DOCTORAL THESIS

Liposomal irinotecan plus fluorouracil/leucovorin in older patients with advanced pancreatic cancer: a single-center retrospective study

(高齢進行膵癌患者に対するリポソーマル型イリノテカン＋フルオロウラシル/ロイコボリン使用例の単施設後ろ向き研究)

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ORIGINAL ARTICLE

Liposomal irinotecan plus fluorouracil/leucovorin in older patients with advanced pancreatic cancer: a single-center retrospective study

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Abstract

Background The global phase 3 NAPOLI -1 trial of patients with pancreatic ductal adenocarcinoma (PDAC) demonstrated an overall survival (OS) benefit from using liposomal irinotecan and 5-fluorouracil/leucovorin (nal-IRI + 5-FU/LV) after treatment with gemcitabine (GEM) compared to 5-FU/LV alone. However, the efficacy and safety of this regimen in older patients are not well studied.

Methods We conducted a single-center retrospective study to compare the therapeutic efficacy of nal-IRI + 5-FU/LV between older and younger patients with cutoff ages of 70 and 75 years, respectively. We included patients with a prior history of one or more GEM-based regimens for locally advanced or metastatic PDAC and were treated with nal-IRI + 5-FU/LV.

Results Of the 115 patients, 54 (47.0%) and 24 (20.9%) were aged ≥ 70 and ≥ 75 years, respectively. The median OS and progression-free survival (PFS) of the entire cohort were 8.5 and 3.6 months, respectively. No significant differences were observed in OS and PFS hazard ratios using age cutoffs of 70 (P = 0.90 and 0.99, respectively) and 75 (P = 0.90 and 0.76, respectively) years. Additionally, no significant differences were found in the incidence of treatment-related adverse events (trAEs) between patients aged ≥ 70 and < 70 years or those aged ≥ 75 and < 75 years. Other than hematological toxicity, no trAEs higher than Grade 4 were observed in either age group.

Conclusion The efficacy and safety of nal-IRI + 5-FU/LV for patients with PDAC are not significantly different for those aged ≥ 70 years compared to younger patients.

Keywords Liposomal irinotecan · Fluorouracil/leucovorin · Aging · Pancreatic ductal adenocarcinoma · Second-line treatment · NAPOLI-1 trial

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the intractable cancers and ranks third and fourth for cancer-related mortality in the United States and Europe, respectively [1, 2]. More than 80% of PDAC cases are diagnosed with distant metastases; curative treatment is difficult for patients with PDAC, contributing to high mortality and low survival rates [3]. Systemic chemotherapy is the standard of care in the treatment of PDAC. For patients with metastatic PDAC, gemcitabine (GEM), nab-paclitaxel (nab-PTX) combination, and fluorouracil, leucovorin, irinotecan (IRI), and oxaliplatin combination have been established as standard first-line treatments [4, 5]. Despite recent advances in chemotherapy, almost all cases of PDAC eventually progress after these first-line treatments. Accordingly, second-line treatments for these patients are essential.

In the NAPOLI-1 phase 3 trial of patients with PDAC, liposomal irinotecan (nal-IRI) in combination with 5-fluorouracil/leucovorin (5-FU/LV) increased overall survival (OS) compared with 5-FU/LV alone [6]. Consequently, nal-IRI + 5-FU/LV is considered standard treatment for patients with PDAC refractory to GEM-based regimens. Pancreatic cancer in older adults is increasing in Japan, with more than 50% of new cases occurring in people aged > 75 years [7]. Subgroup analysis of the NAPOLI-1 study reported that the

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risks of disease progression and mortality in older patients were comparable to those in younger patients. However, the small number of older participants (31 and 14 aged ≥ 70 and ≥ 75 years, respectively) limited a thorough assessment of the efficacy and safety of nal-IRI + 5-FU/LV in these patients [8]. Furthermore, the report did not fully evaluate the usefulness of nal-IRI + 5-FU/LV for older patients in daily practice. Therefore, we aimed to assess the efficacy and safety of second-line nal-IRI + 5-FU/LV treatment for PDAC in older patients within our facility.

Patients and Methods

Overview

This single-center retrospective study was approved by the Kanagawa Cancer Center Institutional Review Board and conducted in accordance with the ethical principles of the Declaration of Helsinki. Although written or oral consent was not obtained from the research participants, the opportunity to decline inclusion was provided.

Patients

Patients were identified using data extracted from our institution's electronic records system. We applied nal-IRI + 5-FU/LV treatment to patients who met the following criteria: an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2, no documentation in their medical records of massive ascites, watery diarrhea, and paralytic ileus, locally advanced or metastatic PDAC, and prior history of one or more GEM-based regimens. This study included consecutive patients with pathologically proven PDAC and initiated nal-IRI + 5-FU/LV between June 2020 and January 2021.

Treatment

Patients received Nal-IRI, 70 mg/m^2 for 90 min; LV, 400 mg/m^2 for 30 min; and 5-FU, 2400 mg/m^2 for 46 h every 2 weeks, as possible [6, 9]. The initial dose was reduced at the physician's discretion, based on the patient's condition. Treatment was continued until disease progression, intolerable toxicity, or patient refusal occurred; subsequent treatment was based on the physician's discretion and the patient's condition.

Outcomes and analyses

The observation period lasted until March 31, 2022. This study's outcomes were progression-free survival (PFS), OS, disease control rate (DCR), objective response rate (ORR), and treatment-related adverse events (trAEs). PFS was defined as the interval from the initial date of nal-IRI + 5-FU/LV treatment to the date of documented disease progression, death from any cause, or last follow-up. OS was calculated from the initial date of nal-IRI + 5-FU/LV treatment to the date of death from any cause or last follow-up. Additionally, objective response was evaluated according to Response Evaluation Criteria in Solid Tumor version 1.1 [10], and ORR was calculated as the number of patients whose best response was complete (CR) or partial (PR), divided by the total number of patients. DCR was calculated as the number of patients whose best response was CR, PR, or stable, divided by the number of those whose radiological response was available. TrAEs were evaluated using the Common Terminology Criteria for Adverse Events, version 5.0 [11].

Statistical analyses

We compared the efficacy and safety between the patient groups aged ≥ 70 and < 70 years and ≥ 75 and < 75 years. The Kaplan–Meier method was used to obtain the median OS and PFS, and the log-rank test was used to compare OS and PFS between the groups. Hazard ratios (HR) were calculated using the Cox proportional hazards model. Multi- and univariate analyses were performed using the Cox proportional hazard model to disclose the prognostic factors for survival. We used age, Union for International Cancer Control (UICC) Stage (III vs. IV), albumin (≤ 3.5 g/dl vs. > 3.5 g/dl, ECOG PS (0 vs. 1–2), and history of IRI-containing regimen (no vs. yes), C-reactive protein (CRP)(≤ 1.0 mg/dl vs. > 1.0 mg/dl) as covariates. Fisher's exact or chi-square test was used to compare nominal variables between the groups if applicable, and the Mann–Whitney U test was used to compare continuous variables. Statistical significance was set as $P < 0.05$.

Results

Patient's background

One hundred and fifteen patients were eligible for this study. Patient characteristics are presented in Table 1. Additionally, 47.0, 20.9, and 7.0% of the patients were aged ≥ 70, ≥ 75, and ≥ 80 years, respectively. The proportion of patients with an ECOG PS of 0 increased with age as follows: 39.3, 48.1, and 50% in patients aged < 70, ≥ 70, and ≥ 75 years, respectively. UICC stages III and IV were 7.4 and 92.6% in patients aged ≥ 70 years and 8.3 and 91.7% in those aged ≥ 75 years, respectively. More than 50% of patients in each age group had a history of receiving two or more chemotherapy regimens.

Table 1 Patient demographic data based on age group

	< 70 years	≥ 70 years	< 75 years	≥ 75 years
Number of patients	61	54	91	24
Gender				
Male	38 (62.3)	34 (63.0)	56 (61.5)	16 (66.7)
Female	23 (37.7)	20 (37.0)	35 (38.5)	8 (33.3)
UICC[a] stage				
Stage III	7 (11.5)	4 (7.4)	9 (9.9)	2 (8.3)
Stage IV	54 (88.5)	50 (92.6)	82 (90.1)	22 (91.7)
ECOG[b] performance status				
0	24 (39.3)	26 (48.1)	38 (41.8)	12 (50.0)
1	35 (57.4)	27 (50.0)	50 (54.9)	12 (50.0)
2	2 (3.3)	1 (1.9)	3 (3.3)	0 (0.0)
Number of prior treatments				
1	27 (44.3)	25 (46.3)	44 (48.4)	8 (33.3)
2	34 (55.7)	29 (53.7)	47 (51.6)	16 (66.7)
History of IRI-containing[c] regimen	19 (31.1)	8 (14.8)	23 (25.3)	4 (16.7)
Albumin (g/dL), median (range)	3.7 (2.4–4.4)	3.5 (2.5–4.8)	3.6 (2.4–4.4)	3.4 (2.7–4.8)
CEA[d] (ng/mL), median (range)	9.0 (1.0–957.2)	7.1 (1.1–458.6)	8.0 (1.0–957.2)	7.7 (1.8–150.9)
CA19-9[e] (U/mL), median (range)	1073.6 (2.0–513560.0)	479.3 (2.0–333420.0)	952.2 (2.0–513560.0)	658.4 (2.0–275630.0)
CRPf (mg/dL)	0.25 (0.03–15.68)	0.31 (0.03–24.0)	0.29 (0.03–24.0)	0.3 (0.04–2.88)

[a]*UICC* union for international cancer control

[b]*ECOG* eastern cooperative oncology group

[c]*IRI* irinotecan

[d]*CEA* carcinoembryonic antigen

[e]*CA* 19–9 carbohydrate antigen 19–9

fCRP C-reactive protein

Treatment

The proportion of patients who initiated treatment with a reduced dosage was significantly higher in older patients than in younger ones: 18% of patients aged < 70 years vs. 37% of those aged ≥ 70 years ($P = 0.04$), and 23% of patients aged < 75 years vs. 42% of those aged ≥ 75 years ($P = 0.12$). Reasons for initiating with a reduced dosage are shown in Online Resource 1. No significant differences were found in the median number of doses between the age groups as follows: six cycles in both patients aged < 70 years and those aged ≥ 70 years ($P = 0.70$), and seven cycles in patients < 75 years vs. five cycles in those aged ≥ 75 years ($P = 0.67$). No significant difference was found in the proportion of patients who experienced one or more treatment delays due to adverse events as follows: 38% of patients aged < 70 years vs. 35% of those aged ≥ 70 years ($P = 0.93$), and 34% of patients aged < 75 years vs. 46% of those aged ≥ 75 years ($P = 0.35$). Reasons for treatment delays are described in Online Resource 2. Moreover, no significant differences were observed in the percentage of patients who received reduced dosages during treatment; the reasons for dose reductions during treatment are described in Online Resource 3.

Efficacy

With a median follow-up time of 10.6 months, the median OS and PFS in the entire cohort were 8.5 and 3.6 months (95% confidence interval [CI], 6.7–10.5 and 3.1–4.6), respectively (Online Resource 4). When patients aged <70 vs. ≥70 years were compared, the median OS was 8.4 (95% CI, 6.4–11.0) and 7.9 (95% CI, 5.8–11.0) months, respectively, with an HR of 1.03 (95% CI, 0.67–1.56; $P = 0.90$) (Fig. 1a). The median PFS for patients aged <70 and ≥70 years were 3.6 (95% CI, 3.1–5.0) and 3.4 (95% CI, 2.8–5.4) months, respectively, with an HR of 1.00 (95% CI, 0.67–1.49; $P = 0.99$) (Fig. 1b). The ORR for patients aged <70 and ≥70 years was 3.4% and 2.0%, respectively ($P = 1.00$), and their DCR was 63.7% and 61.2%, respectively ($P = 1.00$).

Using 75 years as the cutoff age, no significant differences were found in OS and PFS between younger and older patients (Fig. 1c and d).

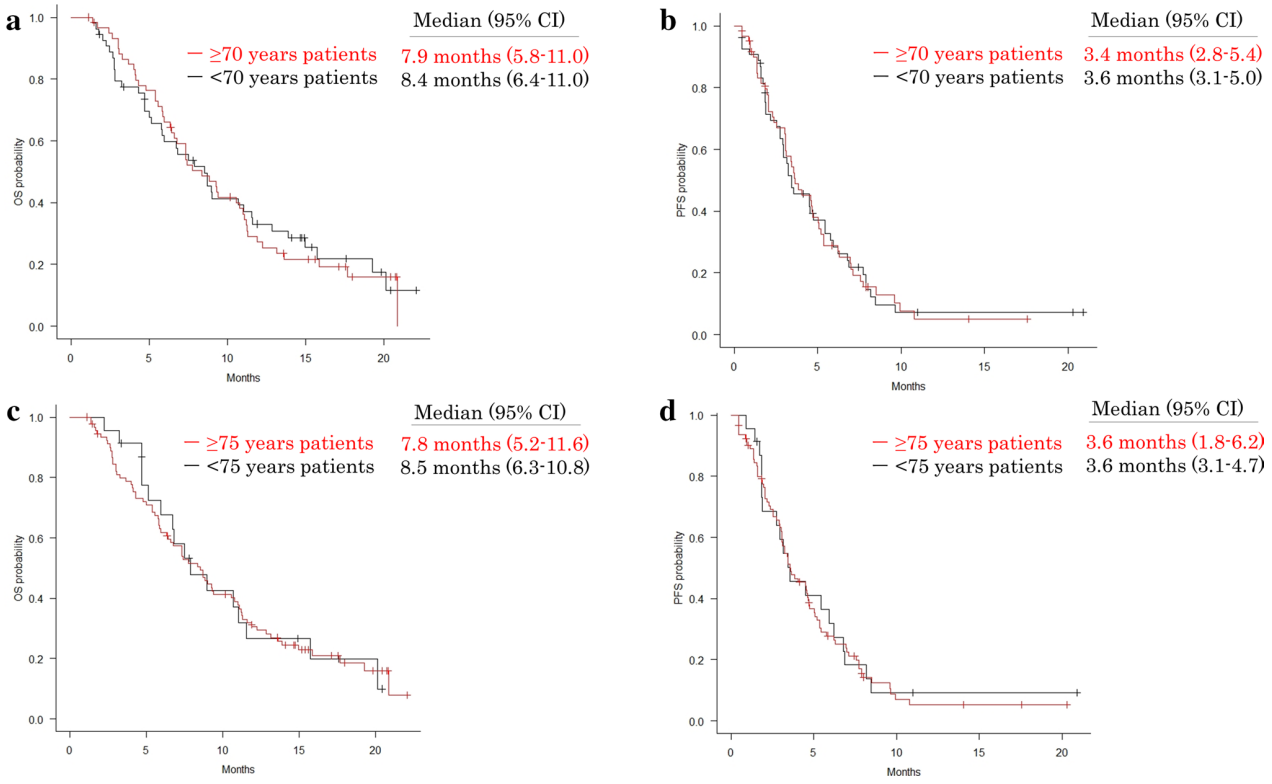

Fig. 1 Overall survival and progression-free survival with comparisons between patients aged < 70 and ≥ 70 years (a and b) and between those aged < 75 and ≥ 75 years (c and d) performance status; [ʃ]IRI, irinotecan; [§]CA 19-9, carbohydrate antigen 19-9; [¶]CRP, C-reactive protein.

Safety

TrAEs observed in patients aged < 70 and ≥ 70 years are presented in Table 2. The most common adverse events were neutropenia, nausea, anorexia, and leukopenia in patients aged < 70 years and anemia, neutropenia, leukopenia, and anorexia in those aged ≥ 70 years. Regarding Grades 3 and 4 trAEs, neutropenia was the most common in both patients aged < 70 (33%) and ≥ 70 (36%) years, while all non-hematological adverse events were < 10%. In patients aged < 70 years, nausea in all grades was significantly higher than in those aged ≥ 70 years ($P = 0.0002$). The results of the safety comparison between patients aged < 75 and ≥ 75 years were similar to those observed in the group using 70 years as the cutoff age (Online Resource 5).

Analysis of prognostic factors

In the multivariate analysis, PS of 1–2, serum levels of CRP ≥ 1.0 mg/mL, and carbohydrate antigen 19–9 ≥ 1000 U/mL were independent prognostic factors for OS (Table 3 and Online Resource 6).

Discussion

We conducted a single-center retrospective study to evaluate the efficacy and safety of nal-IRI + 5-FU/LV in 115 Japanese patients with advanced PDAC, including 54 and 24 patients aged ≥ 70 and ≥ 75 years, respectively. In this study, the efficacy and safety of nal-IRI + 5-FU/LV in older patients were comparable with those in younger patients. Age was not a significant prognostic factor for OS using a cutoff age of either 70 or 75 years.

Patients with PDAC aged ≥ 70 and ≥ 75 years have been reported to account for 50% and 36%–39% of all individuals with pancreatic cancer, respectively [1, 2, 12]. Our study included more older patients with advanced pancreatic cancer than the NAPOLI -1 clinical trial. Therefore, we investigated the outcomes of older patients who received nal-IRI + 5-FU/LV in daily clinical practice. Our findings revealed that PFS did not differ between older and younger patients and that OS was not lower in older patients. Importantly, the OS and PFS obtained in our study were comparable to those of the older subgroups of the NAPOLI-1 trial [8].

Safety is important in older patients because their general condition and activities of daily living can easily deteriorate

Table 2 Incidence of treatment-related adverse events based on patient age group

	Total		All grade	Grade 2	Grade 3	Grade 4
Fatigue	33 (28%)	≥ 70 years	15 (28%)	10 (19%)	1 (2%)	0 (0%)
		< 70 years	17 (28%)	12 (20%)	0 (0%)	0 (0%)
Nausea	40 (34%)	≥ 70 years	9 (17%)	1 (2%)	0 (0%)	0 (0%)
		< 70 years	31 (51%)	18 (30%)	2 (3%)	0 (0%)
Anorexia	48 (41%)	≥ 70 years	19 (35%)	6 (11%)	2 (4%)	0 (0%)
		< 70 years	29 (48%)	17 (28%)	2 (3%)	0 (0%)
Vomiting	8 (7%)	≥ 70 years	1 (2%)	0 (0%)	0 (0%)	0 (0%)
		< 70 years	7 (12%)	1 (2%)	1 (2%)	0 (0%)
Diarrhea	30 (26%)	≥ 70 years	15 (28%)	7 (13%)	3 (6%)	0 (0%)
		< 70 years	15 (25%)	3 (3%)	5 (4%)	0 (0%)
Constipation	14 (12%)	≥ 70 years	5 (9%)	2 (4%)	1 (2%)	0 (0%)
		< 70 years	9 (8%)	5 (4%)	0 (0%)	0 (0%)
Leukopenia	44 (38%)	≥ 70 years	20 (37%)	7 (13%)	10 (19%)	0 (0%)
		< 70 years	24 (39%)	12 (19%)	7 (11%)	0 (0%)
Neutropenia	68 (59%)	≥ 70 years	32 (59%)	9 (17%)	12 (22%)	6 (11%)
		< 70 years	36 (56%)	8 (13%)	19 (30%)	4 (6%)
Thrombocytopenia	14 (12%)	≥ 70 years	6 (11%)	6 (11%)	0 (0%)	0 (0%)
		< 70 years	8 (7%)	10 (2%)	2 (3%)	0 (0%)
Anemia	66 (58%)	≥ 70 years	35 (65%)	23 (43%)	7 (13%)	0 (0%)
		< 70 years	31 (27%)	9 (8%)	8 (7%)	0 (0%)

Table 3 Multivariate analysis of prognostic factors for overall survival by patient age group, using an age cutoff of 70 years

	Univariate analysis	Multivariate analysis		
	P-value	Hazard ratio	95% Confidence interval	*P*-value
< 70 years (vs. ≥ 70 years)	0.90	1.13	0.73–1.77	0.59
UICC[a] Stage III (vs. Stage IV)	0.34	1.70	0.80–3.60	0.17
Albumin ≤ 3.5 g/dl (vs. > 3.5 g/dl)	0.05	1.50	0.91–2.50	0.11
ECOG PS[b] 0 (vs. 1–2)	< 0.001	0.42	0.27–0.66	0.0018
History of IRI[c]-containing regimen: no (vs. yes)	0.52	0.92	0.55–1.53	0.75
CA 19-9[d] < 1000 U/ml (vs. ≥ 1000 U/ml)	0.004	0.60	0.37–0.98	0.042
CRP[e] < 1.0 mg/dL (vs. ≥ 1.0 mg/dL)	3.43	2.74	1.61–4.65	< 0.001

[a] *UICC* union for international cancer control

[b] *ECOG PS* eastern cooperative oncology group performance status

[c] *IRI* irinotecan

[d] *CA* 19–9 carbohydrate antigen 19–9

[e] *CRP* C-reactive protein

when an adverse event occurs, making recovery difficult. Nal-IRI + 5-FU/LV is used as a second- or later-line treatment, and the general condition is likely to be worse than at the start of first-line therapy. Therefore, it was an important finding in our study that the safety of nal-IRI + 5-FU/LV in older patients was comparable to that in younger patients. One of the reasons for this result could be the molecule feature of nal-IRI caused it to be distributed to tumors rather than to normal organs [13]. There have been several studies of GEM + nab-PTX for older patients with pancreatic cancer [14–18], and the incidence of adverse events, such as fatigue, weight loss, and postponement of the treatment, were more common in older patients than in younger patients. In these reports, sarcopenia is thought to be the primary reason for the increased risk of adverse events on GEM + nab-PTX in older patients, and the underlying mechanism might be that fat-free mass were better predictors of clearance and volume of distribution of the cytotoxic agents than body surface area [19]. Asama et al. reported that the presence or absence of sarcopenia was not a prognostic factor at all ages but was a poor prognostic factor at age 70 and older

[20]. Additionally, capecitabine, a prodrug of 5-FU used as an adjuvant therapy after resection in colon cancer and 5-FU as a palliative therapy for metastatic breast cancer, has been reported to have a high incidence of adverse events in patients with sarcopenia [19, 21]. Conversely, nal-IRI is designed to be distributed to tumors rather than to normal organs and may be safer to use in older people with typically low muscle volume. However, we did not evaluate the muscle mass volume and presence of sarcopenia in this study; therefore, a future study is warranted to evaluate the association between the safety of nal-IRI + 5-FU/LV in older patients and their body composition. Another reason for the safety of nal-IRI + 5-FU/LV in older patients was the initial dose reduction. In our study, more physicians prescribed initial dose reduction in older patients than in younger patients, with 37% and 42% for patients aged ≥ 70 and ≥ 75 years compared with 18% and 23% of those aged < 70 and < 75 years, respectively. This may have resulted in comparable results of dose reduction and delays during treatment between the older and younger patients.

Despite the lower intensity of the treatment in older patients than in younger patients, we noted that the efficacy in older patients was comparable to that in young patients. This finding is supported by a previous study that concluded that neither early dose reduction nor treatment delay affected the efficacy of nal-IRI + 5-FU/LV [22]. Overall, in older patients, we recommend considering their condition before determining or adjusting treatment doses and reducing the dose from the initial dose may be an option.

This study had some limitations. First, the number of older patients was small. However, the number of patients aged ≥ 70 years was higher than that reported in previous studies. Second, our comparisons of older and younger patients may have been affected by bias due to background factors, such as a higher proportion of patients with ECOG PS of 0 in the older patients than in the younger ones. This would imply that our older patients receiving nal-IRI + 5-FU/LV were in better health than the younger patients. Moreover, the proportion of patients with a prior history of IRI-containing regimens was higher in the younger group. Therefore, we believe that general conditions, such as a PS of 0, should be considered before administering nal-IRI + 5-FU/LV in older patients. Third, the study design was retrospective, and mild trAEs, such as Grades 1–2, may not have been picked up during data collection. Despite these limitations, we believe that our study will help older patients and physicians consider using nal-IRI + 5-FU/LV as a treatment for advanced pancreatic cancer.

Conclusion

Our study of patients with PDAC found that Nal-IRI + 5-FU/LV is a feasible, safe, and effective second-line treatment in older patients with good general condition as well as younger patients. However, these results should be further evaluated through a larger, prospective study.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10147-023-02432-9.

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Author contributions SN, SK, and MU: study concept and design; SN and SK: data acquisition and review; SN, SK, and MU: data interpretation; SN and SK: statistical analysis; SN, SK, and MU: manuscript writing; all authors: manuscript review and approval.

Declarations

Conflict of interest All authors declare that (i) no support, financial or otherwise, has been received from any organization that may have an interest in the submitted work, and (ii) there are no other relationships or activities that could appear to have influenced the submitted work.

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Ⅰ　主論文

Liposomal irinotecan plus fluorouracil/leucovorin in older patients with advanced pancreatic cancer: a single-center retrospective study

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Ⅱ　副論文
なし

Ⅲ　参考論文

Sarcopenia: Prognostic Value for Unresectable Pancreatic Ductal Adenocarcinoma Patients Treated With Gemcitabine Plus Nab-Paclitaxel

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Modified FOLFIRINOX versus sequential chemotherapy (FOLFIRI/FOLFOX) as a second-line treatment regimen for unresectable pancreatic cancer: A real-world analysis

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FOLFOX regimen after failure of fluorouracil and leucovorin plus nanoliposomal-irinotecan therapy for advanced pancreatic cancer: a retrospective observational study

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