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First-line *Nab*-paclitaxel and Gemcitabine in Patients with Metastatic Pancreatic Cancer from Routine Clinical Practice

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Abstract. *Background: The combination of nab-paclitaxel and gemcitabine is a new effective first-line chemotherapy for patients with metastatic pancreatic cancer. This was demonstrated in the phase III MPACT trial. Patients and Methods: Four patients with metastatic pancreatic cancer from our clinical practice received combination chemotherapy with nab-paclitaxel at doses from 100 to 125 mg/m^2 and gemcitabine at doses from 800 to 1,000 mg/m^2 on days 1, 8 and 15 of a 28-day cycle. Two patients had elevated serum levels of total bilirubin, one older patient had significant comorbidities, another older patient had an Eastern Cooperative Oncology Group performance status of 2. Results: Treatment was manageable. Patients showed clinical remission or disease stabilization. Overall, combination chemotherapy was well tolerated. Conclusion: Patients with metastatic pancreatic cancer that did not meet all criteria, as patients treated in the registration trial, were safely and effectively treated with first-line combination of nab-paclitaxel and gemcitabine.*

Prognosis of patients with metastatic pancreatic cancer (PDAC) is dismal. For decades, median survival times after treatment with gemcitabine were around six months. Recently, data from two large phase III trials demonstrated significant improvements in clinical outcomes for two combination therapies over gemcitabine alone (1-3). The combination of *nab*-paclitaxel and gemcitabine was approved in the EU for the first-line treatment of patients with metastatic pancreatic adenocarcinoma in January 2014 (4).

Nab-paclitaxel is a solvent-free colloidal suspension of paclitaxel and human serum albumin. Besides its linear pharmacokinetics and its distribution properties into the tumor microenvironment utilizing albumin as a carrier protein, potential interaction with secreted protein acidic and rich in cysteine (SPARC), depletion of tumor stroma and synergistic effects with gemcitabine are proposed additional mechanisms of action of *nab*-paclitaxel against pancreatic cancer (5).

In the phase III trial MPACT, 861 patients with metastatic PDAC received first-line chemotherapy either with the combination of *nab*-paclitaxel at 125 mg/m^2 and gemcitabine at 1,000 mg/m^2, both administered on days 1, 8, 15, 29, 36 and 43 of a 56-day cycle with subsequent cycles on days 1, 8, 15 of a 28-day cycle, or with gemcitabine monotherapy at 1,000 mg/m^2 weekly for seven out of eight weeks in the first cycle and in subsequent cycles on days 1, 8, 15 of a 28-day cycle. Significant benefits for treatment with the combination of *nab*-paclitaxel and gemcitabine over gemcitabine monotherapy were observed for the primary end-point overall, survival and for all secondary end-points. Median overall survival (OS) increased to 8.7 months [95% confidence interval (CI)=7.89-9.69 months) as compared to 6.6 months (95% CI=6.01-7.20 months) with gemcitabine alone [hazard ratio (HR) for death =0.72; 95% CI=0.620-0.825; $p<0.0001$). Survival rates at one, two and three years were 35%, 10%, 4% for the combination *vs.* 22%, 5% and 0% for gemcitabine alone (3). Progression-free survival was 5.5 months *vs.* 3.7 months (HR=0.69; 95% CI=0.58-0.82, $p<0.001$), overall response 23% *vs.* 7% ($p<0.001$), respectively. Treatment with the combination *nab*-paclitaxel and gemcitabine was manageable. The most frequently

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observed adverse events of grade 3 or more were neutropenia (38% for *nab*-paclitaxel and gemcitabine *vs.* 27% for gemcitabine alone), leukopenia (31% *vs.* 16%), fatigue (17% *vs.* 7%) and neuropathy (17% *vs.* 1%) (2).

Recently, substantial progress had also been achieved for patients with metastatic PDAC using the quadruple combination of oxaliplatin, 5-fluorouracil, leucovorin and irinotecan (FOLFIRINOX). FOLFIRINOX significantly improved OS to 11.1 months compared to 6.8 months for gemcitabine, as well as all other clinically relevant end-points. The intensive treatment resulted in significantly more adverse events of more than grade 3 in terms of neutropenia (45.7% for FOLFIRINOX *vs.* 21.0% for gemcitabine), febrile neutropenia (5.4% *vs.* 1,2%), thrombocytopenia 89.1% *vs.* 3.6%, diarrhea (12.7% *vs.* 1.8%) and peripheral neuropathy (9.0% *vs.* 0%), while the incidence of elevation of alanin aminotransferase was reduced (7.3% *vs.* 20.8%) (1).

It is commonplace that prospectively randomized, controlled trials provide the highest level of evidence for comparisons of alternative types of treatment and for defining standards of care. Yet it is also undisputed that clinical trials do not always reflect the complete spectrum of clinical reality. Patients in the FOLFIRINOX trial had a median age of 61 years, had predominantly a good performance status (99.3% Eastern cooperative Oncology Group (ECOG) 0-1) and bilirubin levels of 1.5 mg/dl or less (1). Patients in the MPACT study had a median age of 63 years, 60% of patients had a Karnofsky performance status of 90-100, and 39% had a Karnofsky performance status of 70-80. All patients were required to have bilirubin levels at the upper limit of or greater than the normal range. Yet, patients can also profit from these modern chemotherapy options if they do not meet all criteria of the typical study patient. We report four of those cases from our clinical routine practice with *nab*-paclitaxel.

Case Reports

Case 1: High total bilirubin. In October 2012, a 53-year-old patient was diagnosed with a poorly differentiated PDAC and lymph node metastases. Surgery according to the Whipple procedure was performed and resulted in R0 resection. In April 2013, the patient presented with extensive jaundice. He was otherwise asymptomatic and had a good performance status. Total bilirubin in serum was elevated to 11.7 mg/dl *i.e.* more than 10-fold the upper limit of normal (ULN). Serum levels of liver enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), and γ-glutamyltransferase (γ-GT) were also elevated (120 U/l, 340 U/l, 887 U/l and 730 U/l, respectively). Liver function was not compromised as indicated by normal values for international normalized ratio (INR), cholinesterase and serum albumin. Diagnostic imaging showed multiple liver metastases and significant cholestasis, plus bilateral pulmonary metastases and extensive peritoneal carcinomatosis. A percutaneous transhepatic cholangiography was performed and a metal stent was placed in the same session without any acute or late complications.

Two days after this intervention, we started first-line chemotherapy with *nab*-paclitaxel and gemcitabine due to the rapidly progressive disease. Because of the elevated level of total bilirubin, *nab*-paclitaxel was administered at a dose of 100 mg/m^2 on days 1, 8 and 15 and gemcitabine at a dose of 800 mg/m^2 on days 1, 8 and 15 of a 28-day cycle. Chemotherapy was well tolerated and was administered without any delay. Total bilirubin levels dropped rapidly (Figure 1) to normal within three weeks as did liver enzymes, AP and γ-GT. Overall, the patient received six cycles of chemotherapy. From cycle 3 on-wards, the dose of *nab*-paclitaxel was escalated to 125 mg/m^2 and that of gemcitabine to 1,000 mg/m^2 on days 1, 8 and 15. Bilirubin levels remained within the normal range. Chemotherapy was still tolerated well. There were no gastrointestinal or hematological side-effects. The patient did not develop peripheral neuropathy. Disease remained stable until October 2013, when a progression of pulmonary metastasis was detected and prompted the onset of second-line therapy with folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX).

Case 2: High total bilirubin. A 75-year-old patient was diagnosed with PDAC in May 2013. He had suffered from epigastric pain, lack of appetite, weight loss and jaundice since April 2013. Laboratory findings showed an elevation of total serum bilirubin to 8.2 mg/dl. A stent was placed into the *ductus hepatocholedochus* to allow biliary drainage and, as a result, total serum bilirubin dropped to 2.5 mg/dl. During the subsequent exploratory laparatomy, liver metastases were detected. Postoperative computed tomography in June 2013 showed a progressive tumor of the pancreatic head surrounding the superior mesenteric artery and the *truncus coeliacus*, an indentation of the portal vein and multiple liver metastases. Intra-hepatic bile ducts were still slightly dilated and total bilirubin was 2.2 mg/dl.

We then started first-line chemotherapy with *nab*-paclitaxel and gemcitabine on days 1, 8 and 15 of a 28-day-cycle under close clinical and laboratory monitoring. The first dose of *nab*-paclitaxel was given at 100 mg/m^2. However, our aim was to administer the standard doses of *nab*-paclitaxel of 125 mg/m^2 and gemcitabine of 1,000 mg/m^2, whenever possible. Doses were reduced or re-escalated weekly based on bilirubin and side-effects. Table I gives an overview of our therapy management. Total bilirubin in serum remained between 1.6 and 3.7 mg/dl and never dropped to normal during the whole course of therapy.

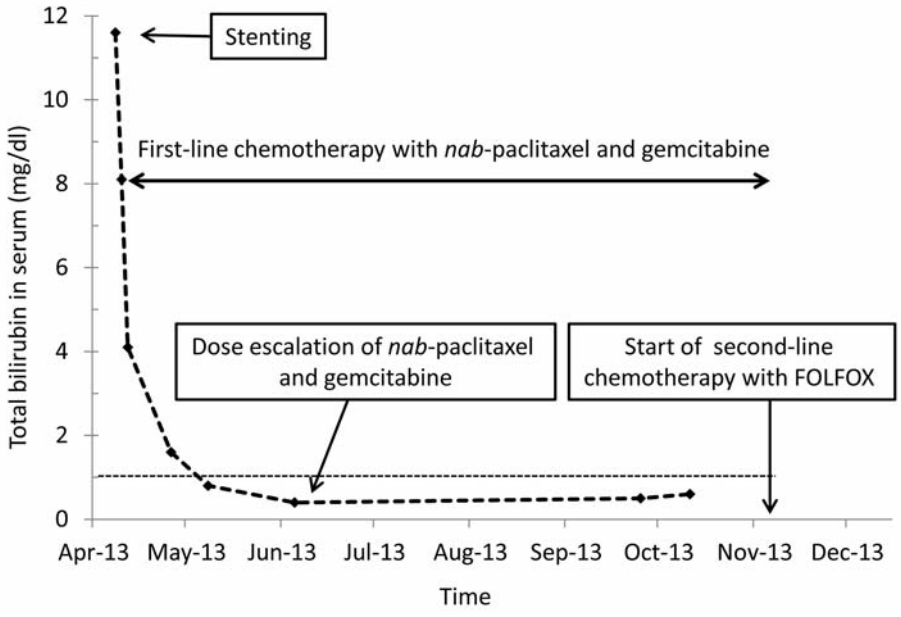

Figure 1. *Case 1. Course of total bilirubin in serum.*

Under first-line therapy, the patient developed neutropenia up to grade 4 and thrombocytopenia of grade 2. There was an episode of fever due to acute cholangitis, which was treated successfully with antibiotics. From cycle 2 onwards, the patient presented symptoms of grade 1 polyneuropathy. In cycle 3, he had a local infection which was managed successfully locally.

Computed tomography performed after cycle 4 in October 2013 showed stable disease. Chemotherapy with *nab*-paclitaxel and gemcitabine was continued until disease progression in February 2014 after cycle 7.

Case 3: Elderly patient with comorbidity. In March 2013, a 72-year-old male presented at our center with painless jaundice. The patient had lost 10 kg of weight within the previous 18 months. He was diagnosed with a pancreatic acinar adenocarcinoma with retroperitoneal lymph node metastases and bilateral pulmonary metastases. He had a 40 pack-year history of smoking. In 1999, the patient had undergone radical prostatectomy due to prostate cancer. Since 2007, he had suffered from insulin-dependent diabetes mellitus type II. Anamnestically, there were further cardiovascular comorbidities. In 2009, the patient underwent two aorto-coronary venous bypass grafts due to coronary heart disease. In the same year, he midwest surgery for an aneurysm of the left iliac artery. In 2011, he suffered a transitory ischemic attack due to stenosis of the left carotid artery.

It is routine practice in our center to perform an extensive and systematic formal geriatric assessment to better assess a patient's situation for treatment decision-making. This includes assessment of functionality by Barthel's scale (6) and Lawton instrumental activity scale (7), of cognition by mini mental state examination (8), of mobility and balance by timed up-and-go test (9), Tinetti balance assessment tool (10), body-mass index and mini nutritional assessment (11), depression by geriatric depression scale (12), and comorbidity by Charlson score (13). The assessment outcome qualified this patient as being fit for standard chemotherapy.

A stent was placed into the biliary duct. Subsequently, we started first-line chemotherapy with *nab*-paclitaxel and gemcitabine. *Nab*-paclitaxel was given at a dose of 125 mg/m^2 on days 1, 8 and 15, and gemcitabine at a dose of 1,000 mg/m^2 on days 1, 8 and 15 of a 28-day cycle. The first cycle was administered in an in patient setting. There was an episode of diarrhea grade 2 and minor glycemic fluctuations that were managed easily. Further cycles were given in an outpatient setting and tolerated well. Hematological toxicity was mild and was restricted to grade 1 anemia. From cycle 3 onwards, the patient suffered from grade 1 fatigue for two days after the administration of chemotherapy. A rash was classified as seborrhoeic eczema without any causal relationship to chemotherapy. There were no signs of sensory polyneuropathy.

Computed tomography after cycle 2 and 4 showed stable disease. The patient gained weight and had a good performance status. Chemotherapy was stopped after cycle 5 when the best response was reached. Disease remained stable for a further two months.

Case 4: ECOG PS 2. In January 2013, a 74-year-old male was diagnosed with PDAC of the pancreatic tail. The tumor

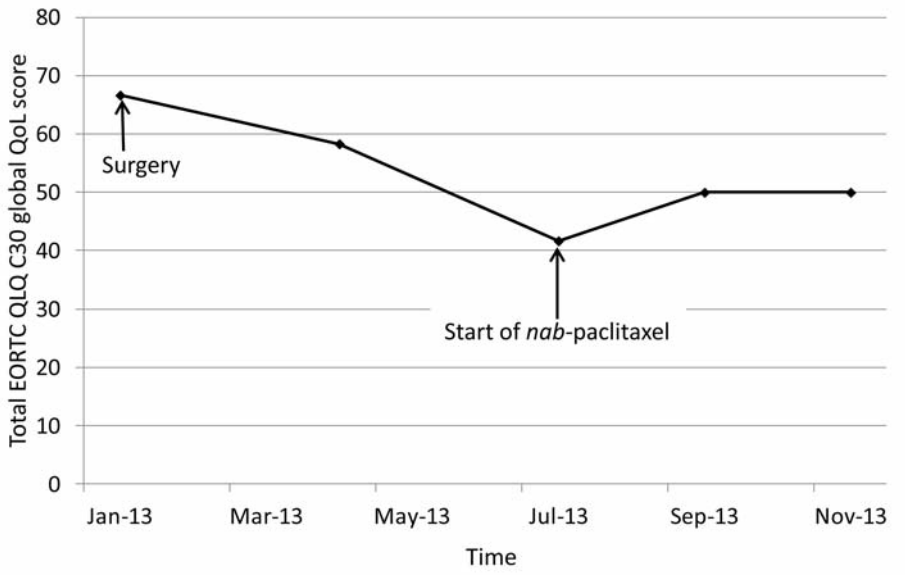

Figure 2. *Case 4. Course of European Organisation of Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ) C30 global quality of life (QoL) score.*

Table I. *Case 2 – Monitoring and management of chemotherapy.*

Cycle	Day	Dose of gemcitabine (mg/m^2)	Dose of *nab*-paclitaxel (mg/m^2)	Total bilirubin in serum (mg/dl)	Adverse event	Intervention
1	1	1000	***100***	**2.2**		Dose reduction on d1
	8	1000	125	2.1	Grade 2 neutropenia	None
	15	1000	125	2,7	Grade 1 neutropenia	None
2	1	1000	125	1.6	Grade 2 neutropenia	None
	8	1000	125	**2.3**		Dose reduction on d15
	15	1000	***100***	2.1	Grade 1 neutropenia	None
3	1	1000	125	2.3		None
	8	***800***	***100***	**3.2**	Grade 2 neutropenia	Dose reduction on d8
	15	***No therapy***	***No therapy***	**3.7**	**Grade 4 neutropenia,** grade 1 thrombopenia, **cholangitis**	Antibiotics, no chemotherapy on d15
4	1	1000	125	1.5	Grade 2 alopecia, grade 1 peripheral polyneuropathy	None
	8	***800***	***100***	**2.3**	**Grade 3 neutropenia**	Dose reduction on d8, G-CSF-support
	15	1000	125	2.1		None
5	1	1000	125	3.2	**Grade 2 *panaritium cutaneum***	Local therapy
	8	1000	125	1.7		None
	15	***800***	***100***	**2.1**	Grade 1 neutropenia, **grade 2 thrombopenia**	Dose reduction on d15
6	1	1000	125	**3.2**	Peripheral neuropathy grade 2	
	8	1000	***0***	**4.3**	**Fever of unknown origin**	Antibiotics, revision of stent, no nab-paclitaxel on d8
	15	***800***	***100***	1.7	**Grade 2 thrombopenia**	Dose reduction on d15
7	1	1000	125	**2.1**		
	8	***800***	***100***	1.8	**Grade 2 thrombopenia**	Dose reduction on d8
	15	***800***	***100***	2.2	**Grade 2 thrombopenia**	Dose reduction on d15

The relevant toxicity which prompted an intervention is marked in bold print. Reduced doses of gemcitabine and nab-paclitaxel are marked in italic bold print. G -CSF: Granulocyte colony-stimulating factor.

had already infiltrated the left colic flexure, the splenic hilum, the superior duodenal fold and the left renal capsule. No formal geriatric assessment was performed. The patient presented with an excellent performance status, a significantly lower biological age and had no comorbidities.

There was no evidence of metastatic disease. Thus, a radical multivisceral resection was performed which resulted in R0 resection. During the course of the subsequent adjuvant chemotherapy with gemcitabine, the patient's performance status deteriorated to an ECOG PS of 2. In July 2013, peritoneal carcinomatosis was detected. The patient suffered severely from nausea, vomiting, fatigue and pain during food intake.

We started first-line chemotherapy for metastatic disease. Gemcitabine was continued at a dose of 1,000 mg/m^2 on days 1, 8 and 15. *Nab*-paclitaxel was added at a dose of 100 mg/m^2 on days 1, 8 and 15 of a 28-day cycle. The dose was reduced *a priori* due to the patient's impaired performance status. After two cycles of therapy, the patient's condition improved significantly. His performance status increased to ECOG PS 1. Treatment was well tolerated. The patient showed a marked clinical remission which was accompanied by a decline of the levels of tumor marker carbohydrate antigen (CA) 19-9. Response to therapy was monitored and assessed clinically. Quality of life was formally evaluated during the whole course of therapy by questionnaire European Organization for Research and Treatment of Cancer (EORTC) QLC30. It reflected the clinical course and showed a continuous decline of the patient's quality of life after surgery and during adjuvant therapy, and a subsequent improvement following first-line chemotherapy with *nab*-paclitaxel and gemcitabine (Figure 2). Overall, the patient received six cycles of first-line chemotherapy until progression of his disease in December 2013.

Discussion

The adoption of new therapies should be based on significantly better patient outcomes *vs*. standard treatment shown in well-controlled phase III trials. However, the populations of these trials do not completely mirror the patients encountered in routine clinical practice.

In the phase III registration trial of *nab*-paclitaxel in patients with pancreatic cancer, patients had to have normal total serum bilirubin (2). Apart from one pilot study that evaluated safety and pharmacokinetics of the three-weekly monotherapy with *nab*-paclitaxel in 30 patients with solid tumors, there is little evidence for the use of *nab*-paclitaxel in patients with elevated bilirubin levels. Overall, the tolerability profile in these patients was acceptable. Total bilirubin levels were inversely correlated to paclitaxel clearance (14). The prescribing information of *nab*-paclitaxel points-out that in patients with impaired liver function, toxicity may be increased and *nab*-paclitaxel should be administered with caution (15). Dose reductions should be considered for patients with bilirubin levels twice the ULN and patients with a heavily impaired liver function (defined as a bilirubin level of more than five-fold the ULN or an elevation of liver enzymes to more than 10-fold the ULN) should not be treated with *nab*-paclitaxel (15). However, elevated bilirubin levels in pancreatic cancer frequently result from cholestasis due to obstruction of the bile duct caused by a tumor of the pancreatic head and are not signs of an impaired liver function. Yet *nab*-paclitaxel metabolism is predominantly hepatic and impairment of biliary excretion by cholestasis can be expected (15). Nevertheless, it is worthwhile considering this treatment option in individual cases with high serum bilirubin levels, especially if they are obviously associated with a subsequently eliminated obstruction. The two cases we described show that the combination therapy of *nab*-paclitaxel and gemcitabine can be adminstered safely to patients with elevated total serum bilirubin levels in conjunction with stenting and under close monitoring that allows for rapid dose adjustments.

Patients with advanced PDAC tend to be older individuals, with a median age at first diagnosis of 70 years for male and 76 years for female patients (16). Treatment decision-making in older patients is complex. However, older age *per se* should not be the main reason to deny a patient active treatment. Yet fewer patients with pancreatic cancer who are older than 70 years of age actually receive chemotherapy compared to younger patients (17). This may partially be due to limited data from clinical trials regarding elderly patients. The median age of all patients treated in the MPACT trial was 63 years, 42% of the patients were 65 years or older, 10% of patients were older than 75 years (2, 15). A prespecified sub-group analysis showed a benefit for treatment with the combination of *nab*-paclitaxel and gemcitabine for patients younger than 65 years and for those aged 65 years or more (2). In patients 75 years of age or older, there was a higher incidence of serious adverse reactions and of adverse reactions under therapy with *nab*-paclitaxel and gemcitabine that led to treatment discontinuation (15). The limited number of patients aged 75 years or more did not allow for robust conclusion drawing regarding the efficacy of the combination in this subpopulation (15).

Cases 2, 3 and 4 we report here demonstrate that elderly patients may profit from first-line chemotherapy with *nab*-paclitaxel and gemcitabine. The treatment decision for first-line chemotherapy with *nab*-paclitaxel should not be limited by the chronological age of patients but should be made individually for each patient in an interdisciplinary team, ideally based on a systematic geriatric assessment.

Finally, case 4 is a good example that more intensive and effective first-line chemotherapy should not be limited to patients with a good performance status. The majority (93%)

of patients recruited into the MPACT trial had a Karnofsky performance status of 80% to 100%, yet 32 patients (8%) had one of 60% to 70%. Both sub-groups derived a clear benefit from the combination of *nab*-paclitaxel and gemcitabine (2). One should bear in mind that tumor-related symptoms can contribute to deterioration of a patient's performance status. As demonstrated in our case, effective chemotherapy can result in sustainable improvement of a patient's performance status and quality of life. An interesting aspect of this case is that the patient responded to the combination of *nab*-paclitaxel and gemcitabine while his disease had progressed under adjuvant gemcitabine monotherapy. This is in line with preclinical data showing a synergistic effect of both agents in combination, which can probably be attributed to *nab*-paclitaxel causing a marked inhibition of cytidine deaminase and stroma depletion (5, 18, 19).

There can be no general treatment recommendations based on single-case experiences. Yet the cases we report highlight that there are individual patients with pancreatic cancer and more unfavorable characteristics than those treated in the pivotal trial who can be safely and effectively treated with the first-line combination of *nab*-paclitaxel and gemcitabine.

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