Original Articles

Detection of risk factors related to administration suspension and severe neutropenia in gemcitabine and nab-paclitaxel treatment

Yoshitaka Saito[1], Yoh Takekuma[1], Masaki Kobayashi[2], Yoshito Komatsu[3], Mitsuru Sugawara*[,1, 4]

[1]*Department of Pharmacy, Hokkaido University Hospital: Kita 14-jo, Nishi 5-chome, Kita-ku, Sapporo 060-8648, Japan*

[2]*Laboratory of Clinical Pharmaceutics & Therapeutics, Faculty of Pharmaceutical Sciences, Hokkaido University: Kita 12-jo, Nishi 6-chome, Kita-ku, Sapporo 060-0812, Japan*

[3]*Cancer Center, Hokkaido University Hospital: Kita 14-jo, Nishi 5-chome, Kita-ku, Sapporo 060-8648, Japan*

[4]*Laboratory of Pharmacokinetics, Faculty of Pharmaceutical Sciences, Hokkaido University: Kita 12-jo, Nishi 6-chome, Kita-ku, Sapporo 060-0812, Japan*

*Corresponding author:

Department of Pharmacy, Hokkaido University Hospital, Kita 14-jo, Nishi 5-chome, Kita-ku, Sapporo 060-8648, Japan Tel/Fax: +81-11-706-5680 and +81-11-706-7616; E-mail: msuga@med.hokudai.ac.jp

ABSTRACT

Purpose

The combination of gemcitabine (GEM) and nanoparticle albumin-bound paclitaxel (nab-PTX) is an effective chemotherapeutic regimen for locally advanced and metastatic pancreatic cancer. The dose-limiting toxicities (DLTs) of this treatment are sepsis and neutropenia, while the relative dose intensity (RDI) of GEM is approximately 75% and of nab-PTX is 70-80%. In this study, we evaluated the risk factor(s) regarding treatment suspension, which leads to reduction in the RDI of these agents, enabling appropriate schedule management.

Methods

Two hundred patients with pancreatic cancer who received GEM + nab-PTX were retrospectively investigated. Frequency and risk factor(s) of suspension of the treatment and grade 3/4 neutropenia in the first course were evaluated.

Results

The frequency of treatment suspension in the first course was 61%. The frequency of grade 3/4 neutropenia was 51%, while that of thrombocytopenia was 7.5%. The RDI was 78.0% for GEM and 77.7% for nab-PTX. Univariate and multivariate analyses to identify risk or preventive factors related to treatment suspension suggested that low platelet count

at baseline was a risk factor, whereas dose reduction from the treatment initiation was a preventive factor. The most common cause of abeyance was grade 3/4 neutropenia (83.6%), the risk factors of which were low platelet count and age ≥65 years at baseline, while dose reduction was a preventive factor.

Conclusion

We found that low platelet levels at baseline was a risk factor, whereas dose reduction from initiation was a preventive factor in regard to treatment suspension and severe neutropenia occurrence in GEM + nab-PTX treatment.

Key words: gemcitabine; nab-paclitaxel; relative dose intensity; neutropenia; treatment suspension; risk factor.

Introduction

The rate of morbidity and death due to cancer has been increasing in Japan, with cancer being the leading cause of death. Off late, the incidence of pancreatic cancer has increased, with most patients having advanced stages of the disease at the time of diagnosis given the difficulty in detecting the cancer at an early stage. Chemotherapy is the main form of treatment to treat locally advanced and metastatic pancreatic cancer [1, 2]. Pancreatic cancer is more intractable to anti-cancer agents than other cancers, and the 5-year survival rate is less than 5% among metastatic patients [3]. Thus, it is important to maintain a high-dose intensity for the enhancement of anti-tumor response. The combination of gemcitabine (GEM) and nanoparticle albumin-bound paclitaxel (nab-PTX) is an effective chemotherapeutic regimen for treating locally advanced and metastatic pancreatic cancer [4-6]. The toxicity of gemcitabine is generally mild, with thrombocytopenia being its dose-limiting toxicity (DLT) [7]; while neutropenia and neuropathy are known to be the DLTs of nab-PTX [8]. The DLTs of the combination of these two medicines are sepsis and neutropenia [9]. A non-smoking history has been recognized as a risk factor of GEM-induced neutropenia [10, 11], although risk factors of DLTs in GEM + nab-PTX have not been identified. Grade 3/4 neutropenia occurs in 23-70% of patients who are treated with GEM + nab-PTX, while thrombocytopenia

develops in 5-15% of patients treated with this regimen [4-6]. The relative dose intensity (RDI) of GEM is approximately 75%, while that of nab-PTX is 70-80% [4, 5], suggesting that treatment is suspended occasionally due to adverse effects in this regimen. Early and appropriate management of the treatment schedule is important as treatment suspension can affect the efficacy of the regimen, and increase the burden on patients undergoing outpatient chemotherapy.

In this study, we aimed to reveal the risk factor(s) associated with treatment suspension that leads to RDI reduction in GEM + nab-PTX treatment.

Patients and Methods

1. Patients

Patients with pancreatic cancer who received the GEM + nab-PTX regimen from January 2015 to May 2020 in Hokkaido University Hospital were enrolled in this study. All patients met the following baseline criteria: (1) age ≥20 years; (2) detailed patient information available from medical records; (3) 0 to 2 performance status; (4) absolute neutrophil count $\geq 1.5 \times 10^3$ cells/μL, platelet count $\geq 1.0 \times 10^5$ cells/μL; (5) sufficient renal or liver function. Patients whose planned schedule was different from the original (± more than one day) and who were not able to complete the first course of the

treatment were excluded. We calculated the number of patients to be 200, as treatment suspension occurs in approximately 60% of patients [5]; we tried to include approximately eight covariates in the multivariate analysis. The study was approved by the Institutional Review Board of Hokkaido University Hospital (approval number: 019-0015), and was carried out in accordance with the Declaration of Helsinki. Since this was a retrospective study, informed consent from the subjects was not mandated.

2. Treatment methods

GEM (1000 mg/m^2) and nab-PTX (125 mg/m^2) were administered on days 1, 8, and 15, every 4 weeks [4-6]. Palonosetron (0.75 mg) and dexamethasone (9.9 mg) were administered before the chemotherapeutic agents [12]. Treatment was discontinued or deferred by the physician according to the criteria in the medical package insert [13].

3. Evaluation of adverse effects and treatment suspension

The required information was retrospectively obtained from the patients' medical records. The primary endpoint of this study was defined as detection of the risk factor(s) for the suspension of chemotherapy in the first course. Secondary endpoints were the elucidation of the primary cause of treatment suspension and its risk factor(s), and comparison of the RDI between specific patient groups. Adverse effects were evaluated in accordance with the Common Terminology Criteria for Adverse Events version 4.0.

4. Statistical analysis

Univariate and multivariate analyses were carried out using logistic analysis to determine the independent risk or preventive factors relating to the frequency of treatment suspension and the primary cause of suspension, using the following covariates: sex, age, performance status (PS), treatment line, body surface area (BSA), neutrophil count, hemoglobin concentration, platelet count, total bilirubin concentration, aspartate aminotransferase (AST) concentration, alanine aminotransferase (ALT) concentration, serum creatinine level, serum albumin level, C-reactive protein (CRP), concomitant diabetes mellitus at baseline, smoking history, and dose reduction from the initiation of chemotherapy. Variables that had potential associations with developing toxicity, as suggested by univariate logistic regression analysis ($P < 0.20$), were considered when building the multivariable model.

The RDI and suspension frequency between specific patient groups were compared using Student's t-test and Fisher's exact probability test, respectively. Baseline leukocyte and neutrophil counts between smokers and non-smokers were compared using the Mann–Whitney *U* test. All analyses were carried out using JMP version 14.0 statistical software (SAS Institute Inc.). Differences were considered statistically significant when *P*-values were less than 0.05.

Results

1. Patient characteristics

Two hundred out of 300 patients were enrolled according to the eligibility criteria of this study (Fig. 1). The baseline patient characteristics and frequency of patients with lower leukocyte, neutrophil, hemoglobin, and platelet levels than the lower limit of normal (LLN) are shown in Table 1. The proportion of patients with lower leukocyte, neutrophil, hemoglobin, and platelet levels at baseline were 4.5%, 6.5%, 62.5%, and 18.5%, respectively. Approximately 60% of the patients were former or current smokers. Sixteen out of 200 patients (8%) received dose-reduced chemotherapy from the initiation of treatment.

2. Frequency of treatment suspension and hematotoxicity

The frequency of treatment suspension and severe hematotoxicity in the first course of GEM + nab-PTX treatment is shown in Table 2. The suspension rate of the treatment was 61% (122 out of 200). Treatment suspension on day 8 occurred in 20% of patients, and on day 15 in 45.5% of patients. The frequency of grade 3/4 neutropenia and thrombocytopenia was 51% and 7.5%, respectively. The cause of suspension was neutropenia in 77.0% of patients, thrombocytopenia in 5.7%, both neutropenia and

thrombocytopenia in 6.6%, and other conditions (infection, liver dysfunction, or gastrointestinal symptoms) in 10.7% of patients. The calculated RDI was 78.0% for GEM and 77.7% for nab-PTX.

3. Univariate and multivariate analyses of risk or preventive factors related to treatment suspension and grade 3/4 neutropenia frequency

The results of the univariate and multivariate analyses carried out to identify risk or preventive factors for the suspension of GEM + nab-PTX are shown in Table 3A. Low platelet levels at baseline was a risk factor, whereas dose reduction of chemotherapy from treatment initiation reduced the risk of treatment suspension. As described above, the primary cause of suspension was grade 3/4 neutropenia, and Table 3B shows the results of the analyses regarding its frequency. Age ≥65 years was identified as a risk factor for grade 3/4 neutropenia, in addition to the factors identified for treatment suspension.

4. Influence of dose reduction from treatment initiation, line of treatment, and of neutropenia and thrombocytopenia at baseline on GEM and nab-PTX RDI

We assessed the influence of dose reduction from the initiation of treatment, line of treatment, and neutropenia and thrombocytopenia at baseline on the RDI of GEM and nab-PTX (Table 4). The RDI in patients with and without dose reduction from initiation

was 74.6% and 78.3% for GEM, respectively, and 73.4% and 78.0% for nab-PTX, respectively, with no significant differences. The RDI in patients receiving first line treatment and second or later line treatment was 78.5% and 77.0%, respectively for GEM, and 78.1% and 76.7%, respectively for nab-PTX, with no significant difference. Moreover, the RDI in patients with low neutrophil levels at baseline was 73.3% for each medicine, which was similar to that in patients with normal levels. However, the RDI in patients with low platelet levels at baseline was 68.8% for each medicine, which was significantly lesser than that in patients with normal levels.

We also evaluated the influence of dose reduction from the initiation on treatment suspension and the RDI in patients with thrombocytopenia at baseline. Treatment suspension was significantly lower in the patients administered a reduced dose than in those administered a full dose, whereas the RDI of both medicines was similar between the two groups (Table 5).

Discussion

GEM + nab-PTX is an effective regimen for locally advanced and metastatic pancreatic cancer [4-6]. Reduction in the RDI decreases the anti-tumor effect of the chemotherapy; therefore, understanding the risk factor(s) for treatment suspension is important for

conducting safe and effective chemotherapy, in addition to decreasing the patient burden. In this study, we investigated the risk factor(s) associated with treatment suspension and severe neutropenia frequency in GEM + nab-PTX treatment in the first course.

Treatment suspension occurred in 61% of patients, which was similar to the results of a previous study [5]. The most common causes of treatment suspension were grade 3/4 neutropenia and thrombocytopenia, which had a frequency of 51% and 7.5%, respectively. An MPACT study reported the frequency of grade 3/4 neutropenia to be 36.1%, and that of thrombocytopenia to be 14.0% [4], whereas a J-0107 study conducted in Japan found grade 3/4 neutropenia to occur in 70.6% of patients, and thrombocytopenia in 14.7% [5], suggesting a higher occurrence of grade 3/4 neutropenia in Japanese cancer patients. Since Asians represented just 2% of participants in the MPACT study, differences in GEM or PTX pharmacokinetics between Asians and other demographic groups might have affected the results. GEM is inactivated by cytidine deaminase (CDA), while PTX is metabolized by cytochrome P450 (CYP) 2C8 and 3A4. There are genetic polymorphisms in CDA, CYP2C8, CYP3A4, and ABCB1, which is the efflux transporter of PTX [14-23]. Differences in these allele frequencies might have induced the difference in neutropenia severity between these studies. Therefore, the results of the present study should be interpreted in consideration of this possibility.

The RDI of GEM was 78.0% and that of nab-PTX was 77.7%, which are similar to previously reported findings [4, 5], suggesting that our treatment schedule was similar to that in previous clinical trials. Multivariate analysis revealed that, in the first course, the risk factor associated with treatment suspension, and with frequency of severe neutropenia, which was the most common cause of treatment suspension, was low platelet levels at baseline. Platelet count is suggested to be a good indicator of bone marrow reserve and therefore can be used to predict appropriate hematological recovery following chemotherapy and autologous stem cell transplantation [24, 25]. This result regarding low platelet levels was also obtained for other chemotherapeutic regimens in previous studies [26, 27]. Although approximately half of the patients with low platelet levels at baseline received prior chemotherapy, prior chemotherapy alone was not a risk factor related to treatment interruption. Compositive factors such as prior chemotherapy or co-administered drugs-induced hematotoxicity, alcohol and lack of vitamin B_{12} and folic acid might have affected the results. In contrast, we found that the preventive factor for treatment suspension and severe neutropenia frequency was dose reduction from the initiation of the treatment.

The RDI values in patients with or without dose reduction from treatment initiation, prior chemotherapy, and in those with low neutrophil levels at baseline were similar.

However, the RDI in patients with low platelet levels at baseline was significantly lower than that in patients with normal levels. We also evaluated how dose reduction from the initiation of treatment affects treatment suspension and the RDI in patients with a low platelet count at baseline. We found that treatment suspension was significantly reduced in patients administered with a reduced dose than in patients given a full dose, whereas the RDI of both GEM and nab-PTX was similar among the two groups. These results suggest that dose reduction could be considered if the patient has a low platelet count at baseline because GEM and PTX are classified as time-dependent chemotherapeutic agents, more frequent dosing could increase anti-tumor effects, even with an almost equivalent RDI [28, 29]. However, in this study, dose reduction from treatment initiation was based on factors, such as PS, age, and treatment history of the patients. Unnecessary dose reduction could decrease the dose intensity of the chemotherapy, and therefore, we should consider increasing the dosage if the tolerability against adverse effects is confirmed.

A non-smoking history is a risk factor for grade 3/4 neutropenia frequency in GEM-included regimens, as patients with a smoking history have a higher neutrophil count [11]. Other studies have also shown that smoking reduces chemotherapy-induced neutropenia due to higher leukocyte or neutrophil counts at baseline [30, 31]. However,

the median leukocyte and neutrophil baseline counts in smokers in the present study were 5,750 (1,800-16,700) and 3,650 (1,002-13,427), respectively, which were not significantly different from those in non-smokers (5,800 (2,900-20,700) and 4,006 (1,876-18,941), respectively). Thus, smoking did not influence treatment suspension and grade 3/4 neutropenia frequency in this study. O'Malley et al. [11] reported that the baseline neutrophil count in former light smokers was similar to that of never smokers. It is speculated that most of the patients who were smokers were former smokers and light smokers, resulting in a non-significant difference in neutrophil count at baseline between the groups. Smoking has recently been decreasing worldwide, this result would reflect the real world.

There were some limitations in this study. First, it was retrospective and conducted in a single institution. Second, we evaluated the risk factors in the first course because the treatment schedule would be constructed mainly according to the degree of myelosuppression in the first course. Multiple courses of chemotherapy can result in more severe effects; therefore, evaluation over multiple courses is needed, although it is necessary to consider the dose reduction due to chemotherapy-induced peripheral neuropathy. Third, although it is speculated that RDI is correlated with the anti-tumor effect, we did not evaluate the efficacy of the chemotherapy. Fourth, we did not evaluate

the polymorphisms of patients' drug metabolizing enzymes or efflux transporters, such as CDA, CYP2C8, CYP3A4, and ABCB1.

In conclusion, low platelet levels at baseline is a risk factor, whereas dose reduction from the initiation of treatment is a preventive factor for treatment suspension and severe neutropenia frequency in the GEM + nab-PTX regimen. Further studies are needed to inform better management of the implementation of this treatment.

Declarations

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest: YS, MK, YT, and MS have no conflicts of interest. YK reports honoraria from Pfizer, Novartis and Bayer, and research funding from Eli Lilly, MSD, Ono Pharmaceutical, Novartis, Bayer, Chugai Pharma, Yakult, and Taiho, having provided speaker services for Eli Lilly, Chugai Pharma, Merck Serono, Novartis, Pfizer, Bayer, and Taiho.

Ethical approval: All the procedures performed in studies involving human participants were carried out in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Consent to participate: For this type of study, formal consent is not required.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions:

Participated in research design: YS, TY, and MK.

Conducted experiments: YS.

Performed data analysis: YS.

Wrote or contributed to the writing of the manuscript: YS, TY, MK, YK, and MS.

References

1. Yip D, Karapetis C, Strickland A, Steer CB, Goldstein D (2006) Chemotherapy and radiotherapy for inoperable advanced pancreatic cancer. *Cochrane Database Syst Rev* **19:** 3, CD002093
2. Sultana A, Smith CT, Cunningham D, Starling N, Neoptolemos JP, Ghaneh P. (2007) Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. *J Clin Oncol* **25:** 2607–2615
3. Bilimoria KY, Bentrem DJ, Ko CY, Ritchey J, Stewart AK, Winchester DP et al (2007) Validation of the 6th edition AJCC pancreatic Cancer staging system: report from the National Cancer Database. *Cancer* 110: 738–744
4. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M et al (2013)

Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* **369:** 1691–1703

5. Ueno H, Ikeda M, Ueno M, Mizuno N, Ioka T, Omuro Y et al (2016) Phase I/II study of nab-paclitaxel plus gemcitabine for chemotherapy-naive Japanese patients with metastatic pancreatic cancer. *Cancer Chemother Pharmacol* **77:** 595–603
6. Blomstrand H, Scheibling U, Bratthäll C, Green H, Elander NO (2019) Real world evidence on gemcitabine and nab-paclitaxel combination chemotherapy in advanced pancreatic cancer. *BMC Cancer* **19:** 40
7. van Putten JW, Eppinga P, Erjavec Z, de Leede G, Nabers J, Smeets JB et al (2000) Activity of high-dose epirubicin combined with gemcitabine in advanced non-small-cell lung cancer: a multicenter phase I and II study. *Br J* Cancer **82:** 806–811
8. Cucinotto I, Fiorillo L, Gualtieri S, Arbitrio M, Ciliberto D, Staropoli N et al (2013) Nanoparticle albumin bound Paclitaxel in the treatment of human cancer: nanodelivery reaches prime-time? *J Drug Deliv* 905091
9. Von Hoff DD, Ramanathan RK, Borad MJ, Laheru DA, Smith LS, Wood TE et al (2011) Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. *J Clin Oncol* **29:** 4548-4554.
10. Kanai M, Morita S, Matsumoto S, Nishimura T, Hatano E, Yazumi S (2009) A history

of smoking is inversely correlated with the incidence of gemcitabine-induced neutropenia. *Ann Oncol* **20:** 1397–1401

11. O'Malley M, Healy P, Daignault S, Ramnath N (2013) Cigarette smoking and gemcitabine-induced neutropenia in advanced solid tumors. *Oncology* **85:** 216–222
12. Takeuchi H, Saeki T, Aiba K, Tamura K, Aogi K, Eguchi K et al (2016) Japanese Society of Clinical Oncology clinical practice guidelines 2010 for antiemesis in oncology: executive summary. *Int J Clin Oncol* **21**: 1-12
13. Abraxane® (nanoparticle albumin-bound paclitaxel) [package insert on the internet]. Tokyo; Taiho pharmaceutical Co., 2014. http://www.info.pmda.go.jp/downfiles/ph/PDF/400107_4240409D1023_1_12.pdf. accessed Apr 19, 2019
14. Tanabe Y, Shimizu C, Hamada A, Hashimoto K, Ikeda K, Nishizawa D et al (2017) Paclitaxel-induced sensory peripheral neuropathy is associated with an ABCB1 single nucleotide polymorphism and older age in Japanese. *Cancer Chemother Pharmacol* **79:** 1179–1186
15. Bergmann TK, Brasch-Andersen C, Gréen H, Mirza M, Pedersen RS, Nielsen F et al (2011) Impact of CYP2C8*3 on paclitaxel clearance: a population pharmacokinetic and pharmacogenomic study in 93 patients with ovarian cancer. *Pharmacogenom J*

11: 113–120

16. Hertz DL, Roy S, Motsinger-Reif AA, Drobish A, Clark LS, McLeod HL et al (2013) CYP2C8*3 increases risk of neuropathy in breast cancer patients treated with paclitaxel. *Ann Oncol* **24:** 1472–1478
17. Kus T, Aktas G, Kalender ME, Demiryurek AT, Ulasli M, Oztuzcu S et al (2016) Polymorphism of CYP3A4 and ABCB1 genes increase the risk of neuropathy in breast cancer patients treated with paclitaxel and docetaxel. *Onco Targets Ther* **9:** 5073–5080
18. Dai D, Zeldin DC, Blaisdell JA, Chanas B, Coulter SJ, Ghanayem BI et al (2001) Polymorphisms in human CYP2C8 decrease metabolism of the anticancer drug paclitaxel and arachidonic acid. *Pharmacogenetics* **11:** 597–607
19. Henningsson A, Marsh S, Loos WJ, Karlsson MO, Garsa A, Mross K et al (2005) Association of CYP2C8, CYP3A4, CYP3A5, and ABCB1 polymorphisms with the pharmacokinetics of paclitaxel. *Clin Cancer Res* **11:** 8097–8104
20. Ding X, Chen W, Fan H, Zhu B (2015) Cytidine deaminase polymorphism predicts toxicity of gemcitabine-based chemotherapy. *Gene* **559:** 31–37

21. Hryciuk B, Szymanowski B, Romanowska A, Salt E, Wasąg B, Grala B et al (2018) Severe acute toxicity following gemcitabine administration: A report of four cases with cytidine deaminase polymorphisms evaluation. *Oncol Lett* **15:** 1912–1916

22. Sugiyama E, Kaniwa N, Kim SR, Kikura-Hanajiri R, Hasegawa R, Maekawa K et al (2007) Pharmacokinetics of gemcitabine in Japanese cancer patients: the impact of a cytidine deaminase polymorphism. *J Clin Oncol* **25:** 32–42

23. Ueno H, Kaniwa N, Okusaka T, Ikeda M, Morizane C, Kondo S et al (2009) Homozygous CDA*3 is a major cause of life-threatening toxicities in gemcitabine-treated Japanese cancer patients. *Br J Cancer* **100:** 870–873

24. Ozkurt ZN, Yegin ZA, Suyani E, Aki SZ, Acar K, Yagci M et al (2010) Factors affecting stem cell mobilization for autologous hematopoietic stem cell transplantation. *J Clin Apher* **25:** 280–286

25. Nieboer P, de Vries EG, Vellenga E, van der Graaf WT, Mulder NH, Sluiter WJ et al (2004) Factors influencing haematological recovery following high-dose chemotherapy and peripheral stem-cell transplantation for haematological malignancies; 1-year analysis. *Eur J Cancer* **40:** 1199–1207

26. Lee M, Yee J, Kim JY, Kim JY, An SH, Lee KE et al (2019) Risk factors for neutropenia and febrile neutropenia following prophylactic pegfilgrastim. *Asia Pac J Clin Oncol* **15:** 231–237

27. Tang NL, Liao CD, Wang X, Mo FK, Chan VT, Ng R et al (2013) Role of pharmacogenetics on adjuvant chemotherapy-induced neutropenia in Chinese breast cancer patients. *J Cancer Res Clin Oncol* **139:** 419–427

28. Kornmann M, Butzer U, Blatter J, Beger HG, Link KH (2000) Pre-clinical evaluation of the activity of gemcitabine as a basis for regional chemotherapy of pancreatic and colorectal cancer. *Eur J Surg Oncol* **26:** 583–587

29. Chang YF, Li LL, Wu CW, Liu TY, Lui WY, P'eng FK et al (1996) Paclitaxel-induced apoptosis in human gastric carcinoma cell lines. *Cancer* **77:** 14–18

30. de Graan AJ, Loos WJ, Friberg LE, Baker SD, van der Bol JM, van Doorn L et al (2012) Influence of smoking on the pharmacokinetics and toxicity profiles of taxane therapy. *Clin Cancer Res* **18:** 4425-4432

31. van der Bol JM, Mathijssen RH, Loos WJ, Friberg LE, van Schaik RH, de Jonge MJ et al (2007) Cigarette smoking and irinotecan treatment: pharmacokinetic interaction and effects on neutropenia. *J Clin Oncol* **25:** 2719–2726

Tables

Table 1 Patient characteristics

Sex (male/female)	112/88
Age (median, range)	67 (33–80)
Performance status	
0-1	198
2	2
Staging	
1-3	58
4	117
Recurrence	25
Location of primary tumor	
Pancreatic head	98
Pancreatic body	61
Pancreatic tail	28
Other	13
Treatment line	
First line	132
Second or later line	68
BSA (m^2) (median, range)	1.58 (1.13–2.18)
Leukocyte (/μL) (median, range)	5,800 (1,800–20,700)
Number of less than LLN	9
Neutrophil (/μL) (median, range)	3,813 (1,003–18,941)
Number of less than LLN	13
Hb (g/dL) (median, range)	12.1 (7.8–17.6)
Number of less than LLN	125
Plt ($\times 10^3$/μL) (median, range)	212 (62–586)
Number of less than LLN	37
Albumin (g/dL) (median, range)	3.8 (1.9–4.8)
Total bilirubin (mg/dL) (median, range)	0.6 (0.2–2.6)
AST (IU/L) (median, range)	25 (12–166)
ALT (IU/L) (median, range)	24 (6–202)
Creatinine (mg/dL) (median, range)	0.67 (0.40–1.52)
CRP (mg/dL) (median, range)	0.22 (0–22.64)

Diabetes mellitus	66
Epigastric and/or back pain	85
Smoking history	
Never	75
Current smoker	37
Former smoker	88
Dose reduction from the beginning	16

BSA; body surface area, LLN; lower limit of normal, Hb; hemoglobin, Plt; platelet, AST; aspartate transaminase, ALT; alanine aminotransferase, CRP; C-reactive protein

Table 2 Frequency of treatment suspension, hematotoxicity caused by GEM + nab-PTX, and RDI of GEM and nab-PTX

Suspension of treatment (n, %)	122 (61%)
Suspension on day 8	40 (20%)
Suspension on day 15	91 (45.5%)
Frequency of grade 3/4 neutropenia (n, %)	102 (51%)
Frequency of grade 3/4 thrombocytopenia (n, %)	15 (7.5%)
Cause of suspension (n, %)	
Neutropenia	94 (77.0%)
Thrombocytopenia	7 (5.7%)
Both of the above	8 (6.6%)
Others	13 (10.7%)
RDI (%, mean ± SD)	
GEM	78.0 ± 18.6
nab-PTX	77.7 ± 18.6

RDI, relative dose intensity; GEM, gemcitabine; nab-PTX, nanoparticle albumin-bound paclitaxel

Table 3 Univariate and multivariate analyses of the risk factors associated with (A) treatment suspension and (B) the frequency of grade 3/4 neutropenia

(A)		Univariate analysis		Multivariate analysis	
	Treatment suspension frequency (n)	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Sex					
Male	64 (57.1%)				
Female	58 (65.9%)	0.69 (0.38–1.23)	0.21	Excluded	-
Age (years)					
≥ 65	81 (64.8%)				
< 65	41 (54.6%)	1.53 (0.85–2.74)	0.16	1.56 (0.84–2.91)	0.16
Performance status					
0 or 1	122 (61.6%)				
2	0 (0%)	6.43×10^{6}	0.99	Excluded	-
Treatment line					
1st line	82 (62.1%)				
2nd or later line	40 (58.8%)	1.15 (0.63–2.09)	0.65	Excluded	-
BSA (m^2)					
≥ 1.5	79 (61.7%)				
< 1.5	43 (59.7%)	1.09 (0.60–1.96)	0.78	Excluded	-
Neutropenia					
Present	11 (84.6%)				
Absent	111 (59.4%)	3.77 (0.81–17.5)	0.09	2.30 (0.46–11.55)	0.31

Anemia					
Present	74 (59.2%)				
Absent	48 (64.0%)	0.82 (0.45–1.47)	0.50	Excluded	-
Thrombocytopenia					
Present	30 (81.1%)				
Absent	92 (56.4%)	3.31 (1.37–7.97)	0.008**	3.55 (1.36–9.24)	0.009**
Total bilirubin (mg/dL)					
≥ grade 1	6 (54.5%)				
< grade 1	116 (61.4%)	0.76 (0.22–2.56)	0.65	Excluded	-
AST (IU/L)					
≥ grade 1	35 (61.4%)				
< grade 1	87 (60.8%)	1.02 (0.55–1.92)	0.94	Excluded	-
ALT (IU/L)					
≥ grade 1	39 (60.9%)				
< grade 1	83 (61.0%)	1.00 (0.54–1.83)	0.99	Excluded	-
Serum creatinine elevation					
Present	6 (50.0%)				
Absent	116 (61.7%)	0.62 (0.19–2.00)	0.42	Excluded	-
Hypoalbuminemia					
≥ grade 1	74 (57.4%)				
< grade 1	48 (67.6%)	0.64 (0.35–1.18)	0.16	0.63 (0.31–1.26)	0.19

CRP					
≥ ULN	64 (55.7%)				
< ULN	58 (68.2%)	0.58 (0.32–1.05)	0.07	0.82 (0.42–1.61)	0.57
Diabetes mellitus					
Present	37 (56.1%)				
Absent	85 (63.4%)	0.74 (0.40–1.34)	0.32	Excluded	-
Smoking history					
Current or former	75 (60.5%)				
Never	47 (61.8%)	0.94 (0.53–1.70)	0.85	Excluded	-
Dose reduction from initiation					
Present	5 (31.3%)				
Absent	117 (63.6%)	0.26 (0.09–0.78)	0.016*	0.22 (0.07–0.73)	0.01*

*P <0.05, **P <0.01

BSA; body surface area, AST; aspartate transaminase, ALT; alanine aminotransferase, CRP; C-reactive protein, ULN; upper limit of normal

(B)		Univariate analysis		Multivariate analysis	
	Treatment suspension frequency (n)	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Sex					
Male	52 (46.4%)				
Female	50 (56.8%)	0.66 (0.38–1.16)	0.15	0.68 (0.37–1.24)	0.20
Age (years)					
≥ 65	71 (56.8%)				
< 65	31 (41.3%)	1.87 (1.04–3.33)	0.03*	1.88 (1.00–3.50)	0.047*
Performance status					
0 or 1	102 (51.5%)				
2	0 (0%)	4.25×10^{6}	0.99	Excluded	-
Treatment line					
1st line	70 (53.0%)				
2nd or later line	32 (47.1%)	1.27 (0.71–2.28)	0.42	Excluded	-
BSA (m^2)					
≥ 1.5	66 (51.6%)				
< 1.5	36 (50.0%)	1.06 (0.60–1.90)	0.83	Excluded	-
Neutropenia					
Present	9 (69.2%)				
Absent	93 (49.7%)	2.27 (0.68–7.64)	0.18	1.27 (0.34–4.77)	0.07
Anemia					
Present	60 (48.0%)				
Absent	42 (56.0%)	0.73 (0.41–1.29)	0.27	Excluded	-

Thrombocytopenia					
Present	26 (70.3%)				
Absent	76 (46.6%)	2.71 (1.25–5.84)	0.01*	2.98 (1.27–6.98)	0.01*
Total bilirubin (mg/dL)					
≥ grade 1	5 (45.5%)				
< grade 1	97 (51.3%)	0.79 (0.23–2.68)	0.71	Excluded	-
AST (IU/L)					
≥ grade 1	28 (49.1%)				
< grade 1	74 (51.7%)	0.90 (0.49–1.66)	0.74	Excluded	-
ALT (IU/L)					
≥ grade 1	34 (53.1%)				
< grade 1	68 (50.0%)	1.13 (0.63–2.05)	0.68	Excluded	-
Serum creatinine elevation					
Present	5 (41.7%)				
Absent	97 (51.6%)	0.67 (0.21–2.19)	0.51	Excluded	-
Hypoalbuminemia					
≥ grade 1	59 (45.7%)				
< grade 1	43 (60.6%)	0.55 (0.30–0.99)	0.046*	0.58 (0.29–1.14)	0.11
CRP					
≥ ULN	49 (42.6%)				
< ULN	53 (62.4%)	0.45 (0.25–0.80)	0.006**	0.65 (0.34–1.25)	0.20

Diabetes mellitus					
Present	33 (50.0%)				
Absent	69 (51.5%)	0.94 (0.52–1.70)	0.84	Excluded	-
Smoking history					
Current or former	59 (47.6%)				
Never	43 (56.6%)	0.70 (0.39–1.24)	0.22	Excluded	-
Dose reduction from initiation					
Present	4 (25.0%)				
Absent	98 (53.3%)	0.29 (0.09–0.94)	0.04*	0.25 (0.07–0.88)	0.03*

*P <0.05, **P <0.01

BSA; body surface area, AST; aspartate transaminase, ALT; alanine aminotransferase, CRP; C-reactive protein, ULN; upper limit of normal

Table 4 RDI of GEM and nab-PTX in patients with or without dose reduction from initiation of treatment, with or without neutropenia at baseline, and with or without thrombocytopenia at baseline

	GEM RDI (%)	*P*- value	nab-PTX RDI (%)	*P*- value
Dose reduction from initiation				
Present (n = 16)	74.6 ± 15.8		73.4 ± 16.5	
Absent (n = 184)	78.3 ± 18.9	0.45	78.0 ± 18.8	0.35
Treatment line				
First-line (n = 132)	78.5 ± 18.6		78.1 ± 18.6	
Second- or later-line (n = 68)	77.0 ± 18.7	0.58	76.7 ± 18.9	0.61
Neutropenia				
Present (n = 13)	73.3 ± 15.6		73.3 ± 15.6	
Absent (n = 187)	78.3 ± 18.8	0.36	78.0 ± 18.8	0.39
Thrombocytopenia				
Present (n = 37)	68.8 ± 17.6		68.8 ± 17.6	
Absent (n = 163)	80.1 ± 18.3	0.001**	79.7 ± 18.3	0.001**

**P <0.01

RDI, relative dose intensity; GEM, gemcitabine; nab-PTX, nanoparticle albumin-bound paclitaxel

Table 5 Influence of dose reduction from initiation on treatment suspension and RDI in patients with thrombocytopenia at baseline

	Treatment suspension	*P*- value	GEM RDI (%)	*P*- value	nab-PTX RDI (%)	*P*- value
Dose reduction from initiation						
Present (n = 4)	1 (25%)		71.7 ± 16.7		71.7 ± 16.7	
Absent (n = 33)	29 (87.9%)	0.016*	68.5 ± 17.9	0.74	68.5 ± 17.9	0.74

**P* <0.05

RDI, relative dose intensity; GEM, gemcitabine; nab-PTX, nanoparticle albumin-bound paclitaxel

Figure captions

Fig. 1 Flow diagram of the cohort and exclusions

Figure 1