. Finally, it should be underlined again that appropriate management of treatment-related toxicities is a crucial element of the therapy of patients with pancreatic cancer, and quite often influences the results of therapy. Recommendations from the protocols of both studies could provide valuable guidance in this case. Especially helpful are also the suggestions of the ASCO experts, developed after publication of trial results and analyses of other publications and reports.

References

1. Didkowska J, Wojciechowska U. Nowotwory złośliwe w Polsce w 2013 roku. Warszawa: Krajowy Rejestr Nowotworów, Warszawa 2015.
2. Burris HA, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol.* 1997; 15(6): 2403–2413, doi: [10.1200/JCO.1997.15.6.2403](https://doi.org/10.1200/JCO.1997.15.6.2403), indexed in Pubmed: [9196156](https://pubmed.ncbi.nlm.nih.gov/9196156/).
3. Cunningham D, Chau I, Stocken DD, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol.* 2009; 27(33): 5513–5518, doi: [10.1200/JCO.2009.24.2446](https://doi.org/10.1200/JCO.2009.24.2446), indexed in Pubmed: [19858379](https://pubmed.ncbi.nlm.nih.gov/19858379/).
4. Heinemann V, Quietzsch D, Gieseler F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. *J Clin Oncol.* 2006; 24(24): 3946–3952, doi: [10.1200/JCO.2005.05.1490](https://doi.org/10.1200/JCO.2005.05.1490), indexed in Pubmed: [16921047](https://pubmed.ncbi.nlm.nih.gov/16921047/).
5. Golan T, Kanji ZS, Epelbaum R, et al. Overall survival and clinical characteristics of pancreatic cancer in BRCA mutation carriers. *Br J Cancer.* 2014; 111(6): 1132–1138, doi: [10.1038/bjc.2014.418](https://doi.org/10.1038/bjc.2014.418), indexed in Pubmed: [25072261](https://pubmed.ncbi.nlm.nih.gov/25072261/).
6. Moore MJ, Goldstein D, Hamm J, et al. National Cancer Institute of Canada Clinical Trials Group. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol.* 2007; 25(15): 1960–1966, doi: [10.1200/JCO.2006.07.9525](https://doi.org/10.1200/JCO.2006.07.9525), indexed in Pubmed: [17452677](https://pubmed.ncbi.nlm.nih.gov/17452677/).
7. Conroy T, Desseigne F, Ychou M, et al. Groupe Tumeurs Digestives of Unicancer, PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med.* 2011; 364(19): 1817–1825, doi: [10.1056/NEJMoa1011923](https://doi.org/10.1056/NEJMoa1011923), indexed in Pubmed: [21561347](https://pubmed.ncbi.nlm.nih.gov/21561347/).
8. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med.* 2013; 369(18): 1691–1703, doi: [10.1056/NEJMoa1304369](https://doi.org/10.1056/NEJMoa1304369), indexed in Pubmed: [24131140](https://pubmed.ncbi.nlm.nih.gov/24131140/).
9. Sohal DP, Mangu PB, Khorana AA, et al. Metastatic Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol.* 2016; 34: 2784–2796.