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ORIGINAL ARTICLE

The efficacy and safety of nab paclitaxel plus gemcitabine in elderly patients over 75 years with unresectable pancreatic cancer compared with younger patients

Utako Ishimoto[1] · Akiyoshi Kinoshita[1] · Yuki Hirose[1] · Keiko Shibata[1] · Ayako Ishii[1] · Ryo Shoji[1] · Takeharu Yokota[1] · Akira Iwaku[1] · Yusuke Mizuno[1] · Kazuhiko Koike[1] · Masayuki Saruta[2]

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Abstract

Purpose To evaluate the efficacy and safety of nab paclitaxel (nab-P) plus gemcitabine (GEM) in elderly patients ≥ 75 years old with unresectable pancreatic cancer (PC) compared with younger patients.

Methods The data of 27 unresectable PC patients treated with nab-P plus GEM as first-line chemotherapy were retrospectively analyzed. The patients were divided into two groups according to their age at inclusion: an elderly group (9 patients ≥ 75 years old) and a younger group (18 patients <75 years old). We compared the disease control rate, median overall survival (OS), and adverse events (AEs) between the two groups. Predictive factors for the OS were also evaluated.

Results The clinical characteristics of patients of the two groups were not significantly different except for the age. The respective values for the disease control rate (66.7% vs. 77.8%, $P = 0.542$) and median OS (277 days vs. 312 days, $P = 0.722$) were also not significantly different between the elderly and younger group, although the relative dose intensity of GEM/nab-P in the elderly group (56.6%/53.1%) was significantly lower than that in the younger group (67.3%/63.1%) ($P = 0.016/0.04$). The absence of biliary drainage and CEA ≥ 6.5 were found to be poor prognostic factors in a multivariate analysis. The most common grade ≥ 3 AE was neutropenia (44% in both groups). No significant differences in the frequency of all AEs were observed between the two groups.

Conclusions Nab-P plus GEM appears effective and well-tolerated for elderly patients ≥ 75 years old with unresectable PC.

Keywords Pancreatic cancer · Elderly · Nab paclitaxel · Gemcitabine

Introduction

The average global life expectancy increased dramatically in the twentieth century, and roughly 60% of new cases and 70% of mortalities from cancer occur in patients over 65 years of age [1]. Thus, the care of elderly patients with cancer, including those with pancreatic cancer (PC), has become an important part of global healthcare.

Japan has the greatest life expectancy in the world, at 81.09 years for men and 87.26 for women. Elderly people ≥ 75 years of age account for 12.3% of the total population in Japan [2]. PC is a highly lethal malignancy, and in Japan, about 31,716 patients are newly diagnosed each year. The incidence rates of the PC have increased rapidly over the past decade, and it is now the fourth leading cause of cancer-related mortality in Japan after lung cancer, gastric cancer, and colon cancer. The number of deaths due to PC was 17,060 in men and 16,415 in women in Japan in 2014 [3]. Surgical resection is the only curative treatment for PC. However, only approximately 15–20% of patients are candidates for surgery, since 80–85% of PC patients have metastatic or locally advanced disease at the diagnosis [4]. Palliative treatments, such as chemotherapy and/or radiation, are indicated for these patients. Therefore, opportunities to treat elderly PC patients with chemotherapy have increased in Japan.

✉ Akiyoshi Kinoshita
aki.kino@jikei.ac.jp

[1] Division of Gastroenterology and Hepatology, The Jikei University Daisan Hospital, 4-11-1 Izumihon-cho, Komae-shi, Tokyo 201-8601, Japan

[2] Division of Gastroenterology and Hepatology, Department of Internal Medicine, the Jikei University School of Medicine, 3-25-8 Nishishinbashi, Minato-ku, Tokyo 105-8461, Japan

Generally, a decline in functional, biological, and physiological characteristics and more comorbidities due to aging can limit elderly patients' ability to tolerate chemotherapy. Despite the high incidence of cancer in elderly patients, they have been underrepresented in clinical trials for standard treatment in oncology practice. Thus, few data exist regarding the risks and benefits of chemotherapy in elderly patients.

Gemcitabine (GEM) has been the standard chemotherapy for the first-line treatment of unresectable locally advanced or metastatic PC [5]. The phase III MPACT trial in patients with metastatic PC showed that nab paclitaxel (nab-P) plus GEM significantly improved the overall survival (OS) (8.7 months vs. 6.6 months), progression-free survival (PFS) (5.5 months vs. 3.7 months), and response rate (23% vs. 7%) compared with placebo [6]. Although elderly PC patients ≥ 75 years of age were eligible for inclusion in the MPACT trial, the efficacy and feasibility of nab-P plus GEM for elderly PC patients ≥ 75 years of age is poorly understood.

Therefore, in this study, we evaluated the efficacy and safety of nab-P plus GEM in elderly patients ≥ 75 years of age with unresectable PC and conducted a comparison with younger patients.

Methods

Patients

Between June 2015 and June 2018, 27, unresectable PC patients treated with nab-P plus GEM as first-line chemotherapy at The Jikei University Daisan Hospital were enrolled in this study. Medical records of patients were retrospectively analyzed. The chronological age of 60 or 65 years is accepted as the definition of an elderly person in many countries. However, in 2017, the Japan Geriatrics Society defined the elderly as those ≥ 75 years of age. Therefore, in this study the patients were divided into two groups according to their age at inclusion: elderly group (≥ 75 years old; 9 patients) and a younger group (< 75 years old; 18 patients).

The diagnosis of PC was confirmed using computed tomography (CT) or magnetic resonance imaging (MRI). Tumor-related factors, such as the primary tumor site (head, body or tail) and progression of the disease (locally advanced or metastatic), were also assessed by imaging.

This study was performed in accordance with the standards of the Declaration of Helsinki and was approved by the institutional ethics board. Written informed consent for participation in this study was not obtained from the patients because this study was not designed to be a clinical trial and the data were collected retrospectively and analyzed anonymously.

Data analyses

Charts and electronic records of patients were reviewed retrospectively for the clinical patient characteristics, OS, and PFS. The tumor response was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria [7] by means of CT or/and MRI.

The OS was defined from day 1 of nab-P plus GEM chemotherapy to the time of patient death or the last follow-up visit. The PFS was defined from day 1 of nab-P plus GEM chemotherapy to the time of evident progression of disease based on the RECIST 1.1 criteria or an acceptable level of adverse events (AEs).

Toxicity severity was graded using the National Cancer Institute Common Toxicity Criteria for Adverse Events version 4 [8]. Relative dose intensity (RDI) is used to describe the proportion of chemotherapy administered to patients to the regimen-directed course of therapy. The RDI was calculated for each single chemotherapeutic agent and for chemotherapy regimens in total.

Factors included in the univariate analyses for OS were the following: age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS), diabetes mellitus history, primary tumor site, tumor size, RDI, and pretreatment laboratory tests, including white blood cell count (WBC), neutrophil count (Neu), hemoglobin concentration (Hb), platelet count (PLT), and serum levels of albumin (Alb), lactate dehydrogenase (LDH), total bilirubin (T-bil), alkaline phosphatase (ALP), C-reactive protein (CRP), carbohydrate antigen 19-9 (CA 19-9), and carcinoembryonic antigen (CEA), hemoglobin A1c (HbA1c), and Charlson Comorbidity Index (CCI).

Treatment and patient follow-up

The diagnosis of unresectable PC was made based on patient-associated factors (poor medical condition or unable to undergo a major operation, or patient refusal to undergo surgical resection) and tumor-associated factors (presence of remote metastasis or major vascular invasion [main portal vein, hepatic artery, celiac artery or superior mesenteric artery]).

The patients were treated with nab-P (125 mg/m^2) plus GEM (1000 mg/m^2). Patients received the chemotherapy until disease progression.

The patient eligibility criteria of the phase III MPACT trial were described previously [9]. The eligibility criteria for chemotherapy were as follows: ≥ 18 years of age and an adequate hematologic, hepatic, and renal function (including an absolute neutrophil count of ≥ 1500/mm^3, platelet count ≥ 10,000/mm^3, hemoglobin level ≥ 9 g/dL,

bilirubin level less than or equal to the upper limit of the normal range × 1.25, aspartate aminotransferase level below the upper limit of the normal range × 1.25, alanine aminotransferase level below the upper limit of the normal range × 1.25, serum creatine level ≤ 1.5 mg/dL).

Percutaneous transhepatic or endoscopic retrograde biliary drainage was performed before starting the initial treatment in patients with obstructive jaundice.

The patients were followed carefully after the initial treatment, including by imaging and tumor marker monitoring. For the patients who showed tumor progression, palliative chemotherapy or best supportive care was provided. The start date of the follow-up was set as the date of the initial diagnosis of PC. The end date of the follow-up was set as the final follow-up in June 2018 or at the time of the patient's death.

Statistical analyses

Comparisons between the two groups were performed using the Mann–Whitney *U* test for continuous and ordinal variables and the χ^2 test for categorical variables. OS and PFS curves were generated using the Kaplan–Meier method, and differences in the survival rates between the groups were compared by the log-rank test. The Cox proportional hazard model was used to estimate hazard ratios (HRs) of potential prognostic factors for the OS. Variables with a *P* value ≤ 0.5 in the univariate analysis were subsequently included in the multivariate analysis. The cutoff value of continuous variables was determined based on the median value. A two-sided $P < 0.05$ was considered statistically significant. All statistical analyses were performed using the IBM SPSS Statistics software program, version 19.0 IBM company.

Results

Patient characteristics

Baseline patient characteristics are listed in Table 1. The median age in the elderly group was 77 years old (range 75–84 years), and that of the younger group was 66 years old (range 44–74 years) ($P < 0.0001$). There were no significant differences between the two groups with regard to sex, PS, history of diabetes mellitus, number of metastatic sites, sites of metastases (liver, lung, peritoneum), tumor location (head, body, tail), biliary intervention, CCI, or values of WBC, Neu, Hb, PLT, Alb, LDH, ALP,CRP, CA19-9, CEA, or HbA1c. Tumors tended to be located at the pancreatic head rather than in the body or tail in both groups. The prevalence of a CCI ≥ 2 was low in both groups.

Treatment exposure, response rate and tumor control rate

The proportion of patients treated with GEM at 1000 mg/m^2 was 67.3% (range 40.0–92.3%) in the younger group and 56.6% (range 33.3–72.4%) in the elderly group ($P = 0.016$). The proportion of patients treated with nab-P at 125 mg / m^2 was 63.1% (range 29.3–86.5%) in the younger group and 53.1% (range 31.3–66.8%) in the elderly group ($P = 0.04$). The applied doses were significantly higher in the younger group than in the elderly group.

The median treatment duration to progression was 104 days (range 56–427 days) in the younger group and 85 days (range 28–257 days) in the elderly group ($P = 0.225$) (Table 2).

Seven patients in the elderly group had one dose reduction of nab-P and GEM from the first day. The remaining two patients started with a full dose and had one dose reduction after 8 days because of AEs.

No patient had a complete response in either group. The rate of partial response was 3 (16.7%) in the younger group and 0 (0%) in the elderly group ($P = 0.202$). The rate of stable disease was 11 (61.1%) in the younger group and 6 (66.7%) in the elderly group ($P = 0.782$). The rate of progressive disease was 4 (8.3%) in the younger group and 3 (33.3%) in the elderly group ($P = 0.542$), resulting in a disease control rate (DCR) of 77.8% in the younger group and 66.7% in the elderly group ($P = 0.542$).

Survival distribution

There was no significant difference in the OS between the 2 groups: 312 days in the younger group (95% confidence interval [CI] 56.8–567.1) and 277 days in the elderly group (95% CI 0.00–573.2) ($P = 0.722$) (Fig. 1).

Prognostic factors

The results of the univariate and multivariate analyses are shown in Table 3. The univariate analysis indicated that the presence of biliary drainage ($P = 0.027$) and CEA ≥ 6.5 ng/mL ($P = 0.002$) were significantly associated with a poor prognosis. A multivariate analysis showed that the presence of biliary drainage (hazard ratio [HR] 0.266; 95% CI 0.083–0.858, $P = 0.027$) and CEA ≥ 6.5 ng/mL (HR 7.950; 95% CI 2.183–28.948, $P = 0.002$) remained significantly associated with the prognosis.

Safety

The AEs are shown in Table 4. The most common grade ≥ 3 AE was neutropenia (44% [8/18] in the younger group vs. 44% [4/9] in the elderly group). The

Table 1 Baseline characteristics of patients

Variable	*N*, younger ($n=18$)	*N*, elderly ($n=9$)	*P*
Median age, years (range)	66 (44–74)	77 (75–84)	**< 0.0001**
Sex			
Male/female	11/7	4/5	0.448
PS			
0/1	10/8	4/5	0.695
DM			
Yes/no	11/7	2/7	0.667
Number of metastatic sites			
0/1/2/≥3	3/7/4/4	4/1/1/3	0.258
Sites of metastases			
Liver	10	3	
Lung	4	2	
Peritoneum	5	1	0.791
Pancreatic tumor location			
Head	10	6	
Body	4	2	
Tail	4	1	0.769
Biliary drainage			
Yes	6	4	
No	12	5	0.683
Charlson comorbidity index			
≥2	6	1	
<1	12	8	0.363
WBC /mm^3 (range)	6450 (5200–16,200)	4800 (4100–11,800)	0.268
Neu /mm^3 (range)	4300 (2900–12,200)	3000 (2800–9500)	0.661
Hb g/dL (range)	12.8 (9.0–15.3)	12.9 (7.0–13.8)	0.328
PLT /mm^3 (range)	25.5 (16.9–42.7)	24.0 (10.7–38.1)	0.504
Alb g/mL (range)	3.8 (3.0–4.2)	3.6 (2.6–4.4)	0.641
LDH IU/L (range)	201 (140–948)	214 (155–363)	0.165
T-bil mg/dL (range)	0.75 (0.2–13.7)	1.6 (0.5–10.6)	0.648
ALP IU/L (range)	604 (160–2976)	779 (152–1837)	0.607
CRP mg/dL (range)	0.39 (0.04–7.9)	0.4 (0.04–9.7)	0.680
CA 19-9 U/mL (range)	990 (43–10,027)	333 (20–16,205)	0.662
CEA ng/mL (range)	8.05 (1.3–15,802.5)	5.2 (1.9–48.7)	0.217
HbA1c % (range)	6.3 (5.2–11.4)	6.3 (5.2–10.4)	0.641

Table 2 Treatment exposure and efficacy

Variable	*N*, younger ($n=18$)	*N*, older ($n=9$)	*P*
GEM relative dose intensity			
Median, % (range)	67.3% (40.0–92.3%)	56.6% (33.3–72.4%)	**0.016**
Nab-P relative dose intensity			
Median, % (range)	63.1% (29.33–86.5%)	53.1% (31.3–66.8%)	**0.04**
Treatment duration			
Median, days (range)	104 (56–427)	85 (28–257)	0.225
Over response rate			
Complete response	0	0	–
Partial response	3 (16.7%)	0	0.202
Stable disease	11 (61.1%)	6 (66.7%)	0.782
Progressive disease	4 (8.3%)	3 (33.3%)	0.542
Disease control rate	14 (77.8%)	6 (66.7%)	0.542

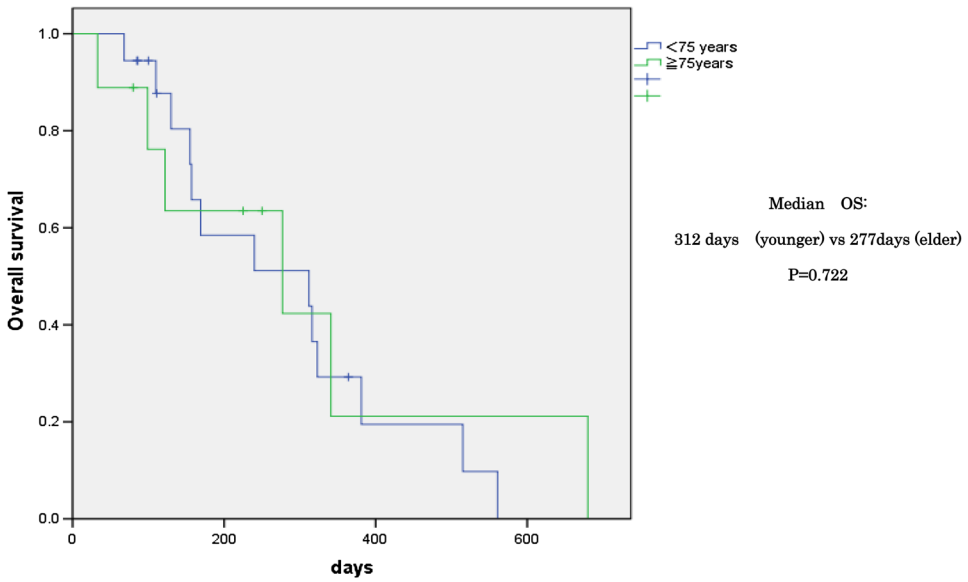

Fig. 1 Kaplan–Meier analysis of overall survival in elderly patients and younger patients. There was no significant difference in the OS between the elderly group and the younger group ($P = 0.722$)

Table 3 Prognostic factors for the overall survival identified by the univariate and multivariate analyses

Variable	Univariate analysis	Multivariate analysis
Age ≥ 75 years	$P = 0.692$	
Sex (male/female)	$P = 0.670$	
Diabetes mellitus (absent/present)	$P = 0.286$	
Number of metastases (0/1/2/3/4/5)	$P = 0.051$	
Biliary drainage (absent/present)	***P* = 0.027**	(HR 0.266; 95% CI 0.083–0.858, $P = 0.027$)
ECOG performance status	$P = 0.546$	
Primary tumor location (head/body/tail)	$P = 0.118$	
tumor size ≥ 40.0 mm	$P = 0.787$	
RDI (GEM) ≥ 65.50%	$P = 0.984$	
RDI (nab-PTX) ≥ 63.55%	$P = 0.984$	
White blood cell count ≥ 6400/mm^3	$P = 0.095$	
Neutrophil count ≥ 4300/mm^3	$P = 0.180$	
NLR ≥ 3.4	$P = 0.271$	
Hemoglobin concentration ≥ 12.9 g/dL	$P = 0.688$	
Platelet count ≥ 25.7/mm^3	$P = 0.311$	
Alb ≥ 3.7 g/mL	$P = 0.439$	
LDH ≥ 205 IU/L	$P = 0.406$	
T-bil ≥ 0.8 mg/dL	$P = 0.064$	
ALP ≥ 637 IU/L	$P = 0.188$	
CRP ≥ 0.4 mg/dL	$P = 0.818$	
CEA ≥ 6.5 ng/mL	***P* = 0.002**	(HR 7.950; 95% CI 2.183–28.948, $P = 0.002$)
CA19-9 ≥ 655 U/mL	$P = 0.731$	
HbA1c ≥ 6.3%	$P = 0.633$	
Charlson Comorbidity Index ≥ 2	$P = 0.645$	

frequency of peripheral neuropathy of grade ≥ 3 was higher in the elderly group than in the younger group (5% [1/18] in the younger group vs. 44% [2/9] in the elderly group) ($P = 0.194$). The incidences of neutropenia, thrombocytopenia, anemia, diarrhea, appetite loss, and interstitial pneumonia were similar between the two groups.

Table 4 Adverse events in patients treated until disease progression

	Younger group, *N* (%)		Elderly group, *N* (%)		*P*	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Neutropenia	9 (50)	8 (44)	5 (56)	4 (44)	0.785	1.00
Thrombocytopenia	13 (72)	2 (11)	5 (56)	2 (22)	0.386	0.444
Anemia	12 (66)	5 (28)	5 (56)	1 (11)	0.573	0.326
Peripheral neuropathy	2 (11)	1 (5)	2 (22)	2 (22)	0.444	0.194
Diarrhea	1 (5)	0	1 (11)	0	0.603	–
Appetite loss	2 (11)	0	1 (11)	0	1	–
Interstitial pneumonia	2 (11)	2 (11)	0	0	0.299	0.299
Other	2 (11)	0	2 (22)	0	0.444	–

Discussion

In the current study, we showed that there were no significant differences in the DCR or OS rates between elderly PC patients and younger PC patients treated with GEM and nab-P not indicated for surgical resection. Palliative chemotherapy has been shown to prolong survival in elderly patients with advanced PC. A multicenter study from Japan showed that elderly PC patients treated with chemotherapy, including GEM only, GEM plus S-1, S-1 only, and 5-fluorouracil, had a significantly longer median OS than those choosing best supportive care [10]. Investigators from Belgium also reported that the toxicity and efficacy of GEM-based chemotherapy in PC patients ≥ 70 years of age were similar to those < 70 years of age [11]. Furthermore, a recent meta-analysis of six randomized controlled trials demonstrated that nab-P plus GEM significantly improved the PFS in elderly PC patients in comparison with GEM alone [12].

The phase III MPACT trial did not set a cutoff age for inclusion. Therefore, the phase III trial included at least 10% of the patients ≥ 75 years of age [6]. The subgroup analysis from the MPACT trial showed that both younger (< 65 years) and elderly (≥ 65 years) patients experienced a treatment benefit compared with GEM alone. However, the HR for the OS of the younger patients was slightly lower than that of the elderly patients (HR 0.65 vs. 0.85), suggesting that the magnitude of the treatment effect was smaller in elderly patients [13, 14]. Furthermore, elderly patients have more comorbidities, such as cardiovascular, liver dysfunction, and renal dysfunction, than younger patients. Therefore, elderly patients are able to have severe adverse events.

In the present study, the clinical characteristics of patients were not significantly different between the elderly and younger groups, except for the age. Although the dose intensity of both GEM and nab-P was significantly lower in the elderly group than in the younger group, the treatment duration was similar between the two groups. The DCR and OS rates were also comparable between the two groups. In our study, the applied doses of both nab-P and GEM were significantly lower in the elderly group than in the younger group. Seven patients in the elderly group had one dose reduction of nab-P and GEM from the first day. The remaining two patients started with a full dose and had one dose reduction after 8 days because of AEs. The definition of 'adequate applied dose' in elderly patients has not been clearly determined. However, a subgroup analysis of the MPACT trial showed that 41% of patients had a nab-P reduction, 71% had a nab-P dose delay, 47% had a GEM reduction, and 70% had a GEM dose delay. The main reasons for dose reductions and delays were side effects, such as neutropenia, peripheral neuropathy, thrombocytopenia, and fatigue [15]. In elderly patients, it is expected that the functional decline of organs and comorbidities with age may increase the toxicity [16]. This may explain why seven patients in the elderly group required one dose reduction of nab-P and GEM from the first day. The similar incidences of AEs between the two groups in our study may be attributed to the dose reduction in the elderly group, leading to favorable DCR and OS rates in the elderly group.

Dose reductions and delays are standard methods of ameliorating the toxic effects of chemotherapy. A relationship has been reported between the dose intensity and efficacy. An exploratory analysis from the MPACT trial indicated that patients who received dose reductions or delays of nab-P had a greater extent of treatment exposure than those who did not in terms of the treatment duration, number of cycles, and cumulative dose of nab-P received. Furthermore, both dose reductions and delays were found to be significantly associated with a longer OS in patients receiving nab-P plus GEM chemotherapy. Dose reductions and delays in the present study were performed due to AEs, such as neutropenia, thrombocytopenia, and peripheral neuropathy [15].

Given that elderly patients show a psychosocial, functional, and biological decline compared to younger patient [17], it is particularly important for these patients to be able to continue chemotherapy with few side effects. Elderly patients, therefore, tend to require dose modifications. A retrospective study showed that a modified regimen of biweekly GEM with nab-P, given on days 1 and 15 of a 28-day cycle, resulted in a favorable median OS (10 months)

and acceptable toxicity compared with the findings of the MPACT trial [18, 19].

In the current study, the absence of biliary drainage and CEA ≥ 6.5 ng/mL were poor prognostic factors according to a multivariate analysis. Several factors, including an increased neutrophil–lymphocyte ratio (NLR), high ECOG PS score, the presence of distant metastasis, and elevated CEA and CA19-9 levels, have been reported to be poor prognostic factors in patients with advanced PC receiving systematic chemotherapy [20–25]. In the setting of metastatic PC treated with nab-P plus GEM, the CA 19-9 level, NLR, Karnofsky performance status score (KPS), presence of liver metastases, age, and number of metastatic sites were prognostic factors for the survival [26, 27].

In the present study, 9 (5 younger patients and 4 elderly patients) in 10 patients who underwent biliary drainage had pancreatic head cancer. In contrast, the 10 (7 younger patients and 3 elderly patients) in 17 patients without biliary drainage had pancreatic body or tail cancer. These differences in tumor location with or without biliary drainage may have affected the survival outcome in our study. Several studies have shown that the OS rates of patients with pancreatic body or tail cancer were significantly worse than those of patients with pancreatic head cancer. A population-based study in the United States reported that the overall 3-year survival rate for patients with pancreatic head cancer was 5.3% (95% CI 5.1–5.5%), while that for patients with pancreatic body or tail cancer was 3.4% (95% CI 3.0–3.8%). Patients with pancreatic head cancer had a 4% lower mortality risk than those with pancreatic body or tail cancer ($P = 0.0005$) [28]. A recent study from the Netherlands also showed that, for PC patients with distant metastases, the median OS was 2.6 months for cancer of the head, 2.4 months for cancer of the body, and 1.9 months for cancer of the tail [29]. One possible reason why PC patients with pancreatic body or tail cancer had a higher mortality than those with pancreatic head cancer is because patients with pancreatic body or tail cancer lack early clinical symptoms, such as obstructive jaundice or pain.

In this study, elevated CEA levels before treatment were associated with a poor prognosis. Several studies have shown not only elevated CEA levels but also elevated CA19-9 levels to be poor prognostic factors for PC patients. Furthermore, CA 19-9 exhibits higher sensitivity than CA 19-9, while no significant differences were noted for the specificity [21, 23, 30, 31]. Using the combination of CEA and CA19-9 levels for prognosis predictions may be useful.

Several limitations associated with the present study warrant mention, including its retrospective design, single-institution setting, and small number of patients. We set the median value as the cutoff point of each variable. There have been debates about the proper definition of optimal cutoff points of variables. These methodological drawbacks may reduce the strength of our statistical conclusions. A phase II trial of nab-P plus GEM as first-line chemotherapy in elderly patients with metastatic PC is ongoing at present (NCT02391662) [32]. In addition, a multicenter phase IV clinical trial assessing the outcomes of elderly PC patients treated with GEM with or without nab-P is also underway [33]. These studies will confirm our findings.

In conclusion, we showed that there were no significant differences in the DCR, AEs, or OS between elderly PC patients and younger PC patients treated with GEM and nab-P who were not indicated for surgical resection. While age had no influence, the absence of biliary drainage and an elevated serum CEA level were found to be independently associated with a poor prognosis. An advanced age itself does not restrict the application of nab-P plus GEM chemotherapy, even in elderly PC patients not indicated for surgical resection. Appropriate dose reduction may improve the treatment feasibility in elderly patients.

Compliance with ethical standards

Conflict of interest The author declares no conflict of interest.

Ethical standards All the 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.

Informed consent Written informed consent for participation in this study was not obtained from the patients because this study was not designed to be a clinical trial and the data were collected retrospectively and analyzed anonymously.

References

1. Noone AM, Howlader N, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds) (2018) SEER cancer statistics review, 1975–2015, National Cancer Institute, Bethesda, MD. https://seer.cancer.gov/archive/csr/1975_2015/. Accessed 1 Feb 2019
2. Vital Statistics Japan (Ministry of Health, Labour and Welfare). https://www.mhlw.go.jp/english/database/db-hw/vs01.html. Accessed 1 Feb 2019
3. Cancer Registry and Statistics. Cancer Information Service, National Cancer Center, Japan. https://ganjoho.jp/en/professional/statistics/brochure/2017_en.html. Accessed 1 Feb 2019
4. Kuroda T, Kumagi T, Yokota T et al (2013) on behalf of the EPOCH Study Group. Improvement of long-term outcomes in pancreatic cancer and its associated factors within the gemcitabine era: a collaborative retrospective multicenter clinical review of 1,082 patients. BMC Gastroenterol 13:134. https://doi.org/10.1186/1471-230X-13-134
5. Burris HA 3rd et al (1997) Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 15(6):2403–2413

6. Von Hoff DD et al (2013) Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 369(18):1691–1703
7. Therasse P, Arbuck SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92:205–216
8. U.S. Department of Health and Human Services. National Institutes of Health. National Cancer Institute (2009) Common Toxicity Criteria for Adverse Events (version 4)
9. Von Hoff DD, Ervin T, Arena FP et al (2013) Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 369:1691–1703
10. Kuroda T, Kumagi T, Yokota T et al (2017) Efficacy of chemotherapy in elderly patients with unresectable pancreatic cancer: a multicenter review of 895 patients. BMC Gastroenterol 17:66
11. Marechal R, Demols A, Gay F et al (2008) Tolerance and efficacy of gemcitabine and gemcitabine-based regimens in elderly patients with advanced pancreatic cancer. Pancreas 36(3):e16–e21
12. Jin J, Teng C, Li T et al (2018) Combination therapy versus gemcitabine monotherapy in the treatment of elderly pancreatic cancer: a meta-analysis of randomized controlled trials. Drug Desi Dev Ther 12:475–480
13. Goldstein D, EI-Hassan R, Heinemann V et al (2015) Nab-paclitaxel plus gemcitabine for metastatic pancreatic cancer: long-term survival from a phase III trial. J Natl Cancer Inst 107(2):dju413
14. Gwenalyn G, Odaimi M (2017) Systemic combination chemotherapy in elderly pancreatic cancer: a review. J Gastrointest Canc 48:121–128
15. Scheithauer W, Ramanathan RK, Moore M et al (2016) Dose modification- ton and efficacy of nab-paclitaxel plus gemcitabine vs. gemcitabine for patients with metastatic pancreatic cancer: phase III MPACT trial. J Gastrointest Oncol 7:469–478
16. Bladucci L, Extermann M (2000) Management of cancer in the older person: a practical approach. Oncologist 5(3):224–237
17. Higuera O, Ghanem M, Nasimi R et al (2016) Management of pancreatic cancer in elderly. World J Gastroenterol 22(2):264–275
18. Ahn DH, Krishna K, Blazer M et al (2017) A modified regimen of bi-weekly gemcitabine and nab-paclitaxel in patients with metastatic pancreatic cancer is both tolerable and effective: a retrospective analysis. Ther Adv Med Oncol 9(2):75–82
19. Osman MAM, McDermott R, Fennelly D (2016) A modified regimen of nab-paclitaxel and gemcitabine in advanced pancreatic cancer. Ann Oncol 27(suppl 6):666P
20. Kou T, Kanai M, Yamamoto M et al (2016) Prognostic model for survival based on readily available pretreatment factors in patients with advanced pancreatic cancer receiving palliative chemotherapy. Int J Clin Oncol. 21:118–125
21. Ueno H, Okada S, Okusaka T et al (2000) Prognostic factors in patients with metastatic pancreatic adenocarcinoma receiving systemic chemotherapy. Oncology 59(4):296–301
22. Morizane C, Okusaka T, Morita S et al (2011) Construction and validation of a prognostic index for patients with metastatic pancreatic adenocarcinoma. Pancreas 40(3):415–421
23. Bauer TM, El-Rayes BF, Li X et al (2013) Carbohydrate antigen 19–9 is a prognostic and predictive biomarker in patients with advanced pancreatic cancer who receive gemcitabine-containing chemotherapy: a pooled analysis of 6 prospective trials. Cancer 119(2):285–292
24. Xue P, Kanai M, Mori Y et al (2014) Neutrophil-to-lymphocyte ratio for predicting palliative chemotherapy outcomes in advanced pancreatic cancer patients. Cancer Med 3(2):406–415
25. Hamada T, Nakai Y, Yasunaga H et al (2014) Prognostic nomogram for nonresectable pancreatic cancer treated with gemcitabine-based chemotherapy. Br J Cancer 110(8):1943–1949
26. De Vita Ferdinando, Ventriglia Jole, Febbraro Antonino et al (2016) NAB-paclitaxel and gemcitabine in metastatic pancreatic ductal adenocarcinoma (PDAC): from clinical trials to clinical practice. BMC Cancer 16:709
27. Josep T, Gabriela E, Jeffrey R et al (2015) Prognostic factors of survival in a randomized phase III trial (MPACT) of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic pancreatic cancer. Oncologist 20:143–150
28. Lau MK, Davila JA, Shaib YH (2010) Incidence and survival of pancreatic head and body and tail cancers: a population-based study in the United States. Pancreas 39:458–462
29. van Erning Felice N, Mackay Tara M, van der Geest Lydia GM et al (2018) Association of the location of pancreatic ductal adenocarcinoma (head, body, tail) with tumor stage, treatment, and survival: a population-based analysis. Acta Oncol 57(12):1655–1662
30. Humphris JL, Chang DK, Johns AL et al (2012) The prognostic and predictive value of serum CA19.9 in pancreatic cancer. Ann Oncol 23(7):1713–1722
31. Meng Q, Shi S, Liang D et al (2017) Diagnostic and prognostic value of carcinoembryonic antigen in pancreatic cancer: a systematic review and meta-analysis. Onco Targetas Ther 10:4591–4598
32. Clinical Trials.gov. NCT02391662: (2017) a phase II study of nab-paclitaxel and gemcitabine, in elderly patients with previously untreated, metastatic pancreatic adenocarcinoma. https://clinicaltrials.gov/ct2/show/NCT02391662. Accessed 15 Feb 2017
33. Betge J, Chi-Kern J, Schulte N et al (2018) A multicenter phase 4 geriatric assessment directed trial to evaluate gemcitabine +/- nab-paclitaxel in elderly pancreatic cancer patients. BMC Cancer 18(1):747