The Effectiveness And Safety of Gemcitabine Plus Nab-Paclitaxel In Elderly Patients With Advanced Pancreatic Cancer: A Single-Center Retrospective Cohort Study

Sae Ohwada

Sapporo Medical University School of Medicine, Sapporo

Akiko Todaka

Shizuoka Cancer Center, Nagaizumi-cho

Hiroshi Nakase

Sapporo Medical University School of Medicine, Sapporo

Hiromichi Shirasu

Shizuoka Cancer Center, Nagaizumi-cho, Sunto-gun

Takeshi Kawakami

Shizuoka Cancer Center, Nagaizumi-cho

Satoshi Hamauchi

Shizuoka Cancer Center, Nagaizumi-cho

Takahiro Tsushima

Shizuoka Cancer Center, Nagaizumi-cho

Tomoya Yokota

Shizuoka Cancer Center, Nagaizumi-cho

Yusuke Onozawa

Shizuoka Cancer Center, Nagaizumi-cho, Sunto-gun

Hirofumi Yasui

Shizuoka Cancer Center, Nagaizumi-cho

Kentaro Yamazaki (✉ k.yamazaki@scchr.jp)

Shizuoka Cancer Center, Nagaizumi-cho <https://orcid.org/0000-0001-6269-9345>

Research Article

Keywords: pancreatic cancer, elderly patient, gemcitabine plus nab-paclitaxel (GnP), S-1, overall survival

Posted Date: January 17th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1180714/v1>

Abstract

Purpose: This study aimed to evaluate the effectiveness and safety of gemcitabine (GEM) plus nab-paclitaxel (GnP) in patients aged ≥ 75 years with advanced pancreatic cancer and compare it with monotherapy (GEM or S-1).

Methods: We retrospectively reviewed the data of patients with advanced pancreatic cancer aged ≥ 75 years who received either GnP or monotherapy (GEM or S-1) between January 2014 and May 2020. The primary efficacy outcome was overall survival (OS).

Results: A total of 96 patients were included in this study; 51 were treated with GnP and 45 with monotherapy (31 with GEM and 14 with S-1). The median OS and progression-free survival were 10.8 and 6.7 months in the GnP group and 10.7 and 4.3 months in the monotherapy group, respectively. The treatment effect on OS was consistently favorable in the GnP group across most subgroups, particularly in patients with locally advanced cancer, modified Glasgow prognostic score of 0 or 1, and neutrophil/lymphocyte ratio < 3.1 . The disease control rates were 76% and 48% in the GnP and monotherapy groups, respectively, and grade 3 or 4 neutropenia occurred in 23 (45%) and 11 (24%) patients of the GnP and monotherapy groups, respectively.

Conclusions: This study demonstrated that GnP was not superior to monotherapy with regard to OS. However, multivariate analysis showed that GnP treatment positively affected the OS and could be considered a treatment option, even for elderly patients.

Introduction

Pancreatic cancer is a worldwide health problem with an increasing incidence and poor prognosis. Although surgical resection is the only curative treatment for pancreatic cancer, most patients have unresectable disease at diagnosis [1]. Distant lesions are observed in 40–45% of patients with pancreatic cancer and locally advanced disease in 15–20% [2]. Unfortunately, the postoperative recurrence rate in patients undergoing surgical resection is high, with relapse in approximately 75–92% of patients [3, 4].

Approximately 40,900 patients are diagnosed with pancreatic cancer annually in Japan, making it the fourth and third leading cause of cancer deaths in men and women, respectively [5]. Advanced age is a high-risk factor for pancreatic cancer; in one report, at least 80% of all patients were aged > 65 years, and more than 60% were older than 75 years in 2018 [5]. Therefore, opportunities to provide chemotherapy to elderly patients with pancreatic cancer are increasing in Japan.

Combinations, such as folinic acid (leucovorin), fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) or gemcitabine (GEM) plus nab-paclitaxel (GnP) demonstrated their superiority over GEM alone in two phase III studies [6, 7] and have been used as a primary treatment in patients with locally advanced and metastatic pancreatic cancer. However, elderly patients are rarely treated with FOLFIRINOX because there are no data on its tolerability in patients older than 75 years. The GnP trial enrolled patients under 80

years of age, with only 10% of them being aged over 75 years. Thus, neither regimen has sufficient data on its effectiveness and safety as a treatment in elderly patients with pancreatic cancer.

On the other hand, it has been reported that monotherapy (GEM or S-1) was useful in elderly patients with fewer adverse events than combination therapy. Some reports have evaluated the effectiveness and safety of GEM as a single-agent therapy in elderly patients. Yamagishi et al. [8] and Katakura et al. [9] evaluated the therapeutic effects of GEM in patients with unresectable pancreatic cancer. They concluded that GEM monotherapy was as safe and effective in elderly patients as in younger patients. Additionally, Imaoka et al. [10] conducted a subgroup analysis in the GEST (Gemcitabine and S-1 Trial) study [11], showing the non-inferiority of S-1 to GEM and lower frequency of hematological toxicity in patients with advanced pancreatic cancer, thereby elucidating the efficacy and safety of S-1 as a first-line treatment in elderly patients. They concluded that S-1 could be a reasonable first-line treatment option in elderly patients with unresectable pancreatic cancer.

A meta-analysis [12] that included patients older than 65 years showed the superiority of GnP over GEM alone in progression-free survival (PFS) but not in overall survival (OS). A retrospective study [9] did not find GnP effective in improving PFS or OS in patients older than 75 years of age. There have been no reports comparing S-1 alone with combination therapy in elderly patients with pancreatic cancer. Hence, the therapeutic effectiveness of GnP, S-1, and GEM in the elderly has not been fully evaluated. In clinical practice, elderly patients often receive a single agent (GEM or S-1 alone) at the discretion of the attending physician. However, the choice of drug(s) for chemotherapy in the elderly is an important clinical issue.

This study retrospectively evaluated the effectiveness and safety of GnP in comparison with monotherapy for patients aged ≥ 75 years with unresectable or recurrent pancreatic cancer.

Materials And Methods

Patients

We retrospectively reviewed the medical records of patients with locally advanced or metastatic pancreatic cancer who were aged ≥ 75 years and received either monotherapy (GEM or S-1) or GnP as the first-line treatment between January 2014 and May 2020 at Shizuoka Cancer Center (Shizuoka, Japan). All patients were histologically or radiologically diagnosed with pancreatic cancer. Patients who relapsed within 6 months at the end of the adjuvant chemotherapy were excluded.

This research was conducted in accordance with the Declaration of Helsinki (as revised in Fortaleza, Brazil in October 2013) and approved by the Institutional Review Board of the Shizuoka Cancer Center (IRB No. J2020-128-2020-1-3).

Treatment

The GnP group received nab-paclitaxel (nab-PTX) at a dose of 125 mg/m² and concomitant GEM at a dose of 1,000 mg/m² intravenously every 4 weeks on days 1, 8, and 15. The monotherapy group received

either intravenous GEM at the dose and schedule as above or oral S-1 twice daily on days 1–28 of a 42-day cycle. The S-1 dose was calculated according to the body surface area: 80 mg/day for 1.25 m², 100 mg/day for 1.25–1.50 m², or 120 mg/day for 1.50 m². The dose and/or treatment schedule of these regimens were modified at the attending physician's discretion or patient's discretion. The patients continued their treatment until disease progression, the occurrence of intolerable adverse events, or patient refusal.

Outcomes

The primary effectiveness outcome was OS, defined as the duration between the start date of first-line treatment and the date of death, the date of the last follow-up, or the cutoff date of this study (November 30, 2020). The secondary effectiveness outcomes were PFS, objective response rate (ORR), disease control rate (DCR), time-to-treatment-failure (TTF), time to deterioration by the Eastern Cooperative Oncology Group performance status (ECOG PS) score, and safety. PFS was defined as the duration between the start date of first-line treatment and the date of documented disease progression or death from any cause. The investigators assessed the response according to the Response Evaluation Criteria in Solid Tumors guidelines, version 1.1, using computed tomography and/or magnetic resonance imaging. TTF was defined as the duration between the start date of treatment and the date of its discontinuation for any reason; in the GnP group, treatment failure was defined as the discontinuation of both GEM and nab-PTX. Time to deterioration by the ECOG PS was defined as the duration between the start of first-line treatment and the date when worsening of the ECOG PS was observed. Safety was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

Factors included in the univariate analyses for OS were age, sex, body mass index (BMI), ECOG PS, disease status, agents, and pretreatment laboratory tests, including neutrophil/lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), modified Glasgow prognostic score (mGPS), and carbohydrate antigen 19-9 (CA 19-9). The mGPS was defined as follows: patients with an elevated C-reactive protein level (>1.0 g/L) and hypoalbuminemia (<3.5 g/dL) were assigned a score of 2; patients with only one of these biochemical abnormalities were assigned a score of 1, and patients with neither of these abnormalities were assigned a score of 0. The NLR was the ratio between the neutrophil and lymphocyte counts, while the PLR was the ratio between the platelet and lymphocyte counts.

Statistical analysis

The treatment groups were compared for the baseline characteristics, adverse events, and response rates using the χ^2 test, Fisher's exact test, or unpaired t-test. OS and PFS were analyzed using the Kaplan-Meier curve, and differences in survival rates between the groups were analyzed using the log-rank test. The Cox proportional hazards models were used to estimate hazard ratios (HRs) of factors affecting the OS; models were adjusted for age, sex, ECOG PS, mGPS, and disease status. The cutoff values for BMI, CA-19, NLR, and PLR were determined based on the median value. All statistical analyses were performed

using Bell Curve for Excel, version 2.21 (Social Survey Research Information Co., Ltd. Tokyo, Japan). Statistical significance was set at $P < 0.05$.

Results

Baseline characteristics

A total of 96 patients were included in the study. Fifty-one received GnP, and 45 received monotherapy (31 were treated with GEM and 14 with S-1). Of the 45 patients who received monotherapy, 21 (47%) did so of their own choice, and the remaining at the discretion of the on-site physicians. The reasons for the decision were age ($n = 13$, 29%), poor ECOG PS ($n = 7$, 16%), and organ dysfunction ($n = 4$, 9%). There were fewer patients aged ≥ 80 years ($n = 8$, 16% vs. $n = 17$, 38%, $P = 0.02$) and more patients with metastasis ($n = 36$, 71% vs. $n = 23$, 51%, $P = 0.02$) in the GnP group than in the monotherapy group. The baseline characteristics of the treatment groups are summarized in Table 1.

Table 1
Baseline characteristics of the 96 patients

	All (<i>n</i> = 96)		^a GnP (<i>n</i> = 51)		Monotherapy (<i>n</i> = 45)		<i>P</i> -value
	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)	
Age, years							0.02
Median [range]	78	[75–87]	78	[75–83]	78	[75–87]	
≥80	25	(26)	8	(16)	17	(38)	
Sex							0.53
Male	61	(64)	31	(61)	30	(67)	
Female	35	(36)	20	(39)	15	(33)	
^b ECOG PS							0.22
0	30	(31)	16	(31)	14	(31)	
1	53	(55)	31	(61)	22	(49)	
2	13	(14)	4	(8)	9	(20)	
^c BMI, kg/m ²	20.9	[12.8–30.8]	20.9	[12.8–30.8]	20.7	[16.2–25.8]	0.91
Median [range]							

^aGnP: gemcitabine plus nab-paclitaxel

^bECOG PS: Eastern Cooperative Oncology Group performance status

^cBMI: body mass index

^dmGPS: modified Glasgow prognostic score

^eNLR: neutrophil/lymphocyte ratio

^fPLR: platelet/lymphocyte ratio

^gCA 19-9: carbohydrate antigen 19-9

^hGEM: gemcitabine

	All (<i>n</i> = 96)		^a GnP (<i>n</i> = 51)		Monotherapy (<i>n</i> = 45)		<i>P</i> -value
Type of tissue						(85)	0.51
Adenocarcinoma	85	(89)	46	(90)	39	(15)	
Mucinous carcinoma	1	(1)	1	(2)	0		
unknown	10	(10)	4	(8)	6		
Disease status							0.02
Locally advanced	22	(23)	12	(24)	10	(22)	
Metastatic	59	(61)	36	(71)	23	(51)	
Recurrence	15	(16)	3	(6)	12	(27)	
Site of metastatic lesions							0.40
	42	(44)	25	(49)	17	(38)	
Liver	16	(17)	7	(14)	9	(20)	
Lung	23	(39)	11	(22)	12	(27)	
Peritoneum							
No. of metastatic disease							0.81
	49	(51)	25	(49)	24	(53)	
1	16	(17)	10	(20)	6	(13)	
2	9	(32)	4	(8)	5	(11)	
≥3							

^a GnP: gemcitabine plus nab-paclitaxel
^b ECOG PS: Eastern Cooperative Oncology Group performance status
^c BMI: body mass index
^d mGPS: modified Glasgow prognostic score
^e NLR: neutrophil/lymphocyte ratio
^f PLR: platelet/lymphocyte ratio
^g CA 19-9: carbohydrate antigen 19-9
^h GEM: gemcitabine

	All (<i>n</i> = 96)		^a GnP (<i>n</i> = 51)		Monotherapy (<i>n</i> = 45)		<i>P</i> -value
History of surgery	15	(16)	3	(6)	12	(27)	0.009
Yes							
Adjuvant chemotherapy	9	(9)	3	(6)	6	(13)	0.18
Yes							
Biliary drainage	24	(25)	15	(29)	9	(20)	0.35
Yes							
^d mGPS							0.36
0	47	(49)	24	(47)	23	(51)	
1	28	(29)	13	(25)	15	(33)	
2	21	(22)	14	(27)	7	(16)	
^e NLR	3.1	[0.3–33.5]	3.9	[0.9–33.5]	2.6	[0.3–14.8]	0.06
Median [range]							
^f PLR	67.4	[13.0–219.0]	60.9	[13.0–219.0]	80.4	[28.5–206.4]	0.05
Median [range]							
^g CA 19-9, U/mL	454	[2–81835]	516	[2–81835]	451	[2–39893]	0.92
Median [range]							

^aGnP: gemcitabine plus nab-paclitaxel

^bECOG PS: Eastern Cooperative Oncology Group performance status

^cBMI: body mass index

^dmGPS: modified Glasgow prognostic score

^eNLR: neutrophil/lymphocyte ratio

^fPLR: platelet/lymphocyte ratio

^gCA 19-9: carbohydrate antigen 19-9

^hGEM: gemcitabine

	All (<i>n</i> = 96)		^a GnP (<i>n</i> = 51)	Monotherapy (<i>n</i> = 45)		<i>P</i> -value
Agents			(100)	(31)		<0.001
GnP	51	(53)	51	0	(69)	
S-1	14	(15)	0	14		
^h GEM	31	(32)	0	31		
^a GnP: gemcitabine plus nab-paclitaxel						
^b ECOG PS: Eastern Cooperative Oncology Group performance status						
^c BMI: body mass index						
^d mGPS: modified Glasgow prognostic score						
^e NLR: neutrophil/lymphocyte ratio						
^f PLR: platelet/lymphocyte ratio						
^g CA 19-9: carbohydrate antigen 19-9						
^h GEM: gemcitabine						

Effectiveness

Survival

The median OS in the GnP and monotherapy groups was 10.8 months (95% confidence interval [CI], 6.1–15.4 months) and 10.7 months (95% CI, 7.2–14.3 months), respectively. GnP therapy was not associated with longer OS than monotherapy (unadjusted HR, 0.77; 95% CI, 0.48–1.23; *P* = 0.27). This trend did not change after adjusting for age, sex, ECOG PS, mGPS, and disease status (adjusted HR, 0.65; 95% CI, 0.37–1.14; *P* = 0.13).

The median PFS in the GnP and monotherapy groups was 6.7 months (95% CI, 4.9–8.6 months) and 4.3 months (95% CI, 2.5–6.1 months), respectively. PFS was longer in patients receiving GnP than in those receiving monotherapy (unadjusted HR, 0.53; 95% CI, 0.34–0.82; *P* = 0.004), and this association remained significant after adjusting for possible confounders (adjusted HR, 0.43; 95% CI, 0.26–0.72; *P* < 0.001; Fig. 1).

Time-to-treatment-failure

The median TTF in the GnP and monotherapy groups was 5.6 months (95% CI, 2.9–8.3 months) and 3.7 months (95% CI, 2.7–4.7 months), respectively. Twelve patients in the GnP group discontinued nab-PTX due to peripheral sensory neuropathy ($n = 10$), fatigue ($n = 4$), pancytopenia ($n = 1$), and nail disorder ($n = 1$).

Response

The ORR in patients with measurable disease ($n = 81$) was higher in the GnP group than the monotherapy group, although the difference was not significant ($n = 9$, 22% vs. $n = 4$, 10%, $P = 0.23$). The DCR was significantly higher in the GnP group than the monotherapy group ($n = 31$, 76% vs. $n = 19$, 48%, $P = 0.01$).

Subgroup analysis of OS

The treatment effect on OS was consistently favorable in the GnP group across most subgroups. Patients with locally advanced cancer, mGPS 0 or 1, and NLR <3.1 tended to have favorable OS in the GnP group. Patients with ECOG PS 2 and mGPS value of 2 tended to have a favorable outcome when receiving monotherapy (Fig. 2). The median OS of patients with ECOG PS of 0–1 and 2 in the GnP group was 11.6 and 2.7 months, respectively ($P = 0.04$). The median OS of patients with mGPS of 0–1 and 2 in the GnP group was 13.4 and 7.4 months, respectively ($P = 0.005$).

Time to deterioration of ECOG PS

Treatment with GnP resulted in a significantly long time to ECOG PS deterioration than monotherapy. The median time to deterioration in the ECOG PS score was 5.1 months in the GnP group and 3.7 months in the monotherapy group, with an HR of 0.61 (95% CI, 0.39–0.96; $P = 0.03$; Online Resource 1a). When categorized by baseline ECOG PS, treatment with GnP tended to extend the time to ECOG PS deterioration in patients with a baseline ECOG PS of 0 or 1 (HR, 0.61; 95% CI, 0.37–1.00; $P = 0.04$). There was no difference in the time to deterioration of ECOG PS between the groups in patients with a baseline ECOG PS of 2 (Online Resource 1b).

Treatment exposure

The number of patients experiencing a reduction of the initial dose was 39 in the GnP group and 29 in the monotherapy group (76% vs. 64%, $P = 0.27$). Of the 51 patients in the GnP group, 38 (75%) had treatment delay at least once; the most common reasons were neutropenia ($n = 27$), thrombocytopenia ($n = 11$), and fatigue ($n = 4$), with some overlaps. The frequency of neutropenia was significantly higher in the GnP group than in the monotherapy group (53% vs. 22%, $P = 0.003$).

Twenty-three patients in the GnP group and 16 in the monotherapy group required dose reduction (45% vs. 35%, $P = 0.41$). Neutropenia (31% vs. 11%, $P = 0.02$) and peripheral sensory neuropathy (10% vs. 0%, $P = 0.06$) as reasons for dose reduction were more frequent in the GnP group.

Treatment discontinuation due to adverse events was observed in six patients in each group. Reasons in the GnP group included pneumonitis ($n = 4$), fatigue ($n = 4$), edema ($n = 2$), and soft tissue infection ($n =$

1). Reasons in the monotherapy group included anorexia ($n = 4$), soft tissue infection ($n = 1$), biliary tract infection ($n = 1$), and pneumonitis ($n = 1$; Table 2).

Table 2
The reasons for dose or treatment modification

	^a GnP (<i>n</i> = 51)		Monotherapy (<i>n</i> = 45)		<i>P</i> -value
	<i>n</i>	(%)	<i>n</i>	(%)	
Initial dose reduction	39	(76)	29	(64)	0.27
Age	36	(71)	24	(53)	0.14
Poor ^b ECOG PS	1	(2)	3	(7)	0.34
Organ dysfunction	2	(4)	2	(4)	1
Required dose reduction	23	(45)	16	(35)	0.41
Neutropenia	16	(31)	5	(11)	0.02
Thrombocytopenia	5	(10)	3	(7)	0.72
Febrile neutropenia	1	(2)	1	(2)	1
Fatigue	3	(6)	2	(4)	1
Anorexia	1	(2)	4	(9)	0.19
Peripheral sensory neuropathy	5	(10)	0	(4)	0.06
Skin rash	1	(2)	2		0.60
Nausea	1	(2)	0		1

*Pancreatic enzymes increased (1) and aspartate aminotransferase (AST) increased (1) in the monotherapy group

**Conversion surgery (1) and progression of dementia (1) in the GnP group, exacerbation of diabetes (1) and progression of dementia (1) in the monotherapy group

^aGnP: gemcitabine plus nab-paclitaxel

^bECOG PS: Eastern Cooperative Oncology Group performance status

Monotherapy (GEM or S-1)

	^a GnP (<i>n</i> = 51)		Monotherapy (<i>n</i> = 45)		<i>P</i> -value
Treatment delay	38	(57)	30	(67)	0.38
Neutropenia	27	(53)	10	(22)	0.003
Thrombocytopenia	11	(22)	8	(18)	0.79
Anemia	1	(2)	1	(2)	1
Fatigue	4	(8)	8	(18)	0.22
Anorexia	1	(2)	3	(7)	0.34
Skin rash	1	(2)	2	(4)	0.60
Constipation	2	(4)	0	(2)	0.50
Diarrhea	1	(2)	1	(4)	1
Biliary tract infection	3	(6)	2	(4)	1
Others*	0	(88)	2	(100)	0.22
Treatment discontinuation	45	(71)	45	(80)	0.03
Progressive disease	32	(24)	36	(16)	0.84
Adverse event	11	(4)	7	(4)	0.60
Others**	2		2		1
*Pancreatic enzymes increased (1) and aspartate aminotransferase (AST) increased (1) in the monotherapy group					
**Conversion surgery (1) and progression of dementia (1) in the GnP group, exacerbation of diabetes (1) and progression of dementia (1) in the monotherapy group					
^a GnP: gemcitabine plus nab-paclitaxel					
^b ECOG PS: Eastern Cooperative Oncology Group performance status					
Monotherapy (GEM or S-1)					

Subsequent therapy was performed in 25 patients (49%) in the GnP group and 23 (51%) in the monotherapy group. The subsequent therapies in the treatment groups are shown in Online Resource 2.

Safety

The adverse events in both treatment groups are shown in Table 3. Grade 3 or 4 non-hematologic adverse events were infrequent. The most frequently observed non-hematologic adverse events of any grade in the GnP group were fatigue (*n* = 38, 75%), anorexia (*n* = 29, 57%), and peripheral sensory neuropathy (*n* =

22, 43%), while that in the monotherapy group were anorexia ($n = 32$, 71%), fatigue ($n = 31$, 69%), and nausea ($n = 12$, 27%). Any grade of peripheral sensory neuropathy (43% vs. 2%, $P < 0.001$), edema (16% vs. 0%, $P = 0.006$), and grades 1–2 alopecia (27% vs. 0%, $P < 0.001$) were significantly higher in the GnP group than in the monotherapy group. Despite the lack of statistical significance, the incidence of grade 3 or 4 neutropenia was numerically higher in the GnP group than in the monotherapy group ($n = 23$, 45% vs. $n = 11$, 24%, $P = 0.05$). Treatment-related deaths were not observed in either of the treatment groups.

Table 3
Adverse events in both groups

Adverse events in both groups									
	^a GnP (<i>n</i> = 51)				Monotherapy (<i>n</i> = 45)				<i>P</i> -value (Grades 3–4)
	Any grade		Grades 3–4		Any grade		Grades 3–4		
	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)	
Hematological adverse event									
Neutropenia	36	(70)	23	(45)	18	(40)	11	(24)	0.05
Thrombocytopenia	37	(73)	6	(12)	19	(42)	3	(7)	0.50
Anemia	41	(80)	4	(8)	27	(60)	1	(2)	0.37
Nonhematological adverse event									
Fatigue	38	(75)	2	(4)	31	(69)	3	(7)	0.66
Anorexia	29	(57)	1	(2)	32	(71)	2	(4)	0.60
Peripheral sensory neuropathy	22	(43)	0		1	(2)	0		1
Constipation	18	(35)	0		12	(27)	0		1
Nausea	16	(31)	0		19	(42)	2	(4)	0.22
Diarrhea	16	(31)	0		13	(29)	0		1
Skin rash	16	(31)	0		13	(29)	0		1
Alopecia	14	(27)	-		0		-		1*
Fever	11	(22)	0		5	(11)	0		1
Vomiting	8	(16)	0		2	(4)	0		1
Edema	8	(16)	1	(2)	0		0		1
Dysgeusia	2	(4)	0		3	(7)	0		1
Febrile neutropenia	2	(4)	2	(4)	1	(2)	1	(2)	1
Biliary infection	8	(16)	8	(16)	4	(9)	4	(9)	0.37
*Comparison of Grades 1–2 adverse events									
^a GnP: gemcitabine plus nab-paclitaxel									
Monotherapy (GEM or S-1)									

	^a GnP (<i>n</i> = 51)		Monotherapy (<i>n</i> = 45)		<i>P</i> -value (Grades 3–4)	
	Any grade	Grades 3–4	Any grade	Grades 3–4		
Pneumonitis	3 (6)	1 (2)	1 (2)	1 (2)	1	
*Comparison of Grades 1–2 adverse events						
^a GnP: gemcitabine plus nab-paclitaxel						
Monotherapy (GEM or S-1)						

Discussion

We found in this retrospective study that GnP was superior to monotherapy in terms of PFS, TTF, and DCR, even though it showed no improvement in OS. Subgroup analysis according to treatment regimens showed that the treatment effect on OS was consistently favorable in the GnP group across most subgroups, especially in patients with locally advanced cancer, mGPS 0 or 1, and NLR <3.1. However, the GnP treatment effect was not observed in patients with an mGPS or ECOG PS of 2. GnP proved to be as safe as monotherapy, even in elderly patients. Furthermore, our data showed that GnP contributed to a delay in ECOG PS deterioration compared with monotherapy.

Elderly patients are heterogeneous in terms of comorbidities and physical capacity. Combination therapies, such as FOLFIRINOX and GnP, are generally recommended as first-line treatment in patients with advanced pancreatic cancer to whom physicians have determined that these therapies could be administered. However, GEM or S-1 monotherapy is used for most elderly patients. A systematic review [12] assessed the efficacy of combination therapy in treating elderly patients with pancreatic cancer. The study showed that combination therapy, especially GnP, significantly improved OS compared to GEM alone. However, the study defined all patients aged ≥ 65 years as “elderly.” Trials that specifically assess the role of combination therapy versus GEM in elderly patients with pancreatic cancer are lacking. Considering that the number of elderly patients with pancreatic cancer is increasing in Japan, an investigation of the effectiveness of anti-cancer therapy in such patients aged ≥ 75 years is required.

We found in this study that GnP was not superior to monotherapy with regard to OS, possibly due to the higher rate of patients with metastatic pancreatic cancer in the GnP group (71%) than in the monotherapy group (51%). In general, the prognosis of patients with metastatic cancer is worse than that of patients with locally advanced pancreatic cancer [13, 14]. On-site physicians tend to select GnP to control disease progression if the patient’s condition is stable. Randomized controlled trials might be necessary to exclude this bias and accurately assess the effects of the various treatments.

We found in the subgroup analysis that mGPS and ECOG PS were predictive factors for the difficulty of achieving therapeutic effects of GnP in patients with advanced pancreatic cancer. ECOG PS has been

widely recognized as an important prognostic factor in multiple cancers [15]. It has also been shown to be associated with OS in pancreatic cancer patients [16–18]. Poor ECOG PS might be due to jaundice, anemia, and/or undernutrition, which might reflect disease progression. The poor condition and decreased tolerability to chemotherapy are possible factors associated with a worse outcome. mGPS is also recognized as a prognostic factor in advanced pancreatic cancer [19, 20]. Hwang et al. [19] reported a significant association between mGPS and OS in pancreatic cancer. Similar to previous reports [19], our study showed that patients with poor ECOG PS and mGPS had significantly worse OS. Therefore, we considered it difficult to determine the therapeutic effect of GnP in patients with an ECOG PS or mGPS of 2.

The hematological toxicity in the GnP group was tolerable, and its frequency was similar to that in a GnP trial that included patients younger than those in our study [7]. Given their age, the higher proportion of patients receiving initial dose reduction in the GnP group could have influenced the frequency of hematological side effects. The pharmacodynamic and pharmacokinetic changes in elderly patients differ from those in younger patients. Elderly patients are more susceptible to the negative effects of chemotherapy on their organs. In this regard, appropriate dose reduction could contribute to tolerability. Our data demonstrated that GnP significantly slowed PS deterioration compared with monotherapy. However, neither GnP nor monotherapy prolonged the time to PS deterioration in patients with ECOG PS of 2, indicating that GnP could relieve symptoms associated with the disease better than monotherapy only for patients in good general condition at the start of treatment.

Our study has several limitations. First, this study might have been affected by a selection bias due to its retrospective nature. In fact, the monotherapy group had a higher proportion of patients with ECOG PS of 2. Second, dose modification at the physician's discretion could affect the effectiveness and safety outcomes. Third, the data were obtained from a single institution, and the number of enrolled patients was relatively small.

In conclusion, this study showed that GnP treatment in elderly patients with unresectable pancreatic cancer led to a better improvement in PFS, TTF, and DCR than monotherapy. Although the Kaplan-Meier curve analysis found no superiority of GnP with regard to OS, multivariate analysis showed that the treatment effect on OS was favorable in the GnP group across most subgroups. Additionally, GnP was as safe as monotherapy when administered at an appropriate dose. Therefore, GnP could be a treatment option for elderly patients. On comparing the effectiveness and safety of GnP in clinical practice with that of monotherapy, we believe that this study provides useful information. Further studies are required to determine which regimen should be selected for elderly patients with pancreatic cancer.

Declarations

Author Declarations

Ethics approval and consent to participate: This research study was conducted in accordance with the Declaration of Helsinki (as revised in Fortaleza, Brazil in October 2013). The study design was approved

by the Institutional Review Board of the Shizuoka Cancer Center (IRB No. J2020-128-2020-1-3). The ethics review board of Shizuoka Cancer Center approved the present study and permitted the use of the opt-out method in lieu of written informed consent.

Consent for publication: Not applicable.

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

Competing interests: All authors declare that they have no conflicts of interest.

Funding: Not applicable.

Authors' contributions: All authors contributed to the study conception and design. Data collection and analysis was performed by Sae Ohwada. The first draft of the manuscript was written by Sae Ohwada and Akiko Todaka. All authors commented on previous versions of the manuscript. All authors read and approved the final version of the manuscript.

Acknowledgements: We would like to thank Editage (www.editage.com) for English language editing.

Compliance with Ethical Standards

Disclosure of potential conflicts of interest: All authors declare that they have no conflicts of interest.

Research involving Human Participants and/or Animals: The study design was approved by the Institutional Review Board of the Shizuoka Cancer Center (IRB No. J2020-128-2020-1-3), and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent: The ethics review board of Shizuoka Cancer Center approved the present study and permitted the use of the opt-out method in lieu of written informed consent.

References

1. Kuroda T, Kumagi T, Yokota T, Seike H, Nishiyama M, Imai Y, Inada N, Shibata N, Imamine S, Okada S, Koizumi M, Yamanishi H, Azemoto N, Miyaike J, Tanaka Y, Tatsukawa H, Utsunomiya H, Ohno Y, Miyake T, Hirooka M, Furukawa S, Abe M, Ikeda Y, Matsuura B, Hiasa Y, Onji M, EPOCH Study Group (2013) 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>
2. Heinemann V (2002) Gemcitabine in the treatment of advanced pancreatic cancer: a comparative analysis of randomized trials. *Semin Oncol* 29 Supplement 20:9–16. <https://doi.org/10.1053/sonc.2002.37372>

3. Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, Schramm H, Fahlke J, Zuelke C, Burkart C, Gutberlet K, Kettner E, Schmalenberg H, Weigang-Koehler K, Bechstein WO, Niedergethmann M, Schmidt-Wolf I, Roll L, Doerken B, Riess H (2007) Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA* 297:267–277. <https://doi.org/10.1001/jama.297.3.267>
4. Van den Broeck A, Sergeant G, Ectors N, Van Steenberghe W, Aerts R, Topal B (2009) Patterns of recurrence after curative resection of pancreatic ductal adenocarcinoma. *Eur J Surg Oncol* 35:600–604. <https://doi.org/10.1016/j.ejso.2008.12.006>
5. Ministry of Health, Labour and Welfare (2018) [Center for Cancer Control and Information Services, National Cancer Center, Japan web site]. Vital Stat Jpn. https://ganjoho.jp/reg_stat/statistics/dl/index.html#mortality. Accessed 26 Nov 2020
6. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M, PRODIGE Intergroup (2011) Groupe Tumeurs Digestives of Unicancer, FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 364:1817–1825. <https://doi.org/10.1056/NEJMoa1011923>
7. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, Renschler MF (2013) Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 369:1691–1703. <https://doi.org/10.1056/NEJMoa1304369>
8. Yamagishi Y, Higuchi H, Izumiya M, Sakai G, Iizuka H, Nakamura S, Adachi M, Hozawa S, Takaishi H, Hibi T (2010) Gemcitabine as first-line chemotherapy in elderly patients with unresectable pancreatic carcinoma. *J Gastroenterol* 45:1146–1154. <https://doi.org/10.1007/s00535-010-0258-9>
9. Katakura Y, Nakahara K, Kobayashi M, Adachi S, Izawa N, Noguchi Y, Nakatsu S, Sato Y, Takagi R, Itoh F (2010) Gemcitabine therapy for unresectable pancreatic cancer in elderly patients. *Nihon Shokakibyo Gakkai Zasshi* 107:396–406. (in Japanese)
10. Imaoka H, Kou T, Tanaka M, Egawa S, Mizuno N, Hijioka S, Hara K, Yazumi S, Shimizu Y, Yamao K (2016) Clinical outcome of elderly patients with unresectable pancreatic cancer treated with gemcitabine plus S-1, S-1 alone, or gemcitabine alone: subgroup analysis of a randomised phase III trial, GEST study. *Eur J Cancer* 54:96–103. <https://doi.org/10.1016/j.ejca.2015.11.002>
11. Ueno H, Ioka T, Ikeda M, Ohkawa S, Yanagimoto H, Boku N, Fukutomi A, Sugimori K, Baba H, Yamao K, Shimamura T, Sho M, Kitano M, Cheng AL, Mizumoto K, Chen JS, Furuse J, Funakoshi A, Hatori T, Yamaguchi T, Egawa S, Sato A, Ohashi Y, Okusaka T, Tanaka M (2013) Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. *J Clin Oncol* 31:1640–1648. <https://doi.org/10.1200/JCO.2012.43.3680>

12. Jin J, Teng C, Li T (2018) Combination therapy versus gemcitabine monotherapy in the treatment of elderly pancreatic cancer: a meta-analysis of randomized controlled trials. *Drug Des Devel Ther* 12:475–480. <https://doi.org/10.2147/DDDT.S156766>
13. Stein SM, James ES, Deng Y, Cong X, Kortmansky JS, Li J, Staugaard C, Indukala D, Boustani AM, Patel V, Cha CH, Salem RR, Chang B, Hochster HS, Lacy J (2016) Final analysis of a phase II study of modified FOLFIRINOX in locally advanced and metastatic pancreatic cancer. *Br J Cancer* 114:737–743. <https://doi.org/10.1038/bjc.2016.45>
14. 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. <https://doi.org/10.1186/s12885-018-5244-2>
15. Sørensen JB, Klee M, Palshof T, Hansen HH (1993) Performance status assessment in cancer patients. An inter-observer variability study. *Br J Cancer* 67:773–775. <https://doi.org/10.1038/bjc.1993.140>
16. Krishnan S, Rana V, Janjan NA, Abbruzzese JL, Gould MS, Das P, Delclos ME, Palla S, Guha S, Varadhachary G, Evans DB, Wolff RA, Crane CH (2006) Prognostic factors in patients with unresectable locally advanced pancreatic adenocarcinoma treated with chemoradiation. *Cancer* 107:2589–2596. <https://doi.org/10.1002/cncr.22328>
17. Weber A, Kehl V, Mittermeyer T, Herberich E, Röthling N, Schmid RM, Prinz C (2010) Prognostic factors for survival in patients with unresectable pancreatic cancer. *Pancreas* 39:1247–1253. <https://doi.org/10.1097/MPA.0b013e3181e21b1b>
18. Tas F, Sen F, Odabas H, Kilic L, Keskin S, Yildiz I (2013) Performance status of patients is the major prognostic factor at all stages of pancreatic cancer. *Int J Clin Oncol* 18:839–846. <https://doi.org/10.1007/s10147-012-0474-9>
19. Hwang I, Kang J, Ip HNN, Jeong JH, Kim KP, Chang HM, Yoo C, Ryoo BY (2019) Prognostic factors in patients with metastatic or recurrent pancreatic cancer treated with first-line nab-paclitaxel plus gemcitabine: implication of inflammation-based scores. *Invest New Drugs* 37:584–590. <https://doi.org/10.1007/s10637-018-0681-y>
20. Shimoda M, Katoh M, Kita J, Sawada T, Kubota K (2010) The Glasgow prognostic score is a good predictor of treatment outcome in patients with unresectable pancreatic cancer. *Chemotherapy* 56:501–506. <https://doi.org/10.1159/000321014>

Figures

Figure 1

Kaplan-Meier estimates of (a) overall survival and (b) progression-free survival according to the treatment groups

GnP, gemcitabine (GEM) plus nab-paclitaxel; Monotherapy (GEM or S-1)

Figure 2

Forest plot of treatment effects on overall survival in subgroup analyses

PS, performance status; BMI, body mass index; mGPS, modified Glasgow prognostic score; NLR, neutrophil/lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; CA 19-9, carbohydrate antigen 19-9; GnP, gemcitabine (GEM) plus nab-paclitaxel; Monotherapy (GEM or S-1); HR, hazard ratio; CI, confidence interval

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [ESM1.pdf](#)
- [ESM2.pdf](#)