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Original Research

Safety and efficacy of *Nab*-paclitaxel plus gemcitabine in patients with advanced pancreatic cancer suffering from cholestatic hyperbilirubinaemia—A retrospective analysis

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Abstract ***Introduction:*** Treatment of patients with advanced pancreatic carcinoma (APC) and hyperbilirubinaemia is problematic because these patients were regularly excluded from clinical studies. *Nanoparticle albumin–bound paclitaxel and gemcitabine (nab-P/G)* is an evidence-based treatment for patients with APC. This retrospective study investigated the safety and efficacy of *nab*-P/G in patients with APC and cholestatic hyperbilirubinaemia.
Methods: We screened our prospective database for patients with APC treated with *nab*-P/G at total bilirubin levels of ≥1.2 mg/dl. Patients were assigned into three groups according to their bilirubin level (A: 1.2–3 mg/dl, B: >3–5 mg/dl, C: >5 mg/dl). Analyses with regard to safety and survival were performed.
Results: Twenty-nine of 168 patients screened between Dec 2013 and Dec 2015 fulfilled the inclusion criteria. Most patients (83%) were male; median age was 63 [41–79] years. N*ab*-P/G administrations in patients with an elevated bilirubin level (median, range) did not result in unexpected toxicities assessed by predefined (non-)haematological parameters. Median overall survival (mOS) for the whole group was 11.7 (95% confidence interval [CI]: 6.8–14.0) months; for A: 11.8 (95% CI: 6.5–16.5), B: 9.2 (95% CI: 1.1 – NA) months and C 11.8 (95% CI: 5.9–20.0] months (p = 0.843). Again, mOS from the first application of *nab*-P/G did not differ between the groups (p = 0.13).

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Conclusion: *Nab*-P/G administrations in our pts with cholestatic hyperbilirubinaemia suffering from APC were feasible and safe with respect to individualised dose administrations. A multicenter phase 1 trial in pts with hyperbilirubinaemia is started (AIO-PAK-0117) to confirm these findings in a prospective setting.

1. Introduction

Pancreatic adenocarcinoma ranks as the fourth deadliest cancer in men and women within Europe [1]. Owing to the late onset of symptoms, 85–90% of patients with pancreatic cancer are diagnosed with locally advanced or metastatic stage when curatively intended resection is no longer an option [2]. Prognosis of these patients is bleak with a 5-year overall survival (OS) rate of less than 5% [3].

For patients with inoperable advanced pancreatic carcinoma (APC), gemcitabine monotherapy had been the standard first-line treatment with palliative intention for almost two decades [4]. Only in the last few years, new regimens were introduced which significantly improved the clinical outcomes compared with gemcitabine alone. The combination of nanoparticle albumin–bound paclitaxel and gemcitabine (*nab*-P/G) [5] and the regimen FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan and oxaliplatin) [6] are currently considered as the standard treatment options for patients with a good performance status [7]. Because patients with elevated bilirubin levels were excluded from the phase 3 clinical studies for FOLFIRINOX and *nab*-P/G, both regimens are not recommended for patients with total bilirubin (TB) levels >1.5 upper limit of normal (ULN) [6,8].

However, hyperbilirubinaemia is common in patients suffering from APC and is mainly due to obstructions of the bile duct system by the primary tumour, lymph nodes or hepatic metastases. The majority of pancreatic cancers (60–70%) arise in the pancreatic head in proximity to the common bile duct [7]. Furthermore, local lymph nodes and the liver are the most frequent sites of metastatic spread. Thus, jaundice is one of the most frequent symptoms at diagnosis, affecting more than 50% of patients [9].

Hence, those patients constitute a considerable patient population whose need for effective medical treatment is currently unmet, and information about the feasibility of newer treatment regimens is scarce [10].

While gemcitabine is mainly eliminated via the kidneys [11], the main elimination pathway of paclitaxel is hydroxylation by CYP450 enzymes in the liver followed by excretion via the bile [8]. However, a recent meta-analysis of pharmacokinetic data from patients with various solid tumours showed that TB levels had only limited effect on paclitaxel elimination if administered in the *nab*-paclitaxel formulation [12]. Because of low numbers, pts with APC could not be analysed in this setting. These results however suggest that *nab*-P/G might also be a feasible treatment option for patients with APC and hyperbilirubinaemia. Currently, only single case reports exist for this constellation, [13] and more data are needed to determine under which circumstances this therapeutic option can be offered to these patients.

Herein we present the results of an investigation evaluating the feasibility, safety and treatment effect of *nab*-P/G in patients with cholestatic hyperbilirubinaemia.

2. Patients/material and methods

We screened our prospective database containing data from patients treated at our cancer centre according to the following criteria: histologically proven locally advanced or metastatic pancreatic carcinoma and total hyperbilirubinaemia at treatment initiation with *nab*-P/G; total hyperbilirubinaemia caused by primary cancer or metastatic extrahepatic or intrahepatic malignant bile duct obstruction (e.g. no haemolysis, hepatitis, hereditary liver function diseases); optimised biliary tract flow with intrahepatic stenting or percutaneous transhepatic drainage (confirmed by the cancer board of our institution) if feasible; no other or secondary types of cancer; with or without primary cancer resection and presence of a full panel of laboratory results (see Assessment of toxicities) at the time of study entry and during follow-up to assess both non-haematological and haematological toxicities.

2.1. Classification

Patients were assigned to three groups according to their elevated TB level at the time of treatment initiation with *nab*-P/G: group A, >1.2–3 mg/dl; group B, > 3–5 mg/dl and group C, >5 mg/dl.

2.2. Assessment of treatment (dose-)intensity

A dose level of 100% was defined as an intravenous infusion of 125 mg/m^2 of *nab*-paclitaxel followed by an infusion of gemcitabine at a dose of 1 g/m^2 at days 1, 8 and 15 every 28 d. Because of missing data, there were