Patients with Advanced Pancreatic Cancer and Hyperbilirubinaemia: Review and German Expert Opinion on Treatment with nab-Paclitaxel plus Gemcitabine

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Keywords

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Summary

In patients with advanced unresectable pancreatic cancer, the prognosis is generally poor. Within recent years, new treatment options such as the FOLFIRINOX regimen (5-fluorouracil, leucovorin, irinotecan and oxaliplatin) or the combination of nanoparticle albumin-bound (nab)-paclitaxel plus gemcitabine have shown a clinically relevant survival benefit over the standard gemcitabine in patients with good performance status. Unfortunately, patients with hyperbilirubinaemia, who constitute a substantial proportion of the pancreatic cancer patients, have been excluded from most clinical studies. Consequently, our knowledge on the appropriate medical treatment of this patient group is limited. In a meeting of German medical oncology experts, the available clinical evidence and own clinical experience regarding the management of patients with advanced pancreatic cancer and hyperbilirubinaemia was discussed. The present publication summarises the discussion outcomes with

regard to appropriate management of these patients, including consensus-based recommendations for nab-paclitaxel/gemcitabine treatment, according to the best available evidence. In summary, knowledge of the underlying aetiology of hyperbilirubinaemia and the metabolism routes of the cytotoxic drugs is crucial before initiating chemotherapy. As effective treatment options should also be made available to patients with comorbid conditions, including hyperbilirubinaemia, the experts provide advice for an initial dose reduction of chemotherapy with nab-paclitaxel/gemcitabine based on the total bilirubin level in patients with biliary obstruction or extensive liver metastasis.

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Introduction

Treatment of Advanced Pancreatic Cancer

Pancreatic carcinoma ranks among the top 5 mortal cancers for both sexes in Europe, despite a relatively low average incidence of 6.8/100,000 [1]. Pancreatic cancer is rare in adults < 40 years of age, with a median age at diagnosis of 71 years [2]. As symptoms usually only appear once the disease has progressed, approximately

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85–90% of patients have unresectable disease at diagnosis [3] and thus a low overall 5-year survival rate of less than 5% [4]. Tumour resection remains the only curative treatment but is only suitable for the minority of patients with early disease [5]. Even after complete resection followed by adjuvant chemotherapy, around 80% of the patients will die within 5 years [6].

The available treatment options for patients with advanced, initially unresectable, relapsed or metastasised pancreatic cancer are still far from satisfactory. The introduction of combination chemotherapies within the last 4 years, such as the multidrug combination of 5-fluorouracil, leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) [7] and the combination of nanoparticle albumin-bound (nab)-paclitaxel plus gemcitabine [8], has nevertheless offered a clinically relevant survival benefit over gemcitabine monotherapy, the former treatment standard for more than 15 years. In a phase III study with selected patients from specialised centres, FOLFIRINOX chemotherapy led to a substantial benefit in overall survival compared to gemcitabine monotherapy (11.1 vs. 6.8 months; hazard ratio (HR) for death = 0.57 (95% confidence interval (CI): 0.45–0.73); $p < 0.001$), although it was also associated with a marked potential for toxicities and was limited to patients ≤ 75 years of age [7, 9]. In an international large-scale phase III study, the combination of nab-paclitaxel plus gemcitabine was associated with a clinically relevant prolongation of overall survival compared to gemcitabine alone (8.7 vs. 6.6 months; HR for death = 0.72 (95% CI: 0.62–0.83); $p < 0.001$) [8]. Although treatment with nab-paclitaxel plus gemcitabine involved adverse reactions including haematological cytopenias and peripheral neuropathy, the tolerability profile was considered as manageable [8, 9]. The recently updated US National Comprehensive Cancer Network (NCCN) guideline recommends FOLFIRINOX and nab-paclitaxel plus gemcitabine as the preferred treatment options for patients with good performance status and metastatic disease and as possible options for the treatment of locally advanced, unresectable pancreatic cancers [10]. Thus, at present, FOLFIRINOX or nab-paclitaxel plus gemcitabine are considered the standard treatment for patients with good performance status who do not have severe comorbidities [2]. Although a head-to-head comparison of both treatment regimens is not available, chemotherapy with nab-paclitaxel plus gemcitabine seems to be less toxic than FOLFIRINOX treatment [9] and is not restricted to patients ≤ 75 years of age [8]. Consequently, we herein focus on recommendations for treatment with nab-paclitaxel plus gemcitabine since it may be used for a broader patient population compared to FOLFIRINOX.

Hyperbilirubinaemia in Patients with Pancreatic Cancer

Around 60–70% of pancreatic cancers are located in the pancreatic head [2], leading to hyperbilirubinaemia caused by obstruction of the central bile duct in 70–80% of these patients [5]. Biliary obstruction and the resulting hyperbilirubinaemia usually complicate the management of patients by increasing the risk of cholangitis and causing frequent hospitalisations [11]; hyperbilirubinaemia has been associated with shorter overall survival in patients with pancreatic cancer [12, 13]. Biliary decompression in patients with

obstructive hyperbilirubinaemia is commonly performed using endoscopic stent placement [10], which not only reduces morbidity [14] but also facilitates treatment with chemotherapy by allowing total bilirubin levels to drop to ≤ 1.5 – 2 times the upper limit of normal (≤ 1.5 – $2 \times \text{ULN}$). Other possible causes of hyperbilirubinaemia in patients with pancreatic cancer are obstruction of the peripheral intrahepatic bile ducts due to tumour metastases, without major impairment of other aspects of liver function, or massive infiltration of the liver by tumour metastases resulting in non-cirrhotic liver failure.

Unmet Need for Medical Treatment of Patients with Advanced Pancreatic Cancer and Hyperbilirubinaemia

Many phase I, II and III studies have excluded patients with abnormal serum liver biochemical tests, including elevated bilirubin, thus probably falsely excluding a considerable patient population from potentially beneficial therapies [15]. Therefore, our knowledge on the most appropriate starting doses of chemotherapy in these individuals is limited [15]. Likewise, pivotal clinical trials with nab-paclitaxel plus gemcitabine have only included patients with bilirubin levels within the normal range [8, 16]. With the exception of single case reports [17], there is currently no evidence from clinical studies to support nab-paclitaxel plus gemcitabine treatment in patients with pancreatic cancer and elevated bilirubin. Thus, according to the current recommendation in the European summary of product characteristics, treatment with nab-paclitaxel is not recommended in pancreatic cancer patients with moderate to severe hepatic impairment (total bilirubin $> 1.5 \times \text{ULN}$ and aspartate aminotransferase $\leq 10 \times \text{ULN}$) since there are insufficient data to permit dosage recommendations [18]. Despite its long-standing use in clinical practice, similar restrictions exist for the recommendation of gemcitabine: Due to insufficient information from clinical studies to allow for clear dose recommendations for this patient population, gemcitabine should be administered with caution in patients with hepatic insufficiency [19]. An ongoing phase I study with nab-paclitaxel plus gemcitabine in patients with advanced pancreatic cancer who have cholestatic hyperbilirubinaemia secondary to bile duct obstruction [20] will hopefully shed more light on the impact of hyperbilirubinaemia on the efficacy and safety of nab-paclitaxel plus gemcitabine. In this publication, experienced experts will give some guidance for the management of patients with advanced pancreatic cancer and hyperbilirubinaemia, especially regarding chemotherapy with nab-paclitaxel plus gemcitabine.

Materials and Methods

Data were retrieved from the published literature indexed in MEDLINE/PubMed. The information was accessed until March 2015. For consensus development, a task force of clinical experts and practicing oncologists in the field of medical oncology with long-standing expertise in the management of patients with pancreatic cancer was established. The task force members discussed the available clinical evidence, reported their clinical practice and agreed on a consensus statement based on a face-to-face meeting in January 2015. A core group of experts summarised the current state of the art of management of patients

Table 1. Selection of laboratory tests in patients with hyperbilirubinaemia

Liver function defect	Parameter	Explanation
Hepatocellular damage	elevated liver transaminases (ALT, AST)	enzymes released when hepatocytes are damaged; ALT more specific to hepatocytes than AST
	elevated GLDH	expressed in mitochondria of liver parenchyma cells; released upon liver cell necrosis
Liver synthetic function	reduced serum albumin	most abundant plasma protein that is exclusively synthesised in the liver; more common in chronic liver disease than in acute toxicity
	increased INR/prothrombin time or reduced factor V	prothrombin (vitamin K dependent) and factor V (vitamin K independent): examples of blood coagulation factors synthesised in the liver; decreased concentration leads to blood coagulation deficiency
	reduced serum cholinesterase	enzyme mainly synthesised in hepatocytes
	elevated unconjugated bilirubin	decreased glucuronidation capacity of the cirrhotic liver
Cholestasis/obstruction	elevated conjugated bilirubin	reflux of bilirubin glucuronides into plasma due to intra- or posthepatic obstruction
	elevated ALP	increased synthesis of plasma ALP in case of any form of biliary obstruction; elevated to a lesser degree in hepatocellular injury
	elevated GGT	differentiation of the source (liver or bone) of elevated ALP: liver dysfunction if GGT increase ≥ 2 times the increase in ALP; greatly increased in hepatocyte damage and cholestasis
CYP450 metabolism	erythromycin breath test [15]	quantitative measure of CYP450 3A4 activity; not routinely applied in clinical practice

ALT = Alanine aminotransferase, AST = aspartate aminotransferase, GLDH = glutamate dehydrogenase, INR = international normalised ratio, ALP = alkaline phosphatase, GGT = gamma-glutamyltransferase.

with pancreatic cancer and hyperbilirubinaemia and verbalised the German perspective on the treatment of this patient population with nab-paclitaxel plus gemcitabine.

Results

Determining the Underlying Cause of Hyperbilirubinaemia in Patients with Pancreatic Cancer

Bilirubin, a breakdown product of haemoproteins, is taken up from plasma into liver hepatocytes where it is conjugated to glucuronic acid; the conjugated form is excreted into bile [21]. The upper limit of the reference range of total bilirubin amounts to 1.2 mg/dl (21 $\mu\text{mol/l}$) [22] and jaundice can be detected when the plasma concentration is 2–3-fold elevated [23]. The reasons for an elevated serum bilirubin concentration can be grouped into 3 main categories: (1) prehepatic dysfunction, e.g. haemolysis, resulting in unconjugated hyperbilirubinaemia, (2) intrahepatic dysfunction, e.g. intrahepatic biliary obstruction or liver damage caused by hepatotoxic drugs, leading to predominantly conjugated hyperbilirubinaemia, and (3) posthepatic biliary obstruction resulting in predominantly conjugated hyperbilirubinaemia [21, 24]. As outlined, in the majority of patients with pancreatic cancer, hyperbilirubinaemia is caused by obstruction of the common bile duct due to a tumour in the pancreas head [5]. In patients with extensive liver metastasis, bilirubin

might be elevated due to intrahepatic biliary obstruction and/or metastasis-related liver insufficiency. Some patients might suffer from hyperbilirubinaemia caused by pre-existing hepatic dysfunction, e.g. liver cirrhosis [21, 25]. The prerequisite for the appropriate management of affected patients is to clearly determine the underlying cause of hyperbilirubinaemia. Therefore, a combination of laboratory parameters should be analysed since patterns of abnormalities are more meaningful than elevations or reductions of individual parameters [21] (table 1). Since the laboratory test results in most cases do not exactly identify the aetiology of predominant conjugated hyperbilirubinaemia, imaging techniques including sonography, computed tomography (CT) and magnetic resonance imaging (MRI) are essential to precisely determine the specific problem [24]. In order to direct therapy and to predict the survival of patients with chronic liver disease, scoring systems have been developed [26]. The long-established Child-(Turcotte-)Pugh score divides patients into classes A–C, based on the extent of clinical ascites, encephalopathy and laboratory parameters including albumin, the international normalised ratio (INR) and bilirubin [27, 28]. The model for end-stage liver disease (MELD) score is based on a mathematical equation incorporating the bilirubin concentration, the INR and the serum creatinine level [29]. Recently, the albumin-bilirubin (ALBI) grade was developed. This is a mathematical equation incorporating only the serum bilirubin and albumin levels and thus eliminating the need for subjective variables such as ascites and encephalopathy [30].

Table 2. Pros and cons of available stents (modified from [11, 34])

Stent type	Duration of patency	Removability	Migration probability	Device costs	Cost-effectiveness
Plastic stent	short	easy	low	low	low due to higher number of endoscopic procedures
Uncovered self-expandable metal stent	long	extremely difficult	low	high	high in patients with expected survival ≥ 4.8 to 6 months [35–38]
Covered self-expandable metal stent		easy	high		

Panel Advice

- The underlying cause of hyperbilirubinaemia should be clearly determined before initiation of chemotherapy.
- Since measurements of bilirubin or other laboratory tests may not exactly identify the aetiology of hyperbilirubinaemia, imaging techniques such as ultrasound and/or CT should be additionally applied.

Biliary Decompression in Patients with Pancreatic Cancer and Obstructive Hyperbilirubinaemia Intended for Chemotherapy

The rationale for biliary decompression in patients with unresectable pancreatic cancer and obstructive cholestasis is the normalisation of the bilirubin levels to allow palliative chemotherapy, and the prevention of other adverse outcomes such as cholangitis and frequent hospitalisations [11]. According to the current German, European and American treatment guidelines, stent placement via endoscopic retrograde cholangiopancreatography (ERCP) is the preferred method for biliary decompression in these patients [5, 10, 31]. In case ERCP is not possible, percutaneous transhepatic biliary drainage (PTCD) is recommended [5, 10, 31]. Endoscopic ultrasound-guided transoesophageal or transduodenal biliary drainage represents a treatment alternative in selected patients not suitable for conventional ERCP and PTCD [32, 33].

Basically, 3 types of stents can be used: plastic stents, uncovered self-expandable metallic stents and covered self-expandable metallic stents [11]. The choice of stent depends on several aspects such as the anatomical situation, the experience of the endoscopist, the expected survival time and cost-effectiveness (table 2). Based on the longer patency time compared to plastic stents, self-expanding metal stents (either covered or uncovered) may be the preferred option for patients with a life expectancy of > 3 months, according to the treatment guidelines [5, 31].

While there is no discussion regarding prophylactic perioperative administration of antibiotics in conjunction with hepatobiliary surgery [31], antibiotic coverage during stent implantation is still a matter of debate. Although severe complications with ERCP procedures are rare, infectious complications remain prevalent [39]. Although no randomised study has been conducted to test the benefit of peri-interventional infection prophylaxis, anti-

biotic prophylaxis should be considered since biliary drainage leads to bacterial contamination of the bile ducts in almost 100% of cases [40].

Panel Advice

- Biliary decompression by endoscopic stenting is an essential part of the palliative treatment of patients with obstructive cholestasis.
- Stenting with either a metal or a plastic stent can be recommended. The choice of stent mainly depends on the anatomical situation and the expected survival time.
- Hospital-adjusted peri-interventional antibiotic prophylaxis should be considered.

Impact of Hyperbilirubinaemia on the Efficacy and Tolerability of Chemotherapy with nab-Paclitaxel plus Gemcitabine

Hepatic dysfunction in patients with pancreatic cancer may affect the pharmacokinetic properties of drugs in different ways. A reduced metabolic capacity of the liver, especially with respect to cytochrome P450 (CYP450) isoenzymes, may change their hepatic clearance [21]. Depending on the metabolic profile, this could either result in impaired bioactivation of a prodrug or in impaired drug inactivation [21]. Obstruction of the common bile duct may interfere with the clearance of drugs excreted via bile [41]. Portal-vein thrombosis caused by a hypercoagulable state or by portal-vein infiltration may compromise vascular supply to healthy liver parenchyma and thereby impair drug metabolism [21]. Consequently, interference with the drug kinetics in patients with hepatic dysfunction may result in reduced effectiveness or increased toxicity of the chemotherapy [21]. Compounds metabolised via CYP450 isoenzymes and secreted via bile are especially affected.

nab-Paclitaxel

Originally, the paclitaxel formulation was based on the solvent Cremophor EL (polyoxyethylated castor oil + dehydrated ethanol) to increase the solubility and bioavailability of paclitaxel. A major drawback of chemotherapy with this formulation is the occurrence of adverse effects including hypersensitivity reactions and neurotoxicity, which are caused by the solvent [42, 43]. Encapsulation of paclitaxel into albumin nanoparticles (nab-paclitaxel) allowed for

solvent-free administration of the lipophilic compound, thus avoiding the toxicity associated with the solvent [42]. Pharmacokinetic studies with solvent-based paclitaxel revealed that the compound is metabolised via hydroxylation by CYP450 isoenzymes to the main metabolite 6- α -hydroxypaclitaxel (CYP2C8) and to 3'-p-hydroxypaclitaxel (CYP3A4), as well as 6- α ,3'-p-dihydroxypaclitaxel (CYP2C8 and CYP3A4). Around 70% of the administered dose is eliminated via biliary excretion [18, 44, 45]. The hydroxy metabolites of paclitaxel are less cytotoxic than the parent compound [44].

Few small studies on the influence of hepatic dysfunction and hyperbilirubinaemia on the pharmacokinetic properties and the toxicity of solvent-based paclitaxel have been performed. Consistent with its mentioned metabolic profile, population-based pharmacokinetic-pharmacodynamic analyses involving patients with solid tumours and varying degrees of hepatic impairment revealed a negative impact of hyperbilirubinaemia on the clearance of paclitaxel: An increase of 0.6 mg/dl (10 μ mol) in total bilirubin was associated with a 12–19% decrease of the elimination capacity of paclitaxel [46–48]. These findings are in agreement with clinical data showing that paclitaxel treatment of patients with hepatic impairment and hyperbilirubinaemia was associated with a higher incidence of haematological and non-haematological toxic effects [49, 50], especially in patients with more advanced hepatic impairment [48]. A pharmacokinetic-pharmacodynamic model, derived from one of the mentioned studies in 35 patients with solid tumours receiving paclitaxel monotherapy, predicted the following recommendation for the initial paclitaxel dose based on the total bilirubin level: $\leq 1.25 \times \text{ULN}$: 175 mg/m² (100% dose), $1.26\text{--}2.0 \times \text{ULN}$: 115 mg/m² (66%), $2.1\text{--}3.5 \times \text{ULN}$: 100 mg/m² (57%) and $3.6\text{--}10 \times \text{ULN}$: 70 mg/m² (40%) [48]. The validity of the recommendation for an initial paclitaxel dose of 40% was confirmed in a pharmacokinetic study in 9 patients with severe hepatic dysfunction caused by liver metastases and a bilirubin level of $3\text{--}11 \times \text{ULN}$: Treatment with 70 mg/m² paclitaxel was safe and led to adequate plasma concentrations [51].

However, interpretation of the results derived from these studies using solvent-based paclitaxel is difficult due to the small sample size and the large heterogeneity of included patients, especially regarding the kind of hepatic dysfunction – the underlying aetiology of hyperbilirubinaemia has not been reported. In addition, data obtained with solvent-based paclitaxel are not directly applicable to solvent-free nab-paclitaxel because of the different distribution and elimination kinetics of the 2 formulations: nab-paclitaxel exhibits a faster distribution and a 9-fold larger distribution volume, as well as a slower elimination compared to solvent-based paclitaxel [52]. The more rapid tissue distribution of paclitaxel when administered as nab-paclitaxel results in a shorter duration of high systemic drug concentrations, which likely contributes to its reduced haematotoxicity in comparison to solvent-based paclitaxel [52]. Furthermore, administration of nab-paclitaxel led to 33% higher intratumoral drug accumulation in animal studies [53].

In accordance with the results for solvent-based paclitaxel [46–48], a pilot study in 15 patients with solid tumours and hyperbilirubinaemia showed that nab-paclitaxel clearance was significantly in-

versely correlated with the total bilirubin levels [54]. The study supports the same dose modification scheme in patients with hepatic dysfunction as recommended for solvent-based paclitaxel [54]. However, its main limitations are that a control group of patients with normal hepatic function was lacking and – as is the case for the studies with solvent-based paclitaxel – that the population was mixed with respect to the underlying aetiology of hyperbilirubinaemia [54]. Recently, a meta-analysis of 8 clinical studies of nab-paclitaxel was conducted: In 150 patients with different solid tumours, mostly melanoma (29%) and breast cancer (16%), 13.3% of the patients had hyperbilirubinaemia [52]. In patients with total bilirubin of > 1 to $\leq 1.5 \times \text{ULN}$, the elimination rate of nab-paclitaxel was not significantly reduced [52]. Total bilirubin concentrations > 1.5 to $\leq 3 \times \text{ULN}$ or > 3 to $\leq 5 \times \text{ULN}$ led to a 22% or 26% decrease in the maximum elimination rate of paclitaxel and to an approximately 20% increase in the mean paclitaxel area under the curve (AUC) [52]. Thus, in contrast to the results of the pilot study [54], changes in total bilirubin had only limited effect on paclitaxel elimination [52]. According to the results of the meta-analysis, a 20% reduction of the nab-paclitaxel dose may be considered a safe starting level for patients with total bilirubin of > 1.5 to $\leq 5 \times \text{ULN}$ to avoid a potential increase in systemic drug exposure [52]. Regarding treatment of metastatic breast cancer, this recommendation has been approved by the European authorities and was added to the summary of product characteristics of nab-paclitaxel [18]. Nevertheless, similar to the pilot study, the validity of this study for the treatment of pancreatic cancer patients is limited due to the small sample size. Furthermore, patients with pancreatic cancer and mechanic obstruction of the bile duct were not included in the analysis [52].

Gemcitabine

Paclitaxel and gemcitabine do not share a common metabolic pathway, making pharmacokinetic interactions unlikely. Gemcitabine (difluorodeoxycytidine) is a nucleoside analogue prodrug requiring intracellular activation by phosphorylation to di- and triphosphates [19]. The compound is rapidly inactivated by cytidine deaminase to its main metabolite difluorodeoxyuridine and 99% of the administered dose is eliminated via renal excretion [19]. Treatment with gemcitabine leads to mild, mostly asymptomatic and transient increases in transaminases in about two-thirds of the patients, and in serum bilirubin in a small proportion of patients [55]. However, rare cases of mostly fatal liver failure in association with gemcitabine therapy have been previously observed – presumably caused by a metabolic idiosyncratic reaction to the compound [56, 57]. Consequently, careful monitoring of hepatic parameters during therapy with gemcitabine is recommended [21].

To study the impact of hepatic dysfunction on gemcitabine-induced toxicity, a prospective dose escalation study of the standard 30-min infusion was performed in 40 patients with hepatic impairment and total bilirubin levels of 1.7–5.7 mg/dl, of whom 17 patients had metastatic gastrointestinal cancer [58]. Patients with hyperbilirubinaemia at baseline were prone to develop substantial but mostly transient increases in the concentrations of bilirubin and liver transaminases [58]. Thus, a reduction of the gemcitabine

Table 3. Panel recommendation for initial doses of nab-paclitaxel and gemcitabine in patients with advanced pancreatic cancer based on the underlying cause of hyperbilirubinaemia

Patient group	Parameters for treatment decision	Total bilirubin level	nab-Paclitaxel dose, mg/m ²	Gemcitabine dose, mg/m ²
Patients with biliary obstruction ^a	albumin level > 3.5 g/dl;	≤ 3 × ULN	125	1,000
	INR < 2.0 (vitamin K deficiency to be considered; substitution if necessary)	> 3 to ≤ 8 × ULN	100	800
Patients with extensive liver metastasis	patient-related factors	≤ 1.5 × ULN	125	1,000
	(including performance status, co-morbidities, expectations);	> 1.5 to ≤ 3 × ULN	100	800
	liver parameters (including albumin, INR, cholinesterase)	> 3 to ≤ 5 × ULN (treatment only with specific care) ^b	75	600
Patients with pre-existing chronic liver disease	no dosage recommendation; each patient to be treated individually based on underlying hepatic dysfunction			

Consider transferring the patient to an experienced study centre for the first treatment cycle; re-evaluate dose intensity (reduction/escalation) prior to every application dependent on treatment-associated toxicity, actual bilirubin level and treatment effect.

^aChemotherapy can be considered as soon as the bilirubin concentration is sufficiently decreased after biliary decompression and stable or further decreasing.

^bBecause of the highly critical situation, patients should be treated with specific care. Very close monitoring is required.

INR, International normalised ratio; ULN, upper limit of normal.

starting dose to 800 mg/m² (= 80% of the standard dose) was recommended [58]. A small phase II study in 43 patients with advanced unresectable hepatobiliary carcinomas revealed a high frequency (30%) of grade 3/4 thrombocytopenias in the 18 patients with hepatocellular carcinoma and liver cirrhosis (Child A: n = 5, Child B: n = 13) of this group [59]. In contrast, a smaller study involving 9 patients with pancreatic (n = 5) or biliary tract cancer (n = 4) and hepatic impairment showed that the full dose of gemcitabine can be safely used in patients with elevated total bilirubin and transaminases when administered via the slower 10-mg/m²/min infusion [60]. Another recent study in 12 patients with advanced pancreatic (n = 7) or biliary tract cancer (n = 5) and extra- or intrahepatic cholestasis, receiving gemcitabine plus capecitabine chemotherapy, revealed a further interesting aspect: A total bilirubin level of ≥ 2 × ULN was associated with an impaired intracellular activation of gemcitabine to gemcitabine triphosphates, suggesting limited anti-tumour activity [61]. A larger study to confirm this finding is warranted.

Panel Advice

- nab-Paclitaxel and gemcitabine should be used with caution in patients with hyperbilirubinaemia. Careful monitoring of liver parameters during chemotherapy is warranted.
- Due to different pharmacokinetic properties, data derived from studies with solvent-based paclitaxel cannot be directly transferred to nab-paclitaxel.
- The main limitations of the available studies are their small sample sizes and the large heterogeneity of the included patients, especially regarding aetiology and degree of hepatic impairment.
- The underlying cause of hyperbilirubinaemia and the metabolism route of the cytotoxic agents have to be considered before initiation of chemotherapy.

Treatment Advice for Chemotherapy with nab-Paclitaxel plus Gemcitabine in Patients with Advanced Pancreatic Cancer and Hyperbilirubinaemia

Based on the underlying cause of hyperbilirubinaemia, patients with pancreatic cancer and elevated total bilirubin can be grouped into individuals with (1) biliary obstruction (mostly caused by a tumour in the pancreas head), (2) extensive liver metastasis and (3) pre-existing chronic liver disease. The percentages of patients in the 3 groups receiving first-line chemotherapy were estimated by the panel to be approximately 70%, 20% and 10%, respectively. According to the current guidelines, the prerequisite for initiation of chemotherapy is as much biliary decompression as possible [10]. The expert panel recommends starting treatment as soon as the bilirubin concentration is sufficiently decreased or further decreasing, since the time between first diagnosis and treatment start may be of prognostic relevance [62]. Due to the increased risk of infections after stent insertion [39] and the risk of leucopenia associated with chemotherapy [8], risks and benefits of an early treatment start, as well as favouring a standard or a reduced starting dose of chemotherapy, have to be weighed against each other. In this context, antibiotic prophylaxis has to be considered. As disease remission is the primary treatment goal, the expert panel prefers to use the combination treatment with nab-paclitaxel plus gemcitabine at a reduced starting dose over gemcitabine monotherapy in patients with hyperbilirubinaemia. The experts' recommendation for starting doses of nab-paclitaxel and gemcitabine in patients with biliary obstruction or extensive liver metastasis based on the total bilirubin level and other parameters is summarised in table 3. Patients with pre-existing chronic liver disease, e.g. liver fibrosis or cirrhosis, are a very heterogeneous patient population with respect to remaining liver function. Therefore, the experts do not provide a general treatment recommendation in this patient group; each individual case should be carefully evaluated. According to the German S3 treatment guideline for pancreatic cancer, treatment with

adjuvant chemotherapy is unrestricted in patients with Child A liver cirrhosis but not recommended in patients with Child B and C liver cirrhosis [31].

Conclusions

Many patients with advanced pancreatic cancer suffer from hyperbilirubinaemia [5], and these constitute a substantial population that has been excluded from most clinical studies [15]. Consequently, treatment of these individuals is complicated as the knowledge of appropriate starting doses of chemotherapy is limited to single case reports or small clinical studies in largely heterogeneous patient populations with regard to the tumour type and underlying aetiology of hyperbilirubinaemia [15]. The recommendations provided by the German expert panel are based on the best available evidence from clinical studies and their long-standing clinical experience in the management of patients with pancreatic cancer. Most importantly, since hyperbilirubinaemia can be a symptom of different types of hepatic dysfunction, its underlying aetiology should be clearly determined before initiation of chemotherapy. Furthermore, the metabolism routes of the cytotoxic agents must be considered. Due to the possible impact of hepatic impairment on the pharmacokinetic route of nab-paclitaxel and gemcitabine that was shown in small clinical studies, these compounds should be used with caution in patients with hyperbilirubinaemia, and careful monitoring of patients and liver parameters during chemotherapy is warranted. It should be kept in mind that data derived from studies with solvent-based paclitaxel cannot be directly transferred to nab-paclitaxel due to large differences in the

pharmacokinetic properties of these 2 formulations. In general, the experts provide advice on reduced starting doses of nab-paclitaxel and gemcitabine based on the total bilirubin level when initiating chemotherapy in patients with biliary obstruction or with extensive liver metastasis (summarised in table 3). Due to large heterogeneity regarding the remaining liver function of patients with pre-existing chronic liver disease, no general treatment recommendation for this patient group can be made.

In summary, effective treatment options including nab-paclitaxel plus gemcitabine should also be made available for patients with advanced pancreatic cancer and primary disease-associated conditions such as hyperbilirubinaemia – provided that the appropriate precautions are considered.

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Erratum

The correct order of authors of the article ‘Patients with Advanced Pancreatic Cancer and Hyperbilirubinaemia: Review and German Expert Opinion on Treatment with nab-Paclitaxel plus Gemcitabine’ (Oncol Res Treat 2015;38:596–603; DOI: 10.1159/000441310) is:

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