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DISSERTATION

Chemotherapeutic treatment options in patients with inoperable pancreatic cancer suffering hyperbilirubinemia.

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1. Abstrakt

1.1 In englischer Sprache

Introduction

Elevated bilirubin levels due to biliary tract obstruction and/or liver metastasis are common problems in patients with advanced pancreatic adenocarcinoma (APC). Therapeutic options are very limited because of lack of studies. The toxicity and safety of using the combination of gemcitabine and nanoparticle albumin-bound paclitaxel (nab-P+Gem) in patients with hyperbilirubinemia was assessed within our retrospective study.

Methods

Patients with APC treated at our institution with nab-paclitaxel and gemcitabine between December 2012 and December 2015 were screened for elevated bilirubin level and analyzed with respect to safety and survival. Their treatment regimens were recorded. The patients were divided into three groups according to respective levels of bilirubin (A: 1.2-3 mg/dl, B: 3-5 mg/dl and C: > 5 mg/dl).

Results

We selected 29 out of 168 patients which met the criteria treated in our hospital. Median overall survival (mOS) for all the patients was 11.7 (95% CI: 6.8-14.0) months. In the groups A, B and C, mOS was 11.8 (95% CI: 6.5-16.5), 9.2 (95% CI: 1.1-N/A) and 11.8 (95% CI: 5.9-20.0) months respectively. We didn’t observe significant changes in non-hematological or hematological markers after administration of nab-P+Gem in patients with an elevated bilirubin level.

Conclusion

The patients with APC and hyperbilirubinemia could benefit from treatment with Nab-paclitaxel/ gemcitabine. Furthermore, our study shows that the combination of nab-P+Gem seems to be a feasible therapy option, if administrated on individual basis.

1.2 In deutscher Sprache

Einführung

Aufgrund von Gallengangsobstruktionen und/ oder Lebermetastasen erhöhte Bilirubinwerte stellen ein häufiges Problem bei Patienten mit Adenokarzinom des Pankreas (APC) dar. Mangels suffizienter Studienlage sind die Therapieoptionen beschränkt. In unserer retrospektiven Studie wurden die Toxizität und Sicherheit der Kombinationstherapie mit Gemcitabin und an Albumin-Nanopartikel gebundenes Paclitaxel (nab-P+ Gem) in Patienten mit Hyperbilirubinämie evaluiert.

Methoden

Eingeschlossen wurden an APC erkrankte Patienten, welche an unserem Institut mit nab-Paclitaxel und Gemcitabin zwischen Dezember 2012 und Dezember 2015 behandelt wurden und erhöhte Bilirubinwerte aufwiesen. Diese wurden hinsichtlich Sicherheit und Überleben analysiert. Das jeweilige Behandlungsschema wurde dokumentiert. Die Patienten wurden in Abhängigkeit von Bilirubinwerten in drei Gruppen unterteilt (A: 1.2-3 mg/dl; B:3-5 mg/dl und C: >5 mg/dl).

Ergebnisse

29 von 168 in unserem Institut behandelte Patienten erfüllten die oben genannten Kriterien. Das mediane Überleben (mOS) betrug für alle Patienten 11.7 (95% KI: 6.8-14.0) Monate. In den Gruppen A, B und C lag das mOS bei 11.8 (95% CI: 6.5-16.5), 9.2 (95% KI: 1.1- NA) und 11.8 (95% KI: 5.9- 20.0) Monaten. Signifikante Änderungen der nichthämatologischen und hämatologischen Marker nach Verabreichung von nab-P+ Gem an Patienten mit erhöhten Bilirubinwerten wurden nicht beobachtet.

Schlussfolgerung

Patienten mit APC und Hyperbilirubinämie könnten von einer Therapie mit nab-Paclitaxel/ Gemcitabin profitieren. Weiterhin zeigt unsere Studie, dass die Kombination nab-P+ Gem eine verträgliche Therapieoption darstellt sofern diese auf individueller Basis verabreicht wird.

2. Manteltext

2.1 State of knowledge

Introduction

Pancreatic cancer (PC) is the fourth most prevalent cause of cancer deaths in the western world, with 337,000 patients diagnosed worldwide annually, 110 000 in Europe alone (1). In the last decades, the development of new screening methods and advanced radiology diagnostics has significantly improved outcomes in many fields of oncology through earlier diagnosis. Nevertheless, pancreatic cancer continues to be diagnosed later for various reasons, including but not limited to the lack of detectable early and unspecified symptoms, limited specific and sensitive biomarkers for early diagnosis as well as fast metastasis. Statistics show that more than 80% of patients have unresectable tumors and/or metastasis at the time of first diagnosis, which makes the prognosis even grimmer (2). It is established that surgical treatment followed by adjuvant therapy is the only potentially curative treatment. However, despite aggressive chemotherapy and radical surgical treatment, the overall 5-year survival rate has barely improved in the last twenty years, from 4% in the early 1990s to 6% today. This number alone highlights PC as one of the deadliest of all malignancies (3).

Hyperbilirubinemia and pancreatic cancer

There are three major causes of elevated bilirubin level in PC patients; biliary tract obstruction caused by tumor in the pancreatic head (localization of more than 60% of all PC tumors), massive hepatic metastasis (obstruction of the peripheral intrahepatic bile ducts) and pre-existing liver disease (4).

Hyperbilirubinemia and further jaundice occurs either at onset as a first symptom of PC in 25-30% of cases or over the course of the disease in 40-70% of PC patients (5,6). This common symptom is mostly due to biliary tract obstruction and these patients will benefit from biliary stenting (endoscopic or percutaneous biliary stent placement) (7). Another finding shows that jaundice at the time of first diagnosis is a negative prognostic factor for patients with pancreatic cancer with significant worse OS, mostly because of significantly larger T- and N-factors according to the UICC Classification compared to patients without elevated bilirubin (8,9). Although most patients with advanced pancreatic cancer (APC) develop hyperbilirubinemia during the disease, the therapy options for this group are particularly limited as patients are typically excluded from clinical trials.

Treatment options in patients with inoperable pancreatic cancer and hyperbilirubinemia

Novel standards of care for palliative therapy such as FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan and oxaliplatin) regimen introduced in 2011 (10), and further combination with albumin-bound paclitaxel (nab-paclitaxel) and gemcitabine (nab-P+G) significantly improved outcomes for advanced APC compared to gemcitabine alone (11).

FOLFIRINOX seems to be the most effective first-line therapy option but is only an appropriate treatment for a subset of about 25%. Patients must have good performance status, no major comorbidity, be aged under 76 and have adequate bone marrow, liver and renal function, due to the high toxicity profile. A clinical trial indicated numerous side effects like thrombocytopenia, neutropenia (grade III and IV), febrile neutropenia, and diarrhea. As such, it is generally younger patients who undergo this type of treatment. Nevertheless, the III phase study shows, despite multiple side effects, a statistically significant benefit in median overall survival - 11.1 months (95% CI, 9.0 to 13.1) in the FOLFIRINOX group vs. 6.8 months (95% CI, 5.5 to 7.6) in the gemcitabine group (HR for death=0.57; 95% CI, 0.45 to 0.73; P<0.001). The entry criteria for the study excluded patients with elevated bilirubin level >1.5 x ULN (4,6).

American (from 2017) and British (from 2014) recommendations have been made regarding the adjustment of dosage according to the bilirubin level in the FOLFIRINOX regime. Irinotecan dosage should be reduced 50% where bilirubin level ranges from 1-1.5 x ULN or in the case of Gilbert's Syndrome, and where greater than 1.5 x ULN it should be omitted entirely. Oxaliplatin should be reduced by 50% where bilirubin is > 3 x ULN, however there is insufficient data about further recommendations > 5 x ULN. For 5-FU there is no need to adjust the dosage under 4 x ULN, but it should be omitted from treatment above this level (12,13). There is a lack of clinical trials proving the feasibility of FOLFIRINOX in patients with hyperbilirubinemia.

Another major breakthrough in PC treatment was the addition of nab-Paclitaxel to gemcitabine (nab-P+Gem), which improved OS (overall survival) 8.7 vs. 6.6 months, HR for death = 0.72 (95% CI: 0.62-0.83), p<0.001, PFS (progression free survival), RR (response rate) compared to gemcitabine alone and became the first-line standard of care for a wider group of APC patients, due to better tolerance in more fragile patients (11,14). Moreover, the combination nab-P+Gem seems to be an effective second-line chemotherapy option for patients after FOLFIRINOX failure or intolerance and is not age restricted (15). Nab-Paclitaxel is mainly metabolized by Cytochrome P450 (CYP450) isoenzymes and drug transporters: CYP2C8, CYP3A4. The current state of

knowledge shows that mild hepatic impairment (total bilirubin >1 to ≤1.5 x ULN) has no clinically significant influence on pharmacokinetics of paclitaxel. Furthermore, moderate (total bilirubin >1.5 to ≤3 x ULN) or severe (total bilirubin >3 to ≤5 x ULN) hepatic impairment has lower elimination rate of paclitaxel (approx. 25%). There is no pharmacokinetic data available for patients with total bilirubin >5 x ULN or with metastatic PC, which is the main limitation in the availability of this therapy for patients with hyperbilirubinemia (16).

The second drug of this regimen, gemcitabine, is metabolized by cytidine deaminase in the liver, kidney, blood and other tissues first to 2'-deoxy-2', 2'-difluorouridine (dFdU) and later eliminated mostly urinarily (99%, mainly in the form of dFdU). Gemcitabine is not recommended over bilirubin level of 5x ULN, while in the range 1.5-5x ULN dosage should be reduced to 80%. Moreover, current studies show that the combination of nab-P+Gem therapy did not influence the pharmacokinetics of either gemcitabine or paclitaxel (17).
The most common side effects of therapy with gemcitabine, reported by almost 60% of patients, are nausea with or without vomiting, hepatobiliary disorders like elevated liver transaminases (AST/ALT) and alkaline phosphatase (AP), renal disorders (proteinuria and hematuria) and influenza-like symptoms. Additionally, hyperbilirubinemia is very common, which limits the possibility of further therapy with nab-P+Gem. Our investigations assessed for the first time the toxicity and safety of using the combination of gemcitabine and nab-Paclitaxel, one of the most popular and effective regimes, in patients with hyperbilirubinemia.

Another well-established second line regime, which shows benefits over BSC, is OFF (oxaliplatin, folinic acid and 5-fluorouracil), proven by the CONKO-003 clinical trial. Median second-line survival was 4.82 (95% CI; 4.29-5.35) months for OFF vs. 2.30 (95% CI; 1.76-2.83) months with BSC alone. Further to this, the combination shows relatively good tolerability and could be given to patients with elevated bilirubin (preferably <5 x ULN up to 100% of the dosage) (18).
More recently, a new alternative in the second line treatment following gemcitabine-based therapy for patients with APC as well as good performance status is liposomal irinotecan (nal-IRI) plus 5-fluorouracil/ leucovorin (5-FU/LV). This regimen not only improves OS and PFS but also has a feasible safety profile and generally manageable AEs (19). Unfortunately, this new therapy regime is not dedicated for patients with bilirubin > 2.0 mg/dl (19).

In the last decade the new clinical focus of researchers and clinicians, both oncologists and surgeons, is the therapy of borderline, primary unresectable and locally advanced tumors. Those patients could potentially benefit from intensive palliative therapy regimen such as nab-P+Gem and FOLFIRINOX (here alternatively neoadjuvant therapy) and subsequently be evaluated for possible surgery, which nowadays leads to the best long-time outcomes (20). Furthermore, patients with locally APC and those with a high risk of an R1-resection should be considered for neoadjuvant therapy to increase the chance of an R0 resection (21,22).

Recent phase 1 and phase 2 clinical trials show significant benefits of using immunotherapy (GVAX, anti-PD-1 or PD-L1 therapies) in patients with APC (23). Unfortunately, the costs of the therapy are still extremely high and data is not so promising compared to other hematological and oncological diseases. In addition, there is no data regarding the use of immunotherapy for patients with APC and hyperbilirubinemia.

2.2 Material and methods

Patients presenting to Charité University Hospital Berlin treated for histologically confirmed Pancreatic Ductal Adenocarcinoma (PDAC) with gemcitabine and nab-paclitaxel with either elevated bilirubin levels from the beginning or during the therapy were scanned. Patients who had shown elevated bilirubin levels at least once during the treatment with this regimen were enrolled in our prospective study and analyzed.

Patients were divided into three cohorts according the total bilirubin level at the time of first bilirubin elevation during the therapy with gemcitabine and nab-Paclitaxel. Group A includes patients with a total bilirubin level (TB) of 1.2-3.0 mg/dl, Group B: TB >3.0-5.0 mg/dl and Group C: TB>5.0 mg/dl.

Both nab-Paclitaxel and gemcitabine were administered intravenously (IV) at a dose of 125 mg/m^2 and 1000 mg/m^2 respectively, on days 1, 8 and 15 every 4 weeks. Any adjustments to these doses were based on the experience of the oncologist (at the time of therapy there were no standards of dose adjustments) and on the individual patient. The therapy was undertaken until drug intolerance, worsening of the patient's condition, progression of the disease or until the patient asked for the therapy to cease. Every dosage was closely monitored as well as bilirubin level during every single treatment. Moreover, we followed the previous therapies as well the following therapies of all patients. Additional data points were collected and analyzed, specifically biliary stenting, number and localization of metastases and tumor location.

Before every dose of the treatment the complete blood count (CBC) was investigated by the automated counter and if necessary, the dose was reduced. Hepatic parameters such as bilirubin (TB), alanine transaminase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), gamma-glutamyl transpeptidase (GGT), kidney markers like creatinine, CRP and tumor marker levels CA 19-9 and CEA were investigated regularly (weekly).

Statistical analysis was performed using SPSS software (version 19.0; SPSS, Chicago, IL) and R program (version 3.01). T- and chi-squared tests were used for correlations and comparisons. We define median overall survival (mOS) as the time from first diagnosis or recurrence in patients who underwent primary tumor resection, to death by any cause or the last follow up. Kaplan-Meier survival estimates and log-rank tests were used for univariable survival analyses. P value of less than 0.05 was considered statistically significant and calculated two-tailed.

2.3 Results

Demographics and baseline characteristics

A total of 29 eligible patients met the criteria to be enrolled in this analysis between December 2013 and December 2015 at our institution (from a total of 168 treated during this time). Patients' characteristics are outlined in **Table 1.**

Patient characteristic	**n (29)**	**%**
Sex		
male	24	83
female	5	17
Age (years)*		
median	63.0 y	
range	41.0-79.0 y	
>65	10	34
Pancreatic tumor location*		
head	18	62
body	4	14
tail	7	24
Metastatic sites*		
hepatic	25	86
lymphatic	16	55
pulmonary	10	34
peritoneal	7	24
others	9	31
Number of metastatic sites*		
0	0	0
1	7	24
2	11	38
3	6	21
4	4	14
5	1	3
Biliary stent		
yes (twice)	13 (7)	45 (24)
no	16	55
Operation (PPPD)		
yes	3	10
no	26	90
Adjuvant treatment with gemcitabine		
yes	1	3
no	28	97

Table 1. Patient demographics and clinical characteristics (* from the commencement of therapy with Gem+ nab-Paclitaxel)

In all the patients PDAC was diagnosed and in 18 (62%) of the cases the tumor was localized in the pancreatic head. All of the patients presented metastasis at time of the therapy with gemcitabine and nab-Paclitaxel, mostly (n=25, 86%) in the liver and lymphatic nodes (n=16, 55%). 7 of the 29 patients had a single metastatic site, while two and three metastatic sites were diagnosed in 11 and 6 patients respectively. Endoscopic biliary stenting was performed in 13 cases (on two occasions in 7 of these cases) because of biliary tract obstruction. Two patients underwent primary PPPD operation (the pylorus preserving pancreatoduodectomy). One of the patients was adjuvantly treated with gemcitabine, whilst another underwent first-line therapy, due to fast progression of the disease. A PPPD operation was possible for one patient, after the treatment with gemcitabine and erlotinib.

With reference to the aforementioned groups that were defined according to total bilirubin level (TB), group A contained eighteen patients (62.1%), group B- four (13.8%) and group C- seven (24.1%) with mean TB level of 1.7 mg/dl, 4.0 mg/dl and 8.9 mg/dl, respectively.

Treatment details

The combination of nab-Paclitaxel (100 mg/m^3 or 125 mg/m^3) with 1000 mg/m^3 Gemcitabine was administered to 21 (70%) of the patients as either first- or second-line therapy. Median treatment duration with nab-P+Gem was twenty-nine days (range 1-144), while median application was three doses (range 1-22). For 25 (86%) of the 29 patients the combination of gemcitabine and nab-Paclitaxel was the last line therapy. FOLFORINOX regimen was given to more than a half of the patients (n=16, 55%) before the gemcitabine plus nab-Paclitaxel combination. Moreover, one third of the patients were treated with gemcitabine either in monotherapy or in the combination with a second drug (ATU027, Erlotinib, Oxaliplatin or IGFR1AK). Four patients underwent radiotherapy (with 5-FU) before nab-P+Gem regimen, whilst a small number were treated with OFF regimen. For most of the patients (86%) the full dose of nab-Paclitaxel was applied from beginning (first application). Here the mean TB level was 2.5 mg/dl (range: 0.2-18.4 mg/dl). Among these patients are patients from all groups: A, B and C. Only three (10%) patients received 75% of the dosage (mean TB=2.3 mg/dl, range 0.33-26.5) while just one patient was treated with 50% of nab-Paclitaxel.

Survival results

Median overall survival (mOS) was 11.7 [95% CI: 6.8–14.0] months for all 29 patients, p=0.843. Median overall survival from the first gemcitabine/ nab-aclitaxel application (mOS-1) was 2.9 months, p=0.129. Median overall survivor from last application (mOS-2) was 1.2 months, p=0.218. The results for the groups A, B and C are summarized in the Table 2. There were no significant differences between groups A, B and C.

	mOS (months)	**mOS-1 (months)**	**mOS-2 (months)**
All (29 pts)	11.7 (95% CI: 6.8-14.0, p=0.843)	2.9 (95% CI: 1.28-5.78, p=0.129)	1.2 (95% CI: 0.9-2.4, p = 0.218)
Group A (18 pts)	11.8 (95% CI: 6.5-16.5)	2.6 (95% CI: 1.3-6.2)	1.2 (95% CI: 0.1-1.4)
Group B (4 pts)	9.2 (95% CI: 1.1-N/A)	1.1 (95% CI: 0.9-N/A)	0.9 (95% CI: 0.7-N/A)
Group C (7 pts)	11.8 (95% CI: 5.9-20.0)	5.8 (95% CI: 1.5-7.8)	3.0 (95% CI: 1.1-5.4)

Table 2. Survival results for all the patients and divided into three groups A, B and C.

Toxicity

Liver damage, detected by elevated aspartate transaminase (AST) and alanine transaminase (ALT) was generally not observed (p=0.3068 and p=0.898 respectively). A strong increase of AST and ALT was observed in only one patient. There was no significant change in hepatobiliary disorder's parameters, specifically TB level, GGT and LDH. The bilirubin level was measured both on the day of the first treatment with the combination of nab-P+Gem and again at the control time following the first dose. The respective median for each subgroup was:

- Group A: 1.6 mg/dl and 1.3 mg/dl,
- Group B: 3.9 mg/dl and 5.0 mg/dl,

- Group C: 8.6 mg/dl and 7.8 mg/dl.

The bilirubin level increased in twelve patients, whilst decreasing in 15 patients. The distribution was rather equal in the A, B and C sub-groups. There were no significant differences in the GGT ($p= 0.277$) and LDH level ($p=0.1448$).

Among the hematological markers, there was no significant difference in the levels of thrombocytes ($p=0.524$) and leucocytes ($p=0.901$) after the first dose application of the combination. Nevertheless, we observed a significant decrease in the hemoglobin level ($p=0.0149$) in all three groups. CRP level ($p=0.793$) did not change significantly in most of the patients and similarly there was no significant evidence of acute renal failure (creatinine level with $p=0.871$). Lastly, no treatment-related deaths occurred.

2.4 Discussion

Hyperbilirubinemia is a common symptom amongst patients with advanced pancreatic cancer, often seen in routine clinical practice (24). The cause of elevated bilirubin level could be obstruction of the common bile duct, due to the tumor growth in the pancreatic head (most of the cases) and/or extensive liver metastases, through intrahepatic biliary obstruction or metastases-related insufficiency (4,25). Furthermore, hyperbilirubinemia caused by obstruction depresses lymphocytic (mostly NK) activity in hepatic nonparenchymal cells and promotes growth of hepatic metastases (26).

Despite the fact that hyperbilirubinemia will occur in the vast majority of patients (5), there is still a deficiency of results from clinical studies and information about toxicity for patients with PDAC and elevated bilirubin level, due to the disqualification of such patients from most clinical trials.

The results of the MPACT study showed a significant survival benefit with the combination gemcitabine/ nab-Paclitaxel over gemcitabine alone. Nevertheless, the strict eligibility criteria excluded the patients with elevated bilirubin levels. Nowadays, palliative treatment with two-drug combination of gemcitabine and nab-Paclitaxel is a widely adopted and recommended treatment for advanced metastatic adenocarcinoma (11,15), but patients with total bilirubin >5 x ULN and AST ≥ 10 x ULN (16) are excluded. In addition, the cutoff for patients with metastatic PC is even more restrictive: nab-Paclitaxel is not recommended in patients with moderate to severe hepatic impairment (total bilirubin > 1.5 x ULN) (16).

In our investigation we enrolled 29 patients with APC with bilirubinemia due to cholestasis. To our knowledge this is the first study evaluating feasibility in patients with advanced pancreatic adenocarcinoma and hyperbilirubinemia of therapy with the combination of gemcitabine and nab-Paclitaxel. The most noteworthy limitations of our study are its retrospective nature and that the data was constrained to 29 patients. Nevertheless, we included all patients meeting the criteria treated in our hospital. The median age was 63 years (range 41-79), with 34% (10) patients over 65 years. As the aforementioned criteria were the only restrictions applied, it is reasonable to conclude that the patients enrolled represented routine clinical practice.

From all the investigated values (hematological and non-hematological markers) the significant toxicity was only observable through decreasing hemoglobin profile. As we didn't observe any other significantly relevant early toxicity after the application nab-P+Gem to the patients with hyperbilirubinemia, our opinion that the toxicity is acceptable in this regime is confirmed.

For our 29 patients, median overall survival (mOS) was 11.7 months, which is similar to the mOS published in the other clinical trials. As previously noted, there was no significant difference between subgroups A, B and even C (bilirubin level >5 mg/dl) in mOS, mOS-1 (form the first application) and mOS-2 (from the last application), which indicated how patients with hyperbilirubinemia could also potentially benefit from the regime.

Our findings show that there was no significant correlation between overall survival and elevation of bilirubin level during the therapy. Despite the fact that the vast majority of the patients was given a 100% dosage, it did not significantly influence the likelihood of severe acute toxicity. However, the main cause of elevated bilirubin levels in our patients was obstruction by the tumor itself (in 62% tumor was localized in pancreatic head) or the presence of metastasis (mostly hepatic or lymphogenic), not due to liver impairment function. Moreover, approachable pharmacokinetic/pharmacodynamic modeling proved that there is no correlation between hepatic function (proved by albumin and bilirubin level) and neutropenia after adjusting for Abraxane exposure (16). According to a small pilot study, nab-Paclitaxel has an acceptable tolerability profile in patients with solid tumors and hepatic dysfunction, but dose modification was needed (27). Recently a German expert panel published the recommendation for initial dosage of nab-P+Gem in patients with hyperbilirubinemia regardless of the cause (biliary obstructions, extensive liver metastases or pre-existing chronic liver disease) (4). At the time of our investigation this recommendation was not yet published.

It’s essential to identify the root cause of elevated bilirubin level before the initiation of therapy. In patients enrolled in our study only 45% underwent biliary drainage with biliary stent placement. In more than half the group, this treatment was not recommended, due to other causes of hyperbilirubinemia (i.e. hepatic metastases, which was observed by 86% of our patients).
The common cause of elevated bilirubin in APC patients is obstruction of the distal common bile duct. In this case, hyperbilirubinemia can be reversed by inserting a stent into the bile duct to achieve relief of jaundice and pruritus (28). On one hand, normalization of TB by this technique can take weeks, but on the other hand it should be performed prior to the commencement of chemotherapy if required to prevent nutritional, metabolic and septic complications, which can lead to frequent hospitalizations and delay the onset or continuation of the chemotherapy (7). For such patients, multidisciplinary treatment is essential and the prophylactic use of antibiotics should be considered. When chemotherapy begins, such patients should be treated as high-risk. To this

end, an experienced oncologist should oversee the treatment, including regular blood tests to monitor the liver, kidneys, inflammation markers and blood count.
In the case of biliary obstruction, the German experts proposed a cutoff for treatment with nab-P+Gem where bilirubin level is above 8 x ULN, with dose reduction (Gem on the 800 mg/m2 and Nab-P on the 100 mg/m2) in the TB range 3-8 x ULN. In the case of metastases and elevated bilirubin, a cutoff of 5 x ULN was proposed, with dose to be reduced already above 1.5 x ULN (4). This minor modification to the bilirubin cutoff could significantly improve generalizability and the treatment could be initiated earlier, if desirable.

A clinical phase 1 trial - PANCHO (AIO-PAK-0117) - which is first dedicated to the patients with inoperable pancreatic cancer suffering hyperbilirubinemia, treated with the combination of gemcitabine + nab-Paclitaxel is ongoing. The tolerability and feasibility of this regimen will be investigated. The patients will be divided into three groups according to the bilirubin level: (I: 1.5-3.0 x ULN, II: 3.0-5.0 x ULN, III: 5.0-10.0x ULN) and there are four adaptations of the dosage. This is the first prospective clinical phase 1 trial, which could confirm the results of our investigation.

2.5 Conclusions

The treatment of patients with inoperable pancreatic cancer suffering from hyperbilirubinemia is challenging, because of the diversity of symptoms and complications and a lack of targeted studies for this group.

In conclusion, our findings show that the combination of Gemcitabine and nab-Paclitaxel might also be an advantageous and suitable therapy option for patients with elevated bilirubin level. This regime is well known and commonly used in APC, however due to a lack of dedicated research and clinical trials there is a necessity to investigate and establish the optimal doses for patients with hyperbilirubinemia and APC treated with nab-P+Gem.

It is erroneous to disregard this regimen based on hyperbilirubinemia diagnosis alone; an individual assessment should be carried out on a case-by-case basis to determine the cause of elevated bilirubin levels and the potential benefit to the patient of this regimen.

Further investigation should be undertaken to exploit the potential benefits of this therapy in a larger study group.

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3. Eidesstattliche Versicherung

„Ich, Lilianna Joanna Wisłocka, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema:

"*Chemotherapeutic treatment options in patients with inoperable pancreatic cancer suffering hyperbilirubinemia."*

selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen werden von mir verantwortet.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem Betreuer, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst."

Datum Unterschrift

4. Anteilserklärung an der erfolgten Publikation

Lilianna Joanna Wisłocka hatte folgenden Anteil an der Publikation:

Pelzer U*, Wislocka L*, Jühling A, Striefler J, Klein F, Roemmler-Zehrer J, Sinn M, Denecke T, Bahra M, Riess H.

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

Eur J Cancer. 2018 Sep.

*contributed equally

Beitrag im Einzelnen der geteilten Autorenschaft mit PD Dr. Uwe Pelzer (Betreuer):

1. Mitarbeit in der Planung des Projektes innerhalb der CONKO Studiengruppe

2. Erarbeitung der Projektstrategie mit PD Dr. U. Pelzer/ Prof. Dr. med. H. Riess

3. Selbstständige retrospektive Datenerhebung:
   - Analyse aller Patienten in der Behandlung in der Charité, welche mit Gemcitabine und Nab- Paclitaxel behandelt wurden
   - Auswahl einer geeigneten Untergruppe von Patienten, die die Kriterien erfüllten (Hyperbilirubinämie bei Therapie mit Gem/nab-P)
   - Erstellung einer umfassenden Datenbank von ausgewählten Patienten
   - Erstellung einer Follow-up-Datenbank (inkl. Dosierung der Chemotherapie und Verlauf der laborchemischen Kontrolle) (Daten zur Fig. 2)

4. Aufarbeitung/Auswertung einschließlich der statistischen Auswertung unter Anleitung
   - Genaue Analyse der Laborwerte, des Krankheitsbilds und des Behandlungsverlaufs der Patienten (Datenbank zur Fig. 1, Fig. 2, 3)
   - Aufteilung der Patienten aufgrund des Bilirubinspiegels und der Bildung von 3 Gruppen (Daten zur Tabelle 2)
   - Aufarbeitung und statistische Auswertung des Patientensüberlebens (OS) (Fig. 3)
   - Aufarbeitung der Follow-up Databank und statistische Auswertung unter Anleitung u.a. der Dosierung der Nab-Paclitaxel (Fig.2) und der Laborwerte (Fig. 4 Box Plot)

5. Erarbeitung grafischer Darstellungen der Ergebnisse
   - Erstellung einer Tabelle mit Patientencharakteristika (Tabelle 1)
   - Erstellung einer Tabelle mit aufgeteilte Subgruppen (ABC) (Tabelle 2)
   - Erstellung der Kaplan- Maier Kurven (Fig. 3)
   - Erarbeitung der erfassten Ergebnisse in Fig. 2 (Violin Plot)

- Erarbeitung der erfassten Ergebnisse in Fig. 4 (Box Plot)

6. Wesentlicher Beitrag zur Diskussion der Resultate in den einzelnen Zwischenschritten

7. Wesentlicher Beitrag zur Diskussion der Kernaussagen/ Limitationen

8. Wesentlicher Beitrag zur Erarbeitung des zur Publikation führenden Manuskripts

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Lilianna Joanna Wisłocka (Doktorandin)

5. Auszug aus der Journal Summary List (ISI Web of KnowledgeSM)

Journal Data Filtered By: **Selected JCR Year: 2017** Selected Editions: SCIE,SSCI
Selected Categories: **"ONCOLOGY"** Selected Category Scheme: WoS
Gesamtanzahl: 222 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	CA-A CANCER JOURNAL FOR CLINICIANS	28,839	244.585	0.066030
2	NATURE REVIEWS CANCER	50,407	42.784	0.079730
3	LANCET ONCOLOGY	44,961	36.418	0.136440
4	JOURNAL OF CLINICAL ONCOLOGY	156,474	26.303	0.285130
5	Nature Reviews Clinical Oncology	8,354	24.653	0.026110
6	Cancer Discovery	11,896	24.373	0.065350
7	CANCER CELL	35,217	22.844	0.096910
8	JAMA Oncology	5,707	20.871	0.027770
9	ANNALS OF ONCOLOGY	38,738	13.926	0.095780
10	JNCI-Journal of the National Cancer Institute	37,933	11.238	0.052550
11	Journal of Thoracic Oncology	15,010	10.336	0.033280
12	CLINICAL CANCER RESEARCH	81,859	10.199	0.132210
13	SEMINARS IN CANCER BIOLOGY	6,330	10.198	0.010740
14	LEUKEMIA	25,265	10.023	0.059580
15	NEURO-ONCOLOGY	10,930	9.384	0.030350
16	Cancer Immunology Research	4,361	9.188	0.021180
17	CANCER RESEARCH	139,291	9.130	0.130190
18	Journal for ImmunoTherapy of Cancer	1,675	8.374	0.007130
19	BIOCHIMICA ET BIOPHYSICA ACTA-REVIEWS ON CANCER	5,276	8.220	0.009300
20	Blood Cancer Journal	1,804	8.125	0.007660
21	CANCER TREATMENT REVIEWS	7,870	8.122	0.015820
22	Molecular Cancer	10,301	7.776	0.017280
23	INTERNATIONAL JOURNAL OF CANCER	51,800	7.360	0.071870
24	Journal of Hematology & Oncology	4,098	7.333	0.009750
25	EUROPEAN JOURNAL OF CANCER	29,883	7.191	0.050170
26	ONCOGENE	66,411	6.854	0.075960
27	CANCER	68,221	6.537	0.074740
28	CANCER LETTERS	29,311	6.491	0.042280
29	Journal of the National Comprehensive Cancer Network	5,143	6.471	0.017530
30	Advances in Cancer Research	2,343	6.422	0.003690
31	JOURNAL OF PATHOLOGY	16,156	6.253	0.024060

6. Druckexemplar der Publikation

Safety and efficacy of Nab-paclitaxel plus gemcitabine in patients with advanced pancreatic cancer suffering from cholestatic hyperbilirubinaemia-A retrospective analysis. Eur J Cancer. 2018 Sep; 100:85-93.

Pelzer U, Wislocka L, Jühling A, Striefler J, Klein F, Roemmler-Zehrer J, Sinn M, Denecke T, Bahra M, Riess H.

DOI link: https://doi.org/10.1016/j.ejca.2018.06.001

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7. Lebenslauf

My curriculum vitae does not appear in the electronic version of my paper for reasons of data protection.

8. Publikationsliste

8.1 Publikationen

1. Pelzer U, Wislocka L, Jühling A, Striefler J, Klein F, Roemmler-Zehrer J, Sinn M, Denecke T, Bahra M, Riess H. Safety and efficacy of Nab-paclitaxel plus gemcitabine in patients with advanced pancreatic cancer suffering from cholestatic hyperbilirubinaemia-A retrospective analysis. Eur J Cancer. 2018 Sep; 100:85-93.

Journal Impact Factor: 7.191, Eigenfactror Score: 0.050170

2. Lohneis P, Sinn M, Klein F, Bischoff S, Striefler JK, Wislocka L, Sinn BV, Pelzer U, Oettle H, Riess H, Denkert C, Bläker H, Jühling A. Tumour buds determine prognosis in resected pancreatic ductal adenocarcinoma. Br J Cancer. 2018 May;118(11):1485-1491.

Journal Impact Factor: 5.922, Eigenfactror Score: 0.065130

3. Lohneis P, Sinn M, Bischoff S, Jühling A, Pelzer U, Wislocka L, Bahra M, Sinn BV, Denkert C, Oettle H, Bläker H, Riess H, Jöhrens K, Striefler JK. Cytotoxic tumour-infiltrating T lymphocytes influence outcome in resected pancreatic ductal adenocarcinoma. Eur J Cancer. 2017 Sep;83:290-301.

Journal Impact Factor: 7.191, Eigenfactror Score: 0.050170

4. Striefler JK, Sinn M, Pelzer U, Jühling A, Wislocka L, Bahra M, Sinn BV, Denkert C, Dörken B, Oettle H, Riess H, Bläker H, Lohneis P. P53 overexpression and Ki67-index are associated with outcome in ductal pancreatic adenocarcinoma with adjuvant gemcitabine treatment. Pathol Res Pract. 2016 Aug;212(8):726-34.

Journal Impact Factor: 1.543, Eigenfactror Score: 0.004030

8.2 Poster und Kongressbeiträge

1. U. Pelzer, L. Wisłocka, A. Jühling, M. Sinn, JK. Striefler, S. Bischoff, M. Bahra, B. Dörken, H. Riess. *Nab-Paclitaxel plus Gemcitabine in Patients with Advanced Pancreatic Cancer and Hyperbilirubinemia*. Deutscher Krebskongress DKK Berlin 2016

2. J. Striefler, L. Wislocka, M. Sinn, U. Pelzer, C. Denkert, A. Juehling, S. Bischoff, M. Bahra, B. Hendrik, H. Oettle, H. Riess, P. Lohneis. *CXCR4, CXCR7 and CXCL12 expression is not a prognostic predictive factor in patients with resected pancreatic cancer - results from the CONKO-001 trial.* Annals of Oncology (2016) 27 (2): 102-117, ESMO World Congress on Gastrointestinal Cancer 2016 - Abstracts book

9. Danksagung

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