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ORIGINAL ARTICLE

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

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Abstract

Background The efficacy and safety of nanoparticle albumin-bound paclitaxel (*nab*-PTX) plus gemcitabine (GEM) in elderly Japanese patients with pancreatic cancer remain unclear. Therefore, we prospectively investigated the tolerability and efficacy of *nab*-PTX + GEM in Japanese patients aged ≥ 75 years with non-curatively resectable pancreatic cancer.

Methods We treated eligible patients ($n = 27$) with *nab*-PTX + GEM until disease progression, appearance of adverse events, or withdrawal of consent. The primary endpoints included adverse events as well as dosing- and survival-related parameters.

Results The rates of 2-cycle completion were 48.1% for *nab*-PTX and 55.6% for GEM; the relative dose intensities for the 7th (median) treatment cycle were 65.1% and 74.1%, respectively, whereas the dose-reduction rates were 81.5% and 48.1%, respectively. Grade 3 or higher hemotoxicity was observed in 14 of 27 subjects (51.9%); moreover, 22% experienced grade ≥ 3 peripheral nerve disorder and 1 patient (3.7%) died owing to chemotherapy-related interstitial pneumonia. The disease control rate was 92.6% (25/27), while the median progression-free and overall survival times were 7 and 10.3 months, respectively.

Conclusion The *nab*-PTX + GEM regimen is as efficacious 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.

Trial registration Clinical trial registration number: UMIN000018907.

Keywords *Nab*-paclitaxel · Gemcitabine · Pancreatic cancer · Chemotherapy · Elderly patients · Clinical trial

Introduction

Despite current advances in medical technology, pancreatic cancer (PC) has a poorer prognosis than most other carcinomas [1, 2]. PC incidence in Japan has increased with the aging population, and approximately half of patients diagnosed with PC in 2011 were 75 years or older [3]. As the number of cancer patients is generally higher among elderly populations, it is often challenging to determine optimal treatment strategies owing to declining organ function and various other aging-related complications.

In a phase III clinical trial of patients with PC, Von Hoff et al. found that nanoparticle albumin-bound paclitaxel (*nab*-PTX) plus gemcitabine (GEM) produced a significantly longer median overall survival (OS; 8.5 months) than GEM alone (6.7 months) [4]. Following a favorable phase I/II clinical trial for the safety and efficacy of *nab*-PTX + GEM in Japan [5], this combination regimen is now widely used. As approximately 10% of the enrollees in Von Hoff et al.'s trial were elderly patients (i.e., aged ≥ 75 years) and 8% of the subjects had Eastern Cooperative Oncology Group (ECOG) performance status (PS) scores of 2, it can be deduced that *nab*-PTX + GEM is relatively well tolerated even among elderly patients. However, Von Hoff et al.'s trial did not enroll any Japanese patients, while the phase I/II clinical

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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 older Japanese patients remain lacking.

Therefore, we conducted a study of Japanese patients aged ≥ 75 years with non-resectable PC to examine the tolerability and efficacy of *nab*-PTX + GEM.

Patients and methods

Patient eligibility

This study was conducted at 3 sites: the Kitasato University Hospital, Kitasato University Medical Center, and Isehara Kyodo Hospital. Patients who were pathologically diagnosed with adenocarcinoma or adenosquamous carcinoma of the pancreas, ineligible for curative resection during the enrollment period (i.e., between September 2015 and June 2018), and 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 or adenosquamous carcinoma, age ≥ 75 years, 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/mm^3, neutrophil count ≥ 1500/mm^3, hemoglobin ≥ 9.0 g/dL, platelets ≥ 100,000/mm^3, 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, history of severe drug hypersensitivity, or severe mental disorder.

Study design and endpoints

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

As this study investigated only elderly patients, it was difficult to predict a final completion rate. Based on previous experiences at the 3 participating facilities, we expected to register 25 patients during the enrollment period. The 95% confidence intervals (CIs) for the completion of 2 cycles of treatment by 14 (56%), 16 (64%), 18 (72%), and 20 (80%) of these 25 potential 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 register provided they did so during the enrollment period.

All enrolled patients provided written informed consent for participation in the study, which was approved in advance by our Institutional Review Board from the standpoints of its ethical, scientific, and medical validity. The study was registered at the University Hospital Medical Information Network (https://www.umin.ac.jp—UMIN000018907).

Treatment

Eligible patients were administered a 30-min intravenous infusion of *nab*-PTX at a dose of 125 mg/m^2, followed by a 30-min intravenous infusion of GEM at a dose of 1000 mg/m^2, on days 1, 8, and 15 every 4 weeks. Dosing criteria, dose adjustments, treatment delays, and dose-reduction criteria were in accordance with the aforementioned phase I/II clinical study performed in Japan.[5] To administer this treatment regimen safely to elderly patients with PC, we subclassified the patients in the previous 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 500–1000/mm^3 or a platelet count of 50,000–74,999/mm^3 on day 8 resulted in a dose decrease to the next lower level. However, in our study, we subdivided the day 8 criteria into ANC ≥ 1000/mm^3/platelet count 50,000–74,999/mm^3, and ANC 500–999/mm^3/platelet count ≥ 50,000/mm^3; 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 if deemed necessary for any reason even if a patient did not meet the dose-reduction criteria. The dose was reduced to 100 or 75 mg/m^2 for *nab*-PTX and to 800 or 600 mg/m^2 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

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 > 1000 and platelets ≥ 75,000	Full dose	ANC ≥ 1000 and platelets ≥ 75,000	Full dose
		ANC ≥ 1000 and platelets 50,000–74,999	Full dose
		ANC < 500 or platelets < 50,000	Skip
ANC ≥ 1000 and platelets 50,000–74,999	Decrease to next lower level	ANC ≥ 1000 and platelets ≥ 75,000	Restore to day 1 dosing level
		ANC ≥ 1000 and platelets 50,000–74,999	Administer at day 8 dosing level
		ANC < 500 or platelets < 50,000	Skip
ANC 500–999 and platelets ≥ 50,000	Skip	ANC ≥ 1000 and platelets ≥ 75,000	Full dose
		ANC ≥ 1000 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 ≥ 1000 and platelets ≥ 75,000	Decrease to next lower level
		ANC ≥ 1000 and platelets 50,000–74,999	Decrease to next lower level
		ANC < 500 or platelets < 50,000	Skip

nab-PTX, nanoparticle albumin-bound paclitaxel; GEM, gemcitabine; ANC, absolute neutrophil count

Terminology Criteria for Adverse Events (version 4.0) were 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 intervals between the date of registration and that of progression and of death from any cause, respectively. Categorical variables were statistically analyzed using Fisher's exact test and analyses were performed using SPSS Base 17.0 (SPSS Inc., Chicago, IL, USA) software.

Results

Patient characteristics

Eighty-six subjects aged ≥ 75 years received a pathological diagnosis of non-resectable PC between September 2015 and June 2018 (Fig. 1). 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, 63.0% of the subjects were male, 29.6% had PS scores of 1, overall history of anticoagulant drug use was 18.5%, the median score of the G8 screening tool was 12.5 points, and median psoas muscle mass index scores were 5.0 points in males and 3.9 in females. Metastatic lesions were most common in the liver (33.3%) followed by the lung (25.9%).

Feasibility of the nab-PTX + GEM regimen

Treatment features of the administered regimen are shown in Table 3. During the observation period that continued until December 31, 2018, a median of 7.0 (range 1–23) cycles of treatments was 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

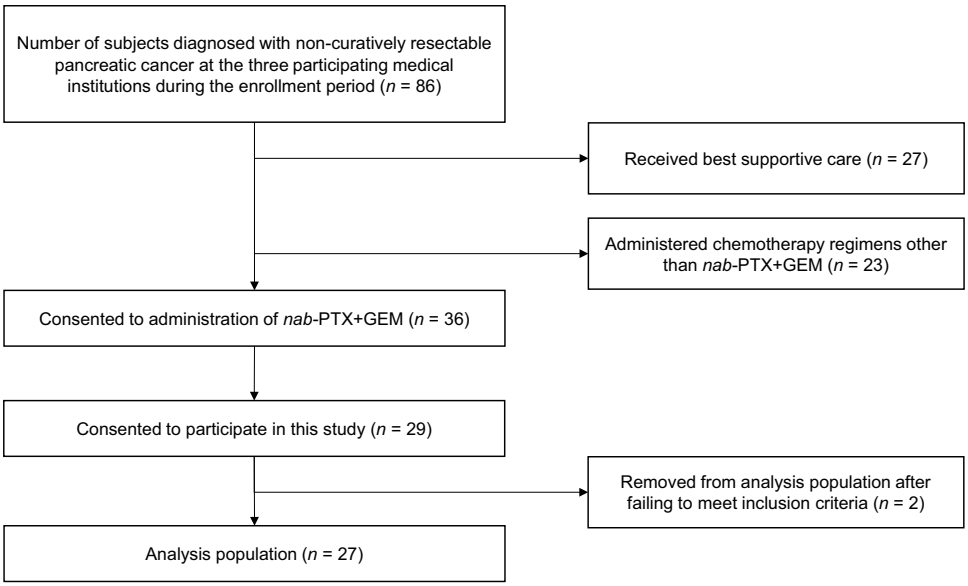

Fig. 1 Patient enrollment flowchart. *nab*-PTX, nanoparticle albumin-bound paclitaxel; *GEM* gemcitabine

non-hemotoxic adverse events occurred in 16 (59.3%), with peripheral nerve disorder being the most common in the latter category (22.2%). 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: 1.8–44.2 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 (Fig. 2a, b.). The treatment outcomes 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 an OS of 9.5 months (95% CI: 7.8–11.2 months) for those with stage IV (Fig. 2c, d).

Discussion

This clinical study aimed to examine the tolerability and efficacy of *nab*-PTX + GEM in elderly patients with PC via prospective observation from time of treatment initiation. Despite lower than anticipated 2-cycle chemotherapy completion rates, relatively high RDIs levels were maintained. 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]. While our RDIs were similar to those reported by Blomstrand et al., they were lower than those found in the other two studies due to a number of possible reasons. First, despite our inclusion criteria being the same as those for the phase I/II study (other than age), dose adjustments and reductions criteria were more stringent than what other studies used 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, treatments were resumed at the previous dose at the start of the subsequent cycle if patients met the dosing criteria; however, very few subjects in our study resumed their original dose following reduction. Third, dose reduction was permitted for any reason in our study, even if the patient did not meet the dose-reduction criteria, if the physician deemed it necessary. 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 similar to those of our study (58.1%), grade 2 or higher non-hemotoxic adverse events occurred in 61.6% of patients in contrast to the higher rate

Table 2 Patient characteristics

Demographic	
Median age in years [range]	77 [75–85]
Sex, *n* (%)	
Male	17 (63.0)
Female	10 (37.0)
ECOG PS score, *n* (%)	
0	19 (70.4)
1	8 (29.6)
History of anticoagulant use, *n* (%)	5 (18.5)
G8 screening tool, median, [range]	12.5 [6–17]
> 14, *n* (%)	4 (14.8)
≤ 14, *n* (%)	23 (85.2)
Psoas muscle mass index, median, cm^2/m^2 [range]	
All	4.6 [1.9–7.1]
Male	5.0 [1.9–7.1]
≥ 6.36, *n* (%)	2 (10.5)
< 6.35, *n* (%)	17 (89.5)
Female	3.9 [2.8–5.1]
≥ 3.92, *n* (%)	5 (50)
< 3.91, *n* (%)	5 (50)
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]

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*-PTX plus GEM 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	51.9

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

Table 4 Adverse events

	Any grade *n* (%)	Grades ≥ 3 *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)
Interstitial pneumonia	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)

NA not applicable

in our study (88.9%). These data collectively imply that care is required to avoid non-hemotoxic adverse events when treating elderly patients with *nab*-PTX + GEM. In addition, 74.1% (20/27) of cases were below the sarcopenia cut-off value in elderly patients proposed by Hamaguchi et al. [9] at the time of pre-chemotherapy. Non-hematological toxicity (grades ≥ 3)-associated adverse events occurred in 14% (1/7) of non-sarcopenia and 65% (13/20) of sarcopenia cases. Sarcopenia patients had a significantly higher incidence of non-hematological toxicity when compared to non-sarcopenia patients. However, to further assess psoas muscle index utility, additional multicenter prospective studies are required to evaluate differences in adverse event rates between non-sarcopenia and sarcopenia cases, since the current clinical trial had

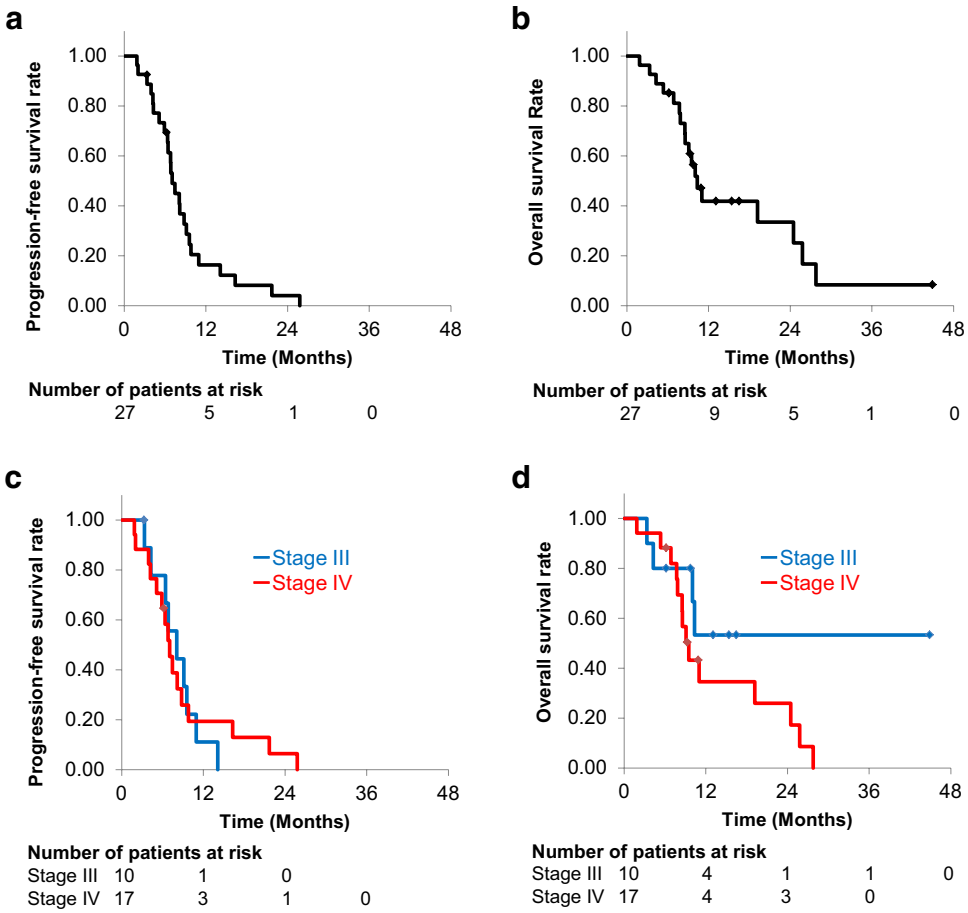

Fig. 2 Kaplan–Meier survival plots for elderly patients with advanced pancreatic cancer. Patients ≥ 75 years of age were treated with nanoparticle albumin-bound paclitaxel plus gemcitabine. **a** Progression-free survival [median 7.0 months; 95% confidence interval (CI) 6.0–8.1 months] and **b** overall 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

a relatively small sample size. One of the three subjects who developed chemotherapy-related interstitial pneumonia in our study failed to improve despite corticosteroid treatment, and ultimately experienced respiratory failure leading to death. Incidence rates of interstitial pneumonia in prospective studies conducted thus far are 3–4% [4, 5]; hence, the occurrence of this adverse event was expected. Furthermore, Ogawa et al. reported that 5 of their 26 subjects (19.2%) treated with *nab*-PTX + GEM developed interstitial pneumonia [10]. In the GEST study, the GEM and GEM + S-1 groups each had one subject who experienced chemotherapy-related death due to interstitial pneumonia [11], indicating 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 deteriorated lung reserve capacity; however, this was difficult to determine among our patients and should be investigated in future large-scale studies. Excluding the two remaining patients who developed interstitial pneumonia, only one other subject discontinued treatment upon request after developing grade 2 anorexia. The remaining 23 subjects (85%) showed no adverse events that met discontinuation criteria after undergoing any necessary dose adjustments or reductions; 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 [12]. However, to administer such an intense regimen to elderly patients, there is an urgent need to develop pre-therapy indicators that can predict adverse event likelihoods. The patient who experienced chemotherapy-related death in our study was 77 years old, had a PS score of 0, psoas muscle mass index of 3.81, and 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” [13], 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 conducting the "GrantPax" multicenter, open label phase IV interventional trial with elderly patients with PC 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 [14] and aims to develop a reliable method to objectively identify the effects of this regimen in elderly patients allowing for personalized treatments.

With respect to efficacy, the DCR and PFS rates 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). Importantly, our cohort included 10 subjects (37.1%) with locally advanced PC; 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 97.0% of subjects in that study were able to switch to secondary treatments compared to only 48.2% of the subjects in our study. Nevertheless, the main observation in our study was that *nab*-PTX + GEM can delay the progression of advanced PC in elderly patients similar to non-elderly patients. Similarly, Jin et al. reported that *nab*-PTX + GEM significantly improved the OS of elderly pancreatic cancer patients [15].

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 elderly patients who have lower organ function status.

In conclusion, 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.

Author contributions KO designed the study. RH and KO were major contributors in writing the manuscript. MK, HY, TI, and HI contributed to analysis and interpretation of data and assisted in the preparation of the manuscript. All other authors have contributed to data collection and interpretation, and critically reviewed the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval All procedures performed in studies involving human participants were 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.

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