学位論文

A clinical trial to assess the feasibility and efficacy of *nab*-paclitaxel plus gemcitabine for elderly patients with unresectable advanced pancreatic cancer

(治癒切除不能高齢膵癌患者に対するGEM+nab-paclitaxel療法の忍容性と有効性の検証)

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著者の宣言

本学位論文は、著者の責任において実験を遂行し、得られた真実の結果に基づいて正確に作成したものに相違ないことをここに宣言する。

論文要旨

背景：膵癌は代表的な難治性がんの一つであり根治切除不能例では極めて予後不良である。高齢膵癌患者の治療において、特に化学療法に関しては十分な検討がなされていない。膵癌に対する化学療法は、nab-paclitaxel+Gemcitabine(nab-PTX+GEM；GnP）療法の有効性が報告され、その安全性と有効性を検討した国内臨床第 I/II 相試験の結果を受け、2014 年 12 月から本邦でも使用可能となり広く用いられている。海外の報告では 75 歳以上の登録が約 10%を占めていたのに対し、第 I/II 相試験においては 75 歳以上の症例はわずか 1 例しか登録されておらず、その検討は不十分である。そこで、高齢膵癌患者に対する GnP 療法の忍容性と有効性を検証する臨床研究を実施した。

目的：本邦で、治癒切除不能と診断された 75 歳以上膵癌症例における GnP 療法の忍容性と有効性を検討する。

方法：75 歳以上で治癒切除不能膵癌と組織学的に診断され、GnP 療法の方針となった症例のうち、国内第 I/II 相試験と同様の選択基準を満たし、本研究への参加に同意が得られた症例を対象とした。本研究は北里大学病院、北里メディカルセンター、伊勢原協同病院で実施された多施設前向き観察研究である。治療の方法は国内で広く用いられる適正使用ガイドに準じて施行された。Progressive Disease(PD)の判定、許容できない有害事象の出現、患者からの同意撤回の要請があるまで治療を継続した。Primary endpoint は有害事象の頻度および重症度、2 サイクルの完遂率、Relative dose intensity（RDI)、減量率、延期率、病勢コントロール率(disease control rate;DCR)、無増悪生存期間(progression free survival;PFS)、全生存期間(overall survival:OS)である。2 サイクルの完遂は両薬剤の RDI を 75%以上に保って投与可能であることと定義した。

結果：期間中に 86 例が 75 歳以上の切除不能膵癌と診断され、36 例に GnP 療法が施行された。このうち、27 例が本研究に参加した。年齢は中央値 77 歳(75-85)、男性 16 例、PS1 は 8 例、stageⅣが 17 例であった。2 サイクルの完遂率は、nab-PTX で 48.1%、GEM で 55.6%であった。治療サイクルの中央値は 7 コース(1-23)であった。期間中の各薬剤の RDI は 65.1%と 74.1%であり、延期率は 81.5%、各薬剤の減量率は nab-PTX で 48.1%、GEM で 55.6%であった。延期の理由は好中球減少症が最多であった。減量の理由は nab-PTX では末梢神経障害、GEM では好中球減少症が最多であった Grade3 以上の血液毒性は 14/27 例（51.9%）で観察され、主に白血球減少症（29.6%)、好中球減少症（48.1%)、貧血（7.4%)、血小板減少症（7.4%）であった。主な Grade3 以上の非血液毒性は末梢神経障害 6 例（22.2%)、発熱性好中球減少症 3 例（11.1%)、間質性肺炎 3 例（7.4%）であった。間質性肺炎を発症した 3 例中 1 例は、化学療法を中止し副腎皮質ステロイドによる治療を行ったが、化学療法の最終投与日から 25 日後に呼吸不全のため死亡した（grade 4)。残りの 2 例は治療により軽快し、GnP 療法は中止した。有効性においては、DCR は 92.6%（25/27）であり、PFS と OS の中央値はそれぞれ 7.0 か月と 10.3 か月であった。

考察：本研究において、2 コース完遂率は約半数であり、RDI も既報と比較し低い結果であった。減量や延期の基準は前向き研究よりも低く設定していることに加え、基準に満たなくとも担当医の判断で減量や延期が許容されており、高齢者が対象ということでより安全に施行されたことによる結果と思われる。結果として、高齢者を対象としながらも Grade3 以上の血液毒性の発生率は既報とほぼ同等であり、有効性に関しても同等の結果が得られている。一方、非血液毒性の発生は既報と比べて頻度が高く、注意を要することが明らかとなった。このうち、3 例で間質性肺炎を生じており、1 例は化学療法関連死に至った。残りの 2 例も治療中止を余儀なくされている。間質性肺炎の予測が今後の課題と思われる。また、腸腰筋の面積を測定することで定義されたサルコペニアの症例では、非サルコペニアの症例と比較し非血液毒性の発生率が有意に高かった。本研究の結果を解釈する上で、症例数が 27 例と小規模な研究であること、局所進行癌の症例が含まれていること、選択基準として臓器機能が比較的保たれている症例に限定されていることに注意を要する。
結論：適格な基準を満たす症例に限定すると、高齢者であっても GnP 療法は非高齢者と同様に有効で、適切に用量調整や投与の可否を判定した上で投与期間の調整を行えば、十分に許容できる治療レジメンであると考える。今後は、大規模試験での再検討と、どのような症例が重篤な有害事象を生じ得るのかを評価する客観性に富んだ新たなツールの開発が望まれる。

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Introduction

Despite current advances in medical technology, pancreatic ductal adenocarcinoma has a poorer prognosis than most other carcinomas [1, 2]. The incidence of pancreatic cancer in Japan has increased with the aging population, and approximately half of the patients diagnosed with pancreatic cancer in 2011 were 75 years or older [3]. As the number of cancer patients is generally high among elderly populations, it is often challenging to determine such patients' optimal treatment strategy, particularly chemotherapy, owing to declining organ function and various other complications that occur with advancing age.

In a phase III clinical trial of patients with pancreatic cancer, Von Hoff et al. found that nab-paclitaxel (nab-PTX) plus gemcitabine (GEM) produced a significantly longer median overall survival (OS; 8.5 months) than GEM alone (6.7 months) [4]. After a phase I/II clinical trial performed in Japan to examine the safety and efficacy of nab-PTX+GEM yielded favorable results [5], this combination regimen is now widely used in this country. When considering that approximately 10% of the enrollees in the MPACT trial were elderly patients (i.e., 75 years or older), and that approximately 8% of subjects had Eastern Cooperative Oncology Group (ECOG) performance status (PS) scores of 2, it can be deduced that nab-PTX+GEM is a relatively well-tolerated treatment regimen even among elderly patients. However, the MPACT trial did not enroll any Japanese patients; moreover, the phase I/II clinical trial conducted in Japan enrolled only a single patient older than 75 years. Hence, studies of the safety and efficacy of nab-PTX+GEM in Japanese patients ≥75 years remain lacking.

With this background, we conducted a study of Japanese patients with non-resectable pancreatic cancer who were 75 years of age or older to examine the tolerability and efficacy of nab-PTX+GEM.

Materials and methods

Patient eligibility

This study was conducted at 3 sites: the Kitasato University Hospital, Kitasato University Medical Center, and Isehara Kyodo Hospital. Patients 75 years of age or older who had received a pathological diagnosis of adenocarcinoma or adenosquamous carcinoma of the pancreas, who were ineligible for curative resection during the enrollment period (i.e., between September 2015 and June 2018), and who had already provided written informed consent to start nab-PTX+GEM treatment were identified. All who met the following inclusion criteria were analyzed: histologically or cytologically confirmed unresectable advanced pancreas adenocarcinoma, age ≥75 years, an expected survival period of more than 3 months, ECOG PS score 0–1, measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1., no prior chemotherapy or radiotherapy, and adequate organ function as evidenced by laboratory data obtained within 7 days prior to enrollment (leukocyte count ≥12,000/mm3, neutrophil count ≥1,500/mm3, hemoglobin ≥9.0 g/dL, platelets ≥100,000/mm3, aspartate aminotransferase/alanine aminotransferase ≤2.5-fold the upper limits of normal, total bilirubin ≤1.25-fold the upper limits of normal, creatinine clearance ≥60 mL/min by measured value or according to the Cockcroft-Gault equation, C-reactive protein ≤1.5 mg/dL, and glycated hemoglobin ≤8.4%). Patients were excluded if they had peripheral sensory neuropathy, a history of severe drug hypersensitivity, and/or severe mental disorders.

Study design and endpoints

This was multicenter observational trial to evaluate the feasibility and efficacy of nab-PTX+GEM in elderly Japanese patients with unresectable advanced pancreatic cancer. The primary endpoints were adverse events, rate of completion of 2 cycles of chemotherapy, relative dose intensity (RDI), rate of dose reduction, rate of chemotherapy interruption, disease control rate (DCR), progression-free survival (PFS), and OS.

As this study investigated only elderly patients (i.e., 75 years and older), it was difficult to predict a final completion rate. We expected to enroll approximately 25 patients during the enrollment period, based on historical experiences at the 3 participating facilities. The 95% confidence intervals (CIs)

for the completion of 2 cycles of treatment by 14 (56%), 16 (64%), 18 (72%), and 20 (80%) of the proposed 25 subjects,
based on historical data, were 34.9–75.6, 42.5–82.0, 50.6–87.9 and 59.3–93.2, respectively, which were valid ranges. As such, we aimed to enroll at least 25 subjects; more would be allowed to enroll provided they did so during the enrollment period.

All enrolled patients provided written informed consent for their participation in the study, which was approved in advance by the Institutional Review Board of our institution from the standpoints of its ethical, scientific, and medical validity. The study was registered at the University Hospital Medical Information Network

(http://www.umin.ac.jp - UMIN000018907).

Treatment

Eligible patients were administered a 30 min intravenous infusion of nab-PTX at a dose of 125 mg/m2, followed by a 30 min intravenous infusion of GEM at a dose of 1000 mg/m2, on days 1, 8, and 15 every 4 weeks. The dosing criteria, methods of dose adjustment and treatment postponement, and dose reduction criteria were in accordance with a previously described phase I/II clinical study performed in Japan [5]. To administer this treatment regimen safely to elderly pancreatic cancer patients, we subclassified the patients in the aforementioned phase I/II study based on their absolute neutrophil count (ANC) and platelet count on day 8, which facilitated decision-making on dose adjustment, dose reduction, and treatment administration in our own study.

In the previous Japanese phase I/II clinical study, an ANC of 500–1,000/mm3 or a platelet count of 50,000–74,999/mm3 on day 8 resulted in a dose decrease to next lower level. However, in our study, we subdivided the day 8 criteria to ANC ≥1,000/mm3 and platelet count 50,000–74,999/mm3, and ANC 500–999/mm3 and platelet count ≥50,000/mm3; these response measures were also obtained on day 15. Furthermore, treatment in patients with grade 2 or higher peripheral nerve disorder was suspended until they recovered to grade 0–1, whereupon only nab-PTX alone was reintroduced at a dose that was reduced by 1 level. Dose reduction was permitted for any reason if the physician determined it to be necessary even if a patient did not meet the dose reduction criteria. The dose was reduced to 100 or 75 mg/m2 for nab-PTX and to 800 or 600 mg/m2 for GEM. Treatment continued until disease progression, unacceptable adverse events, or withdrawal of consent, whichever occurred

first. The dosing criteria used in our present study are summarized in Table 1.

Study evaluations

Tumor imaging was performed using computed tomography at baseline and at least every 8 weeks thereafter. Complete blood counts, hematological analyses, and urinalyses were performed weekly during the treatment period. The Common Terminology Criteria for Adverse Events (version 4.0) was used to assess toxicity. The completion of 2 cycles of chemotherapy was defined as maintaining an RDI for nab-PTX and GEM at 75% or higher during these cycles. The rate of chemotherapy interruption was defined as the proportion of subjects who did not receive 1 or more doses on days 1,8, and 15 of each cycle for failing to meet the dosing criteria, while the rate of dose reduction was defined as the proportion of subjects for whom the dose of each drug was reduced 1 or more times on days 1, 8, and 15 of each cycle owing to adverse events, as determined by the dose reduction criteria. The response to treatment was assessed according to the RECIST (version 1.1). Complete and partial responses required confirmation ≥4 weeks post-treatment. The DCR was defined as the proportion of patients with complete response, partial response, and stable disease maintained for 4 weeks or longer. The median survival time and corresponding 95% CIs for PFS and OS were estimated using the Kaplan-Meier method. PFS and OS were defined as the time from registration until progression or death due to any cause, respectively. Statistical analyses were performed using the statistical package SPSS Base 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

As shown in Figure 1, 86 subjects aged 75 years or older received a pathological diagnosis of non-resectable pancreatic cancer between September 2015 and June 2018. Of these, nab-PTX+GEM was administered to 36 subjects (42%), 27 (31%) of whom were enrolled in this study after meeting the inclusion criteria. The patients' characteristics are shown in Table 2. The median age was 77 years (range, 75–85 years), 16 subjects (59.3%) were male, 8 (29.6%) had PS scores of 1, and the median score of the G8 screening tool was 12.5 points (range, 6–17 points). Metastatic lesions were most common in the liver (33.3%) followed by the lung (25.9%). Four patients (14.8%) underwent biliary tract drainage prior to commencing chemotherapy.

Feasibility of the nab-PTX+GEM regimen

The treatment features of the administered regimen are shown in Table 3. The rates of completion of 2 cycles of chemotherapy were 48.1% for nab-PTX and 55.6% for GEM; the RDIs were 76.6% for nab-PTX and 78.0% for GEM. During the observation period that continued until December 31, 2018, a median of 7.0 (range, 1–23) cycles of treatments were performed with mean RDIs of 65.1% for nab-PTX and 74.1% for GEM. The rate of chemotherapy interruption was 81.5% while the rates of dose reduction for nab-PTX and GEM were 81.5% and 48.1%, respectively. The main reasons for failure to meet the dosing criteria on a scheduled dosing date (and consequently forgoing a dose) were neutropenia (55.6%) and anorexia (11.1%). The most common reasons for reducing the dose of nab-PTX were peripheral nerve disorder (37.0%) and neutropenia (18.5%), while the reasons for reducing GEM doses were neutropenia (18.5%) and rash/malaise (11.1%).

Adverse events of all grades were observed in all 27 subjects (Table 4). Grade 3 or higher hemotoxic adverse events occurred in 14 subjects (51.9%), while grade 3 or higher non-hemotoxic adverse events occurred in 16 (59.3%), with peripheral nerve disorder being the most common in the latter category (22.2%) followed by interstitial pneumonia (11.1%), febrile neutropenia (11.1%), rash (11.1%), fatigue (7.4%), constipation (7.4%), anorexia (3.7%), and oral mucositis (3.7%). Although 1 of 3 subjects who developed interstitial pneumonia received corticosteroid treatments after discontinuing chemotherapy, the subject died 25

days after the last chemotherapy dose owing to grade 4 respiratory failure. The conditions of the remaining 2 patients improved with treatment, although treatment with nab-PTX+GEM was not resumed.

Efficacy

Twelve subjects (44.4%) achieved a partial response, 13 (48.1%) had stable disease, 1 (3.7%) had progressive disease, and 1 (3.7%) was not evaluated; the DCR was 92.6%. The median PFS across the median observation period of 9.4 months (range: 1.8 to 44.2 months) in all 27 subjects was 7.0 months (95% CI, 6.0–8.1 months), while the median OS was 10.3 months (95% CI, 8.2–12.5 months). The 6-month and 1-year PFS rates were 69.4% and 16.3%, respectively, whereas those for OS were 85.2% and 41.9%, respectively (Figure 2a–b.). The treatment results according to disease stage were a PFS of 8.1 months (95% CI, 4.4–11.8 months) and an OS of "not reached" for patients with Union for International Cancer Control stage III, and a PFS of 7.0 months (95% CI: 5.7–8.4 months) and OS of 9.5 months (95% CI: 7.8–11.2 months) for those with stage IV (Figure 2c–d).

Discussion

We conducted this clinical study to examine the tolerability and efficacy of nab-PTX+GEM in elderly pancreatic cancer patients via prospective observation from the time of commencing treatment. Despite lower-than-anticipated 2-cycle chemotherapy completion rates, the RDIs were maintained at relatively high levels in our elderly patients. The RDIs in the phase III MPACT trial were 81% for nab-PTX and 75% for GEM [6]; these values were 72.5% and 77.1%, respectively, in the Japanese phase I/II study [5] and 69% and 78%, respectively, in a study by Blomstrand et al. [7]. Our RDIs were similar to those reported by Blomstrand et al. and lower than those found in the other 2 studies. The reasons our RDIs were lower than those in the MPACT and Japanese phase I/II studies may have been as follows: First, despite our inclusion criteria being the same as those for the phase I/II study (other than age), we made dose adjustments and reductions according to more stringent criteria than those used in that study to address hemotoxicity and peripheral nerve disorder, thus enabling safer therapy. Second, while the phase I/II study reduced doses during a cycle of treatment, the treatment was resumed at the previous dose at the start of the subsequent cycle if the patient met the dosing criteria; however, very few subjects in our study resumed their original dose after its reduction. Third, dose reduction was permitted for any reason in our study, even if the patient did not meet the dose reduction criteria, as long as the physician deemed it necessary. The incidence rates of grade 3 or higher hemotoxic adverse events that occurred based on these guidelines were lower in our study than in the Japanese phase I/II study, and were within permissible range. On the other hand, non-hemotoxic adverse events of grades 3 and higher were more frequent in our study than in the phase I/II study. A recent sub-analysis of patients older than 70 years performed by Imaoka et al. [8] as part of the GEST study showed that, while the incidence of grade 3 or higher hemotoxic adverse events following GEM monotherapy was the same as that in our study (58.1%), grade 2 or higher non-hemotoxic adverse events occurred in 61.6% of their patients, which contrasted with the much higher rate in our study (88.9%). These data collectively imply that particular care must be taken to avoid non-hemotoxic adverse events when treating elderly patients with

nab-PTX+GEM. One of the 3 subjects who developed chemotherapy-related interstitial pneumonia in our study failed to improve despite corticosteroid treatment, and ultimately experienced respiratory failure leading to death. The incidence rates of interstitial pneumonia in prospective studies conducted thus far are 3–4% [4, 5]; hence, this adverse event is expected to a certain extent. Furthermore, Ogawa et al. reported that 5 of their 26 subjects (19.2%) treated with nab-PTX+GEM developed interstitial pneumonia [9]. In the GEST study, the GEM and GEM+S-1 groups each had 1 subject who experienced chemotherapy-related death due to interstitial pneumonia [10], as in our cohort, which indicates that interstitial pneumonia is a serious adverse event that can lead to death even in younger patients. The cause of death may be associated with the deteriorated reserve capacity in the lung; however, this was difficult to determine among our patients and should be investigated in future large-scale studies. If we exclude the 2 remaining patients who developed interstitial pneumonia, only 1 other subject discontinued treatment owing to an adverse event manifesting as grade 2 anorexia; the patient requested treatment cessation. The remaining 23 subjects (85%) showed no adverse events that met the discontinuation criteria after undergoing any necessary dose adjustments or reductions per the aforementioned description; therefore, they were able to continue nab-PTX+GEM until their conditions deteriorated.

Macarulla et al. reported that the nab-PTX+GEM regimen is effective in patients with ECOG PS scores of 2 [11]. However, in order to administer such an intense regimen to elderly patients, there is an urgent need to develop a pre-therapy indicator that can predict the likelihood of adverse events. The patient who experienced chemotherapy-related death in our study was 77 years old and had a PS score of 0 and a G8 screening tool score of 12.5. There was nothing particularly unique about this patient relative to the rest of the cohort, which made it difficult to predict adverse events in advance. The European Organisation for Research and Treatment of Cancer (EORTC) elderly task force classifies elderly patients as “fit”, “vulnerable”, and “frail” [12], and our patient’s status may have fallen between the latter 2 categories. Geriatric assessment in our study was based only on the ECOG PS and G8 screening tool scores, which may not have been adequate. Betge et al. are currently administering the "GrantPax" multicenter, open label phase IV interventional trial in elderly patients with pancreatic cancer who are being stratified according to a ‘Comprehensive Geriatric Assessment (CGA)’ that includes the Activities of

Daily Living/Instrumental Activities of Daily Living tools, G8 screening tool, ECOG PS, Charlson Comorbidity Index, and other parameters. The CGA is applied before and after nab-PTX+GEM treatment [13]; their aim is to develop a reliable method to objectively identify the effects of this regimen in elderly patients and thereby offer personalized treatments.

With respect to efficacy, the DCR and PFS rate in our study were satisfactory even when compared to the Japanese phase I/II study. Our data showed that nab-PTX+GEM may improve PFS over GEM monotherapy in elderly patients based on a sub-analysis of patients ≥70 years who were investigated in the GEST study (their PFS was 4.5 months). It is important to note that our cohort included 10 subjects (37.1%) with locally advanced pancreatic cancer; however, even when limited to patients with stage IV disease, the DCR and PFS were favorable. On the other hand, the OS rates of our patients were inconsistent with those of patients in the Japanese phase I/II study, which may be attributed to the fact that, while 97.0% of subjects in that study were able to switch to secondary treatments, only 48.2% of the subjects in our study were able to do the same. Nevertheless, the main observation in our study was that nab-PTX+GEM is able to delay the progression of advanced pancreatic cancer in elderly patients in a similar fashion to their non-elderly counterparts. Similarly, Jin et al. reported that nab-PTX+GEM significantly improved the OS of elderly pancreatic patients [14].

This study had several limitations. First, as a small-scale investigation conducted at 3 facilities, it may not be adequately representative; hence, it is necessary to investigate the nab-PTX+GEM regimen in large-scale studies to validate our data. Second, our cohort was limited to a population that met inclusion criteria similar to those of the Japanese phase I/II study; i.e., the patients' organ functions were relatively intact. While many elderly patients tend to have lower organ function than non-elderly counterparts owing to age-related comorbid diseases, our study did not determine whether the tolerability and efficacy of nab-PTX+GEM are as favorable in those elderly patients who have lower organ function status.

Our data show that nab-PTX+GEM is as efficacious in elderly patients who meet certain criteria as it is in non-elderly patients, and is a feasible treatment when appropriate dose adjustments, dose reductions, and treatment-related decisions are managed appropriately. However, elderly patients appear to be particularly more prone to non-hemotoxic adverse events than their non-elderly

counterparts. It is necessary to re-examine the efficacy of the nab-PTX+GEM regimen in a large-scale study and to develop a reliable indicator that objectively identifies patients who are likely to develop serious adverse events owing to this regimen.

Conclusion

The nab-PTX+GEM regimen is as efcacious in elderly patients who meet certain criteria as it is in previously reported non-elderly patients. The regimen is feasible with appropriate dose adjustments and attention to adverse events.

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Tables and Figures

Table 1. Dose modification for hematologic toxicity within a cycle on days 8 and 15

Day 8		Day 15	
Counts and toxicity (/mm^3)	*nab*-PTX and GEM	Counts and toxicity (/mm^3)	*nab*-PTX and GEM
ANC >1,000 and platelets ≥75,000	Full Dose	ANC ≥1,000 and platelets ≥75,000	Full dose
		ANC ≥1,000 and platelets 50,000–74,999	Full dose
		ANC <500 or platelets <50,000	Skip
ANC ≥1,000 and platelets 50,000–74,999	Decrease to next lower level	ANC ≥1,000 and platelets ≥75,000	Return to previous dose (day 8) level
		ANC ≥1,000 and platelets 50,000–74,999	Decrease to next lower level
		ANC <500 or platelets <50,000	Skip
ANC 500–999 and platelets ≥50,000	Skip	ANC ≥1,000 and platelets ≥75,000	Full dose
		ANC ≥1,000 and platelets 50,000–74,999	Decrease to next lower level
		ANC <500 or platelets <50,000	Skip
ANC <500 or platelets <50.000	Skip	ANC ≥1,000 and platelets ≥75,000	Decrease to next lower level
		ANC ≥1,000 and platelets 50,000–74,999	Decrease to next lower level
		ANC <500 or platelets <50,000	Skip

Abbreviations: nab-PTX, nab-paclitaxel; GEM, gemcitabine; ANC, absolute neutrophil count.

Table 2. Patient characteristics

Demographic	
Median age in years (range)	77 (75–85)
Sex, n (%)	
Male	16 (59.3)
Female	11 (40.7)
ECOG PS score, n (%)	
0	19 (70.4)
1	8 (29.6)
G8 screening tool, median, (range)	12.5 (6–17)
>14	4 (14.8)
≤14	23 (85.2)
Greatest median tumor dimension, mm (range)	30 (14–53)
Location of pancreatic carcinoma, n (%)	
Head	9 (33.3)
Body	15 (55.6)
Tail	3 (11.1)
TNM stage: UICC 7th edition, n (%)	
III	10 (37.1)
IV	17 (62.9)
Metastatic site, n (%)	
Liver	9 (33.3)
Lung	6 (22.2)
Peritoneum	3 (11.1)
Others	2 (7.4)
Biliary drainage, n (%)	
No	23 (85.2)
Yes	4 (14.8)
Pancreatic resection, n (%)	
No	27 (100)
Yes	0
CA19-9, median, U/mL, (range)	558 (7–588.000)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; TNM, TNM Classification of Malignant Tumors; UICC, Union for International Cancer Control; CA19-9, carbohydrate antigen 19-9.

Table 3. Treatment features of *nab*-paclitaxel plus gemcitabine for elderly Japanese patients with unresectable advanced pancreatic cancer

Median treatment cycle (range)	7.0 (1–23)
Completion rates of 2 cycles chemotherapy, %	
nab-PTX	48.1
GEM	55.6
RDI of 2 cycles of chemotherapy, %	
nab-PTX	76.6
GEM	78.0
RDI for the median treatment cycle of 7, %	
nab-PTX	65.1
GEM	74.1
Rate of chemotherapy interruption, %	81.5
Rate of dose reduction, %	
nab-PTX	81.5
GEM	48.1

Abbreviations: *nab*-PTX, *nab*-paclitaxel; GEM, gemcitabine; RDI, relative dose intensity.

Table 4. Adverse events

	Any grade		Grades ≥3	
	n	(%)	n	(%)
Hematological toxicities				
Thrombocytopenia	20	(74.1)	2	(7.4)
Leukopenia	19	(70.4)	8	(29.6)
Neutropenia	19	(70.4)	13	(48.1)
Anemia	24	(88.9)	2	(7.4)
Non-hematological toxicities				
Febrile neutropenia	3	(11.1)	3	(11.1)
Alopecia	23	(85.2)	NA	
Peripheral sensory neuropathy	21	(77.8)	6	(22.2)
Anorexia	21	(77.8)	1	(3.7)
Dysgeusia	12	(44.4)	0	0
Nausea	14	(51.9)	0	0
Fatigue	24	(88.9)	2	(7.4)
Constipation	21	(77.8)	2	(7.4)
Oral Mucositis	3	(11.1)	1	(3.7)
Rash	10	(37.0)	3	(11.1)
Pulmonary fibrosis	3	(10.7)	3	(11.1)
Eye disorders (macular edema)	3	(10.7)	0	0
Edema limbs	6	(22.2)	1	(3.7)
Arthralgia	5	(18.5)	0	0
Myalgia	5	(18.5)	0	0
Nail discoloration	7	(25.9)	0	0

Abbreviations: NA, not applicable.

Figure Legends

Fig. 1
Patient enrollment flowchart. *nab*-PTX, *nab*-paclitaxel; GEM, gemcitabine

Fig. 2
Kaplan-Meier survival plots for patients ≥75 years of age with advanced pancreatic cancer who received *nab*-paclitaxel plus gemcitabine. (a) Progression-free survival (median, 7.0 months; 95% confidence interval [CI], 6.0–8.1 months) and (b) overall survival (median, 10.3 months; 95% CI, 8.2–12.5 months). (c) Progression-free survival and (d) overall survival according to disease stage. The median progression-free and overall survival of patients with stage III disease were 8.1 months (95% CI, 4.4–11.8 months) and not reached, respectively; those of patients with stage IV disease were 7.0 months (95% CI: 5.7–8.4 months) and 9.5 months (95% CI: 7.8–11.2 months), respectively

Figure.1

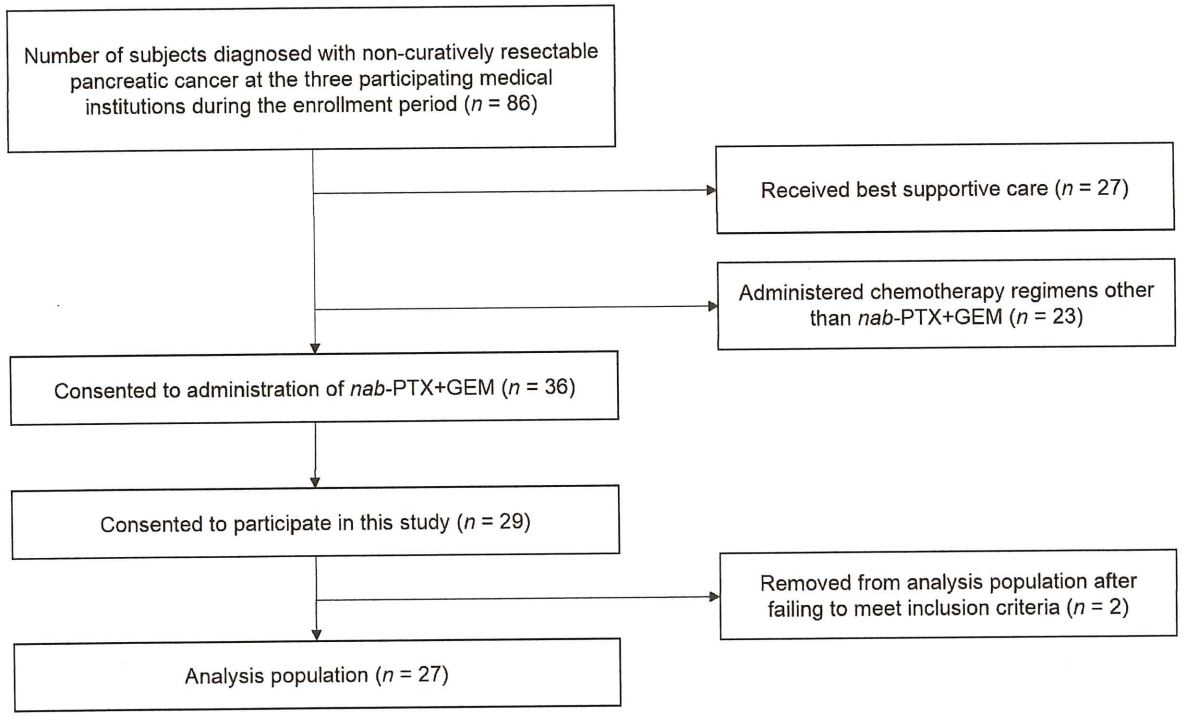
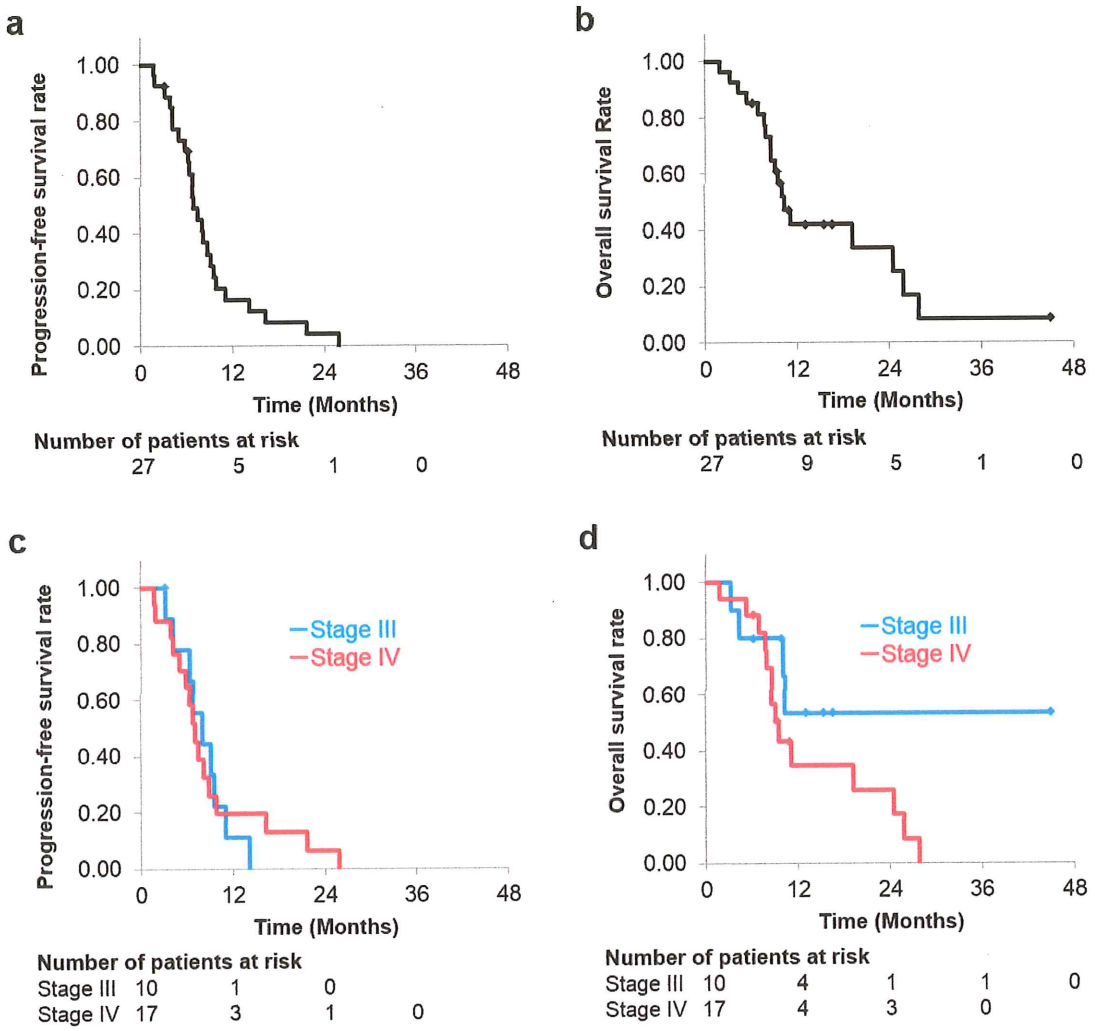


Figure.2


a
Progression-free survival rate
1.00
0.80
0.60
0.40
0.20
0.00
0
12
24
36
48
Time (Months)
Number of patients at risk
27
5
1
0
b
Overall survival Rate
1.00
0.80
0.60
0.40
0.20
0.00
0
12
24
36
48
Time (Months)
Number of patients at risk
27
9
5
1
0
c
Progression-free survival rate
1.00
0.80
0.60
0.40
0.20
0.00
Stage III
Stage IV
0
12
24
36
48
Time (Months)
Number of patients at risk
Stage III 10 1 0
Stage IV 17 3 1 0
d
Overall survival rate
1.00
0.80
0.60
0.40
0.20
0.00
Stage III
Stage IV
0
12
24
36
48
Time (Months)
Number of patients at risk
Stage III 10 4 1 1 0
Stage IV 17 4 3 0

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