Nanoliposomal irinotecan with 5-fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy: A real-world experience

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Abstract

Background: Nanoliposomal irinotecan (nal-IRI), accompanied by 5-fluorouracil (5-FU) and leucovorin (LV), is an effective and safe therapy for patients in whom metastatic pancreatic ductal adenocarcinoma has progressed after gemcitabine-based chemotherapy. Our aim was to evaluate the effectiveness and safety of a nal-IRI + 5-FU/LV regimen for patients with metastatic pancreatic cancer and gemcitabine-based treatment failure in the real world.

Methods: We retrospectively collected the baseline characteristics, treatment courses and dosage, treatment response, overall survival (OS), progression-free survival (PFS), and adverse effects of patients treated with the nal-IRI-based regimen at Taipei Veterans General Hospital.

Results: Sixty-seven patients who received the nal-IRI + 5-FU/LV regimen from August 2018 to June 2019 were identified. Their median age was 65 years and 52% were male. Most patients had an Eastern Cooperative Oncology Group performance status of 0 to 1, but patients with an Eastern Cooperative Oncology Group performance status of 2 to 4 before initiation of the nal-IRI regimen were also enrolled (31%). The median dose intensity was 40.4 mg/m^2 and the median treatment duration was 8.3 weeks (range: 5 days–75.7 weeks). Objective response and disease control rates were 10.4% and 38.8%, respectively. The median OS) was 7.9 months (95% confidence interval [CI]: 5.6–10.1 months) and the median PFS was 2.9 months (95% CI: 1.6–4.1 months). Elevated total bilirubin (hazard ratio [HR]: 4.31, 95% CI: 1.21–15.30, p = 0.024), carcinomatosis (HR: 3.75, 95% CI: 1.46–9.66, p = 0.006), and previous treatment with irinotecan (HR: 4.86, 95% CI: 1.67–14.10, p = 0.004) were associated with a worse OS. Previous treatment with irinotecan (HR: 3.03, 95% CI: 1.22–7.49, p = 0.02) was associated with a worse PFS. The most common all-grade adverse effects were anemia (73.9%), nausea (66.2%), and fatigue (61.5%). The most common grade 3–4 adverse effects were neutropenia (21.5%), anemia (18.5%), and diarrhea (15.4%).

Conclusion: Clinically, nal-IRI + 5-FU/LV is effective and tolerable at reduced doses in patients with metastatic pancreatic adenocarcinoma that has progressed after gemcitabine-based therapy

Keywords: Metastatic pancreatic adenocarcinoma; Nanoliposomal irinotecan; Real-world experience

1. INTRODUCTION

Pancreatic cancer is one of the most lethal malignancies[1,2] due to its late diagnosis and poor response to current treatment. Pancreatic ductal adenocarcinoma is the most common type of pancreatic cancer.[2] In past decades, gemcitabine was the main regimen. It was proved to have a benefit in patient survival.[3] In recent years, some combination chemotherapy regimens have been developed and approved as first-line chemotherapy regimens, including the modified FOLFIRINOX regimen (oxaliplatin, irinotecan, 5-fluorouracil [5-FU], and leucovorin [LV]),[4] and gemcitabine plus nab-paclitaxel.[5] However, the possibility of treatment failure with first-line chemotherapy is still high and effective second-line chemotherapy for rescue therapy is required. Therefore, the US Food and Drug Administration approved nanoliposomal irinotecan (nal-IRI) accompanied by 5-FU and LV as second-line chemotherapy in cases of treatment failure with previous gemcitabine-based chemotherapy. However, clinical experience of second-line therapy with the nal-IRI regimen is still limited.

Irinotecan is a prodrug that can be metabolized to SN-38, an inhibitor of topoisomerase I, and has a role in pancreatic adenocarcinoma treatment as one of the chemotherapeutic agents in FOLFIRINOX. Liposomes are common drug carriers that can

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avoid unwanted drug metabolism in the plasma, increase the drug level in tumors via the enhanced permeability and retention effect, and overcome tissue barriers, leading to better efficacy and safety.[6] Nal-IRI was therefore developed to enhance the effect and reduce the side effects of free-form irinotecan. In NAPOLI-1, the nal-IRI with 5-FU and LV regimen proved to be a better regimen in patients with metastatic pancreatic cancer who had failed to control their disease with the first-line gemcitabine-based regimen. It led to a significant improvement in the overall survival (OS) and had tolerable side effects.[7] Several adverse drug reactions were, however, observed in patients treated with nal-IRI, 5-FU, and LV in the NAPOLI-1 trial, including diarrhea (59%), vomiting (52%), and anorexia (44%). Neutropenia (39%) and anemia (38%) were also documented. In the Asian subgroup analysis, the response and survival analyses were consistent with those of the general population. However, there was more neutropenia and less diarrhea in the Asian group.[8] In current real-world data, there are only a few patients with poor ECOG performance status (>1) who have undergone nal-IRI therapy.[7,9–13]

The aim of this study was to assess the real-world clinical responses and adverse drug reactions of patients with advanced pancreatic cancer treated with the regimen of nal-IRI, 5-FU, and LV in Taiwan.

2. METHODS

2.1. Study design and participants

This was a retrospective study to assess treatment with nal-IRI for metastatic pancreatic cancer in Taipei Veterans General Hospital, Taipei, Taiwan, which provides primary to tertiary medical care to the residents of northern Taiwan, an region of 12 million inhabitants. We enrolled patients who were diagnosed with metastatic pancreatic adenocarcinoma and underwent nal-IRI therapy following failure to control their disease with gemcitabine-based chemotherapy. We recorded patients' baseline characteristics, including sex, age, body mass index (BMI), Eastern Cooperative Oncology Group (ECOG) performance status, total bilirubin, creatinine, albumin, tumor location, initial stage by image, previous lines of chemotherapy, sites and numbers of metastases, and carbohydrate antigen 19–9 (CA19–9) level. We also collected the treatment courses, duration of treatment, starting dose of nal-IRI, and dose adjustment during treatment. The dose intensity was defined as the average dose, adjusting for body surface area during the entire treatment course. This study was approved by the Institutional Review Board of Taipei Veterans General Hospital (2021-03-006AC) and followed the Helsinki Declaration.

2.2. Outcomes

We analyzed the responses and survival of patients who underwent the nal-IRI, 5-FU, and LV regimen, including cancer response, percentage change in size in measurable lesions, OS, and progression-free survival (PFS). The initial staging at diagnosis was based on computed tomography (CT) or magnetic resonance imaging (MRI). Treatment duration was calculated from the day of nal-IRI initiation to the day of disease progression, a shift to other treatment regimens, or when the patient was lost to follow up. We followed up tumor response by either abdominal CT or MRI, according to Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1),[14] and CA19-9 levels. OS was defined as the time from the initiation of the nal-IRI, 5-FU, and LV regimen to the day of any-cause death. PFS was defined as the time from the initiation of nal-IRI to the time of disease progression or death. Serum CA19-9 response was defined as a decrease in the level of CA19-9 of more than 50% from baseline during the treatment period. All adverse effects were recognized based on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

2.3. Statistical analysis

We analyzed the data using the Statistical Package for the Social Sciences (IBM, Armonk, NY) version 23.0 and survival package of R version 3.6.1. Survival outcomes were estimated using the Kaplan–Meier method. Univariate and multivariate analyses of OS and PFS were performed using the Cox proportional hazards model. All variables were considered statistically significant at $p < 0.05$.

3. RESULTS

3.1. Patient characteristics

The enrollment and exclusion profiles are summarized in Fig. 1. A total of 86 patients who were diagnosed with metastatic pancreatic adenocarcinoma and failed to achieve disease control with previous gemcitabine-based therapy were enrolled in this study. However, 19 patients did not receive

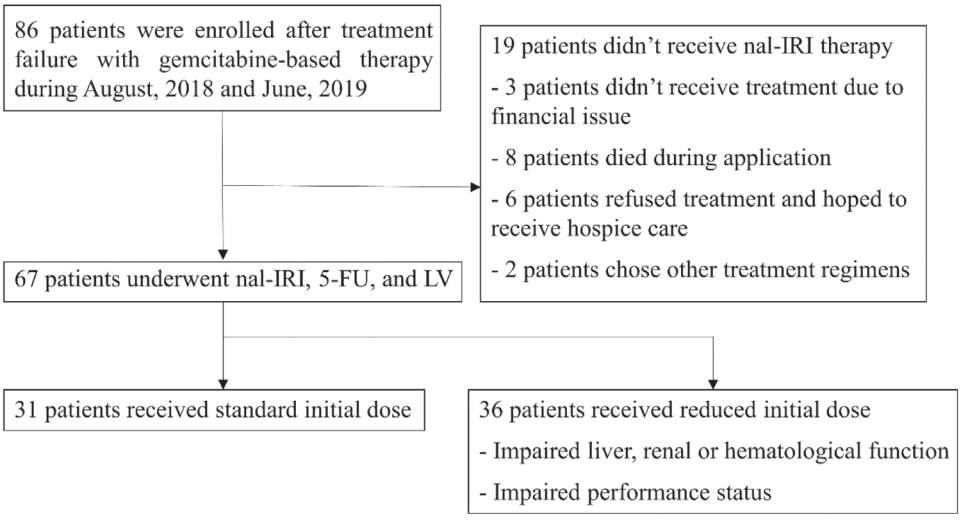

Fig. 1 Flowchart. Nal-IRI = nanoliposomal irinotecan; 5-FU = 5-fluorouracil; LV = leucovorin.

the nal-IRI regimen. Among these, three patients' applications for National Health Insurance to cover nal-IRI were not successful, eight patients died during application for nal-IRI, six patients refused treatment and hoped to receive hospice care, and two patients chose other treatment regimens. Therefore, we enrolled 67 patients who received at least one dose of nal-IRI, 5-FU, and LV between August 1, 2018, and June 30, 2019. The median follow-up time from initiation of the nal-IRI regimen to the cutoff day on June 30, 2020 was 19 months. Baseline patient characteristics are summarized in Table 1. The median age was 63 years (range, 33–83 years), and 35 patients were male (52%). The primary tumor site was most commonly at the pancreatic head in 37 patients (55%). Most patients had an ECOG score of 0 or 1 (28% and 40%, respectively), but there were 21 patients (31%) who had an ECOG stage of 2–4 before the nal-IRI regimen. There were 29 patients (43%) who had received curative surgery with recurrence and/or metastases. The most common metastatic site was the liver (n = 41, 61.2%), followed by the peritoneum (n = 35, 52.2%), lung (n = 12, 17.9%), and other sites (n = 12, 17.9%, including the spleen, n = 6; bone, n = 3; adrenal gland, n = 2; and ovary, n = 1). Thirteen patients (19.4%) had CA19-9 levels <37 U/mL. Eight patients (12%) had received an irinotecan-included regimen and 13 patients (19.4%) had received a 5-FU-included regimen. Twenty-five patients (37%) received radiotherapy before initiating the nal-IRI regimen.

Table 1

Baseline characteristics of the patients

Characteristics	n	%
Age, y		
Median	63	
Range	33–83	
Age ≥ 65 y/o	27	40.3
Male sex	35	52
BMI < 18	13	19.4
ECOG performance status		
0	19	28
1	27	40
2	16	24
3	4	6
4	1	1
Pancreatic tumor location		
Head	37	55
Nonhead	28	42
Missing data	2	3
Initial stage		
IIB	8	11.9
IIIa	19	28.4
IIIB	8	11.9
IV	32	47.8
Previous lines of treatment		
1	24	35.8
2	25	37.3
≥3	18	26.9
Sites of metastases		
Liver	41	61.2
Lung	12	17.9
Peritoneum	35	52.2
Other	12	17.9
Measurable metastatic sites		
1	34	50.7
2	18	26.9
3	9	13.4
4	1	1.5
Initial CA19-9, U/mL		
<37	13	19.4
≥37	54	80.6
Previous treatment		
Irinotecan	8	12
5-FU	13	19
Surgery	29	43
Radiotherapy	25	37

5-FU = 5-fluorouracil; BMI = body mass index; CA19-9 = carbohydrate antigen 19-9; ECOG = Eastern Cooperative Oncology Group.

3.2. Starting dose, cumulative dose, treatment courses, duration of treatment, and dose intensity

The starting dose, cumulative dose, treatment course, duration of treatment, and dose intensity are summarized in Table 2. Dose intensity was defined as the average dose at each time of treatment, adjusted by body surface area. Nal-IRI was administered at 80 mg/m^2. However, a lower starting dose was allowed in patients with old age, impaired ECOG, impaired renal or hepatic function, anemia, or neutropenia. The median starting dose was 36.8 mg/m^2, ranging from 26.1 to 80.5 mg/m^2. The median cumulative dose was 161.5 mg/m^2, ranging from 31.7 to 2248.7 mg/m^2, and the median treatment course was four courses (range: 1–29). The median duration of treatment was 8.3 weeks (range: 0.7–75.7). The median dose intensity was 40.4 mg/m^2.

3.3. Clinical response and survival

The effectiveness data are summarized in Table 3, and the survival analysis is summarized in Table 4. No patient achieved a complete response. Seven patients (10.4%) showed a partial response. Nineteen patients (28.4%) had stable disease, and 25 (37.3%) showed progressive disease. The objective response rate was 10.4% and the disease control rate was 38.8%. The CA19-9 response rate was 28.4%, with 19 patients achieving a CA19-9 response. Logistic regression was performed to analyze the possible predictor of the good or poor tumor responses in these patients (Table 5). In multivariate analysis, age ≥ 65 years was a worse prognostic factor (hazard ratio [HR]: 4.52, 95% confidence interval [CI]: 1.01–20.34; p = 0.049).

Table 2

Dose delivery

Dose and duration of treatment	n (%)
Starting dose of nal-IRI, mg/m^2	
Median	36.8
≥49	31 (46.3%)
<49	36 (67.2%)
Cumulative dose of nal-IRI, mg/m^2	
Median	161.5
Range	31.7–2248.7
Treatment courses	
Median	4
Range	1–29
Duration of treatment, wks	
Median	8.3
Range	0.7–75.7
Dose intensity of nal-IRI, mg/m^2	
Median	40.4
≥49	21 (31.3%)
<49	46 (68.7%)

Nal-IRI = nanoliposomal irinotecan.

Table 3

Tumor responses

nal-IRI + 5-FU/LV (n = 67)	n	%
Best response		
CR	0	0
PR	7	10.4
SD	19	28.4
PD	25	37.3
N/A	16	23.9
CA19-9 response	19	28.4
Objective response (CR + PR)	7	10.4
Disease control (CR + PR + SD)	26	38.8

5-FU = 5-fluorouracil; CR = complete response; LV = leucovorin; N/A = not available; Nal-IRI = nanoliposomal irinotecan; PD = progressive disease; PR = partial response; SD = stable disease.

Table 4

Survival analysis

nal-IRI + 5-FU/LV (n = 67)	Months or %	95% CI
Median OS	7.9	5.6–10.1
6-mo OS	59%	47–73
Median PFS	2.9	1.6–4.1
6-mo PFS	22%	14–35

5-FU = 5-fluorouracil; 95% CI = 95% confidence interval; LV = leucovorin; Nal-IRI = nanoliposomal irinotecan; OS = overall survival; PFS = progression-free survival.

Table 5

Regression analysis of clinical responses

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*	HR	95% CI	*p*
Sex (male vs female)	2.50	0.91–6.86	0.08	2.93	0.67–12.81	0.15
Age (≥65 vs <65 y)	1.98	0.72–5.47	0.19	4.52	1.01–20.34	0.049
BMI (<17 vs ≥17)	1.21	0.25–5.89	0.82	1.20	0.13–10.96	0.87
ECOG (2–4 vs 0–1)	0.78	0.27–2.24	0.65	0.20	0.03–1.35	0.10
T. bilirubin (≥1.2 vs <1.2 mg/dL)	1.55	0.42–5.66	0.51	3.23	0.39–27.09	0.28
Albumin (<3 vs ≥3 mg/dL)	2.47	0.61–10.01	0.20	4.32	0.64–29.41	0.14
Creatinine (≥1.2 vs <1.2 mg/dL)	0.95	0.15–6.09	0.96	0.39	0.03–5.27	0.48
Location (head vs other sites)	1.23	0.45–3.35	0.68	1.04	0.28–3.91	0.96
Liver metastases	3.72	1.31–10.53	0.01	4.59	0.92–22.81	0.06
Carcinomatosis	0.70	0.26–1.88	0.48	1.22	0.25–5.99	0.80
Previous treatment with 5-FU	2.47	0.61–10.01	0.20	2.17	0.16–29.51	0.56
Previous treatment with irinotecan	5.15	0.60–44.54	0.14	4.21	0.15–120.34	0.40
Previous lines of treatment (3rd line or later vs 2nd line)	1.21	0.44–3.34	0.72	0.54	0.10–2.93	0.47
Starting dose (≥49 vs <49 mg/m^2)	1.01	0.38–2.70	0.99	2.39	0.28–20.08	0.42
Dose intensity (≥49 vs <49 mg/m^2)	1.30	0.46–3.70	0.63	0.63	0.08–4.71	0.65
Adverse effects (gr. 3–4 vs gr. 0–2)	0.83	0.31–2.23	0.71	0.94	0.20–4.46	0.94

95% CI = 95% confidence interval; BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio.

In this real-world analysis, no patients received other second-line chemotherapy. A total of 60 patients received best supportive care. Because there was no second-line chemotherapy starting date in the best supportive care patients, we used the last date of the first line chemotherapy as the starting day index to compare to the last date of the first line chemotherapy as the starting day index in the nal-IRI plus 5-FU and LV group. Median OS in patients assigned nal-IRI plus 5-FU and LV was 9.1 months (95% CI: 6.8–11.3 months) vs 0.9 months (0.4–1.4 months) with best supportive care (HR: 0.14, 95% CI: 0.1–0.2; $p < 0.001$). However, there were many confounding factors and further prospective studies are needed.

The best percentage change in tumor size is depicted in Fig. 2. The median OS was 7.9 months (95% CI: 5.6–10.1 months) and the median PFS was 2.9 months (95% CI: 1.6–4.1 months). The 6-month OS rate was 59% (95% CI: 47%–73%) and the 6-month PFS rate was 40% (95% CI: 29%–56%). In the swimmer plot (Fig. 3), most patients with ECOG 2–4 were in the lower dose intensity group ($p = 0.04$). The duration of therapy was similar between the higher and lower intensity groups (median: 9.1 vs 7.6 weeks, $p = 0.8$). A better OS was observed in patients with ECOG 0–1 ($p = 0.0028$, Fig. 4A). However, statistical significance was not reached in PFS ($p = 0.051$, Fig. 4B).

3.4. The relationship between dose intensity and survival

Further evaluation was performed of patients in the higher dose intensity group (dose intensity ≥ 49 mg/m^2), and the lower dose intensity group (dose intensity < 49 mg/m^2). The response rates were similar (lower dose intensity 11% vs higher dose intensity 10%, $p = 0.85$). Both OS (8.6 vs 7.4 months) and PFS (3.3 vs 2.5 months) showed no statistical significance (Fig. 5A, B). There was also a similar duration of treatment (median: 1.8 vs 2.1 months, $p = 0.91$).

3.5. Multivariate analysis of OS and PFS

Multivariate analyses were performed for possible predictive factors of OS and PFS (Tables 6 and 7). Elevated total bilirubin (HR: 4.46, 95% CI: 1.21–16.44, $p = 0.03$), carcinomatosis (HR: 4.18 95% CI: 1.58–11.05, $p = 0.004$), and previous treatment with irinotecan (HR: 5.36, 95% CI: 1.84–15.61, $p = 0.002$) were associated with a worse OS. Previous treatment with irinotecan (HR: 3.41, 95% CI: 1.37–8.46, $p = 0.01$) was associated with a worse PFS.

3.6. Adverse effects

Sixty-six patients (99%) suffered from any-grade adverse effects and 31 patients (46%) suffered from grade 3 or 4 adverse effects (Table 8). The most common any-grade adverse effect was anemia (n = 62, 93%), followed by nausea (n = 51, 76%), neutropenia (n = 44, 66%), and fatigue (n = 44, 66%). The most common grade 3–4 adverse effects were neutropenia (n = 14, 21%), anemia (n = 13, 19%), and diarrhea (n = 10, 15%). Univariate analysis and multivariate analysis were performed for the survival analysis of patients with or without grade 3 or 4 adverse effects, and showed no significant differences. We also compared the relationship between patients with grade 3 or 4 adverse effects and tumor responses. However, there were no significant differences. Both may be due to the limited number of patients in our study.

4. DISCUSSION

Nal-IRI with 5-FU and LV regimens is the second-line chemotherapy treatment of choice for patients with pancreatic ductal adenocarcinoma and disease progression after gemcitabine-based chemotherapy.[7] However, a relatively higher percentage of

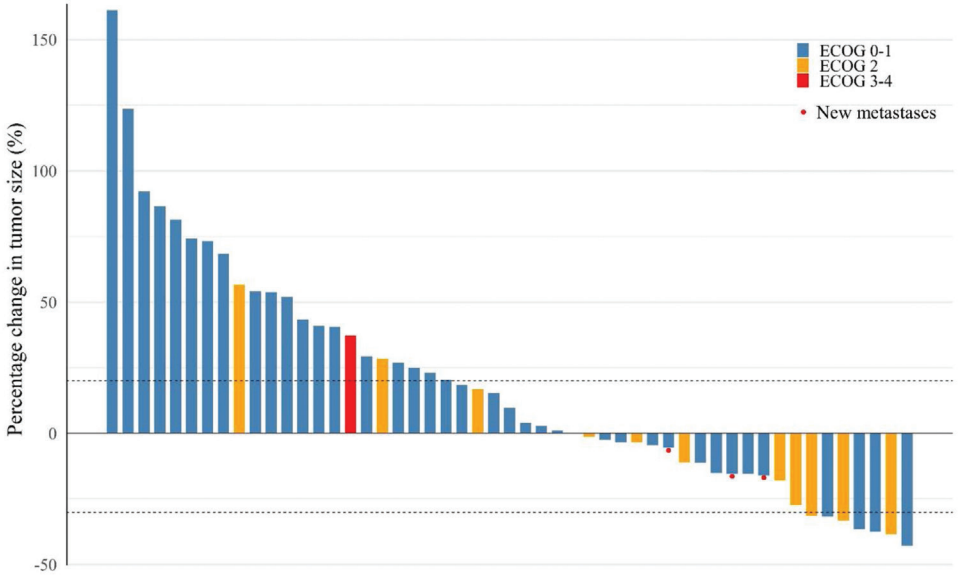

Fig. 2 Waterfall plots demonstrate the percentage of the best measurable tumor size change after nanoliposomal irinotecan treatment. Different color reveal different ECOG performance status, 0–1 (dark blue), 2 (orange), and 3–4 (red). Red dots revealed newly found metastatic lesions in follow-up image studies. ECOG = Eastern Cooperative Oncology Group.

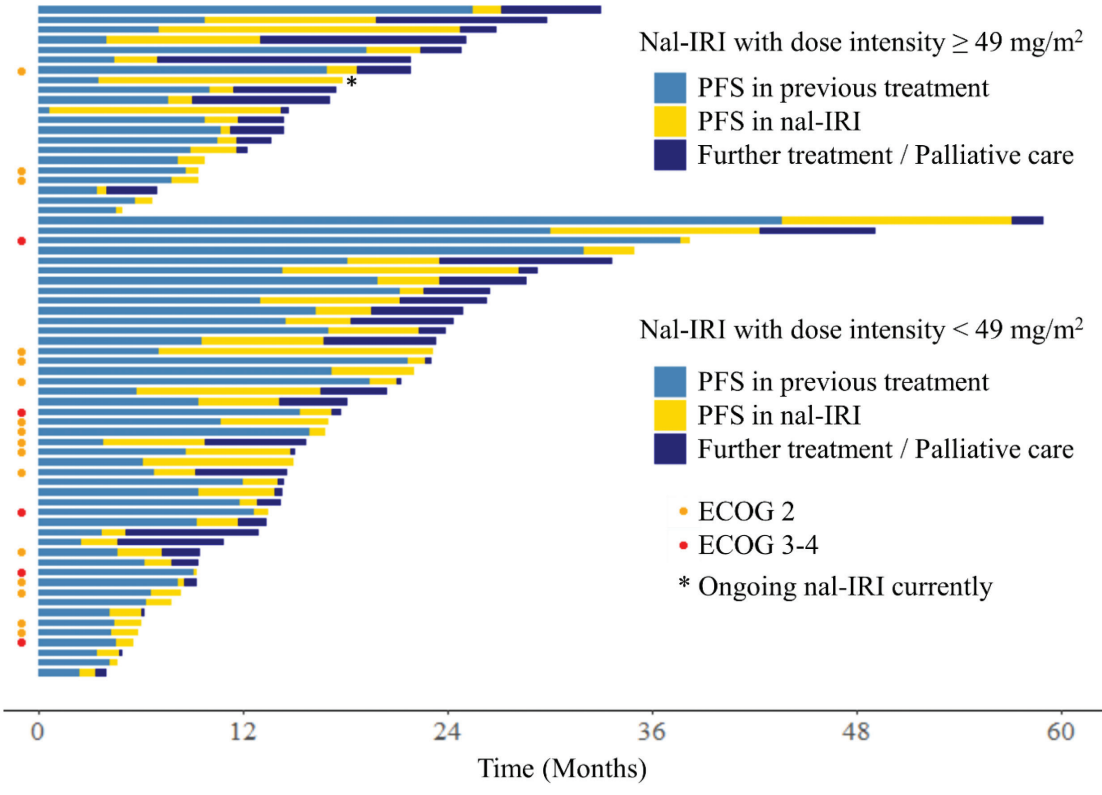

Fig. 3 The swimmer plot demonstrates the duration of previous treatment (in light blue), nal-IRI treatment period (yellow), and further treatment or palliative care period after nal-IRI treatment (deep blue). Two groups were separated by dose intensity during nal-IRI treatment period. Dot color in the front reveal the ECOG performance status. The star marked the patient who still received nal-IRI therapy on June 30, 2020. ECOG = Eastern Cooperative Oncology Group; Nal-IRI = nanoliposomal irinotecan; PFS = progression-free survival.

neutropenia occurs during treatment and sometimes is severe or causes neutropenic fever, leading to morbidity or even mortality during medical treatment in Asia.[8] We report a single-center real-world experience of nal-IRI with 5-FU and LV therapy for metastatic pancreatic cancer. In the current study, all outcomes, including response rates (10.4%), OS (median: 7.9 months), and PFS (median 2.9 months), were consistent with those of recently reported studies,[7,9–13,15] even though 31% of the patients with

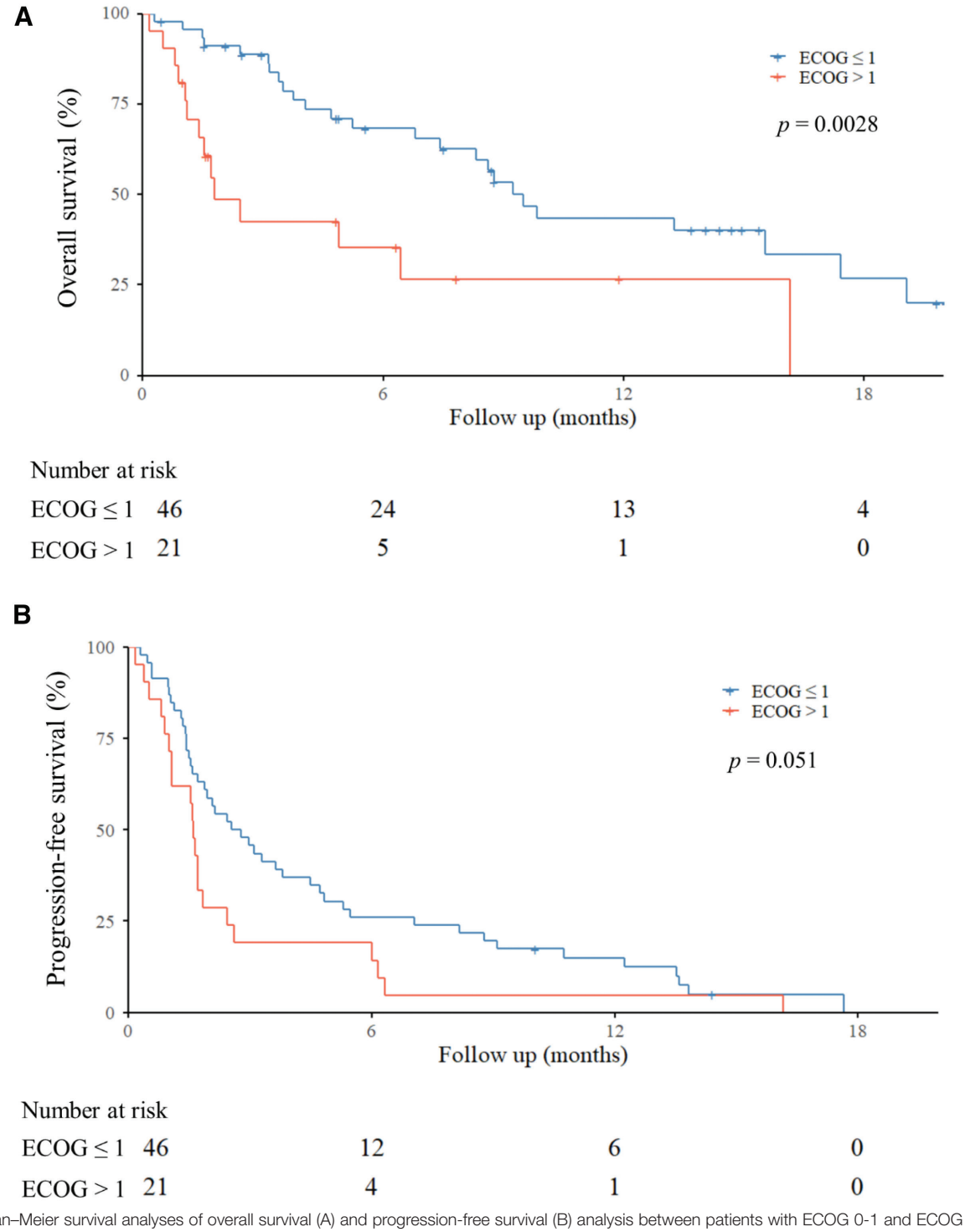

Fig. 4 Kaplan–Meier survival analyses of overall survival (A) and progression-free survival (B) analysis between patients with ECOG 0-1 and ECOG 2-4. ECOG = Eastern Cooperative Oncology Group.

a relatively poor condition (ECOG ≥ 2) were enrolled in this study. Further multivariate analysis was performed to identify predictive markers for patient prognosis. In multivariate analysis, high total bilirubin before treatment, liver metastases, carcinomatosis, and previous irinotecan use were associated with poor OS. Currently, there are limited real-world data to evaluate the relationship between ECOG and outcome. Glassman et al[10] enrolled 12 patients (21%) with ECOG performance status 2 and reported that ECOG performance status at the start of the nal-IRI regimen was not significantly associated with PFS or OS. However, Barzi et al[13] reported that the OS was worse with poor performance status. The relationship between ECOG 2–4 and a poor outcome, which was identified by Kaplan–Meier analysis in this study, was not seen in multivariate analysis.

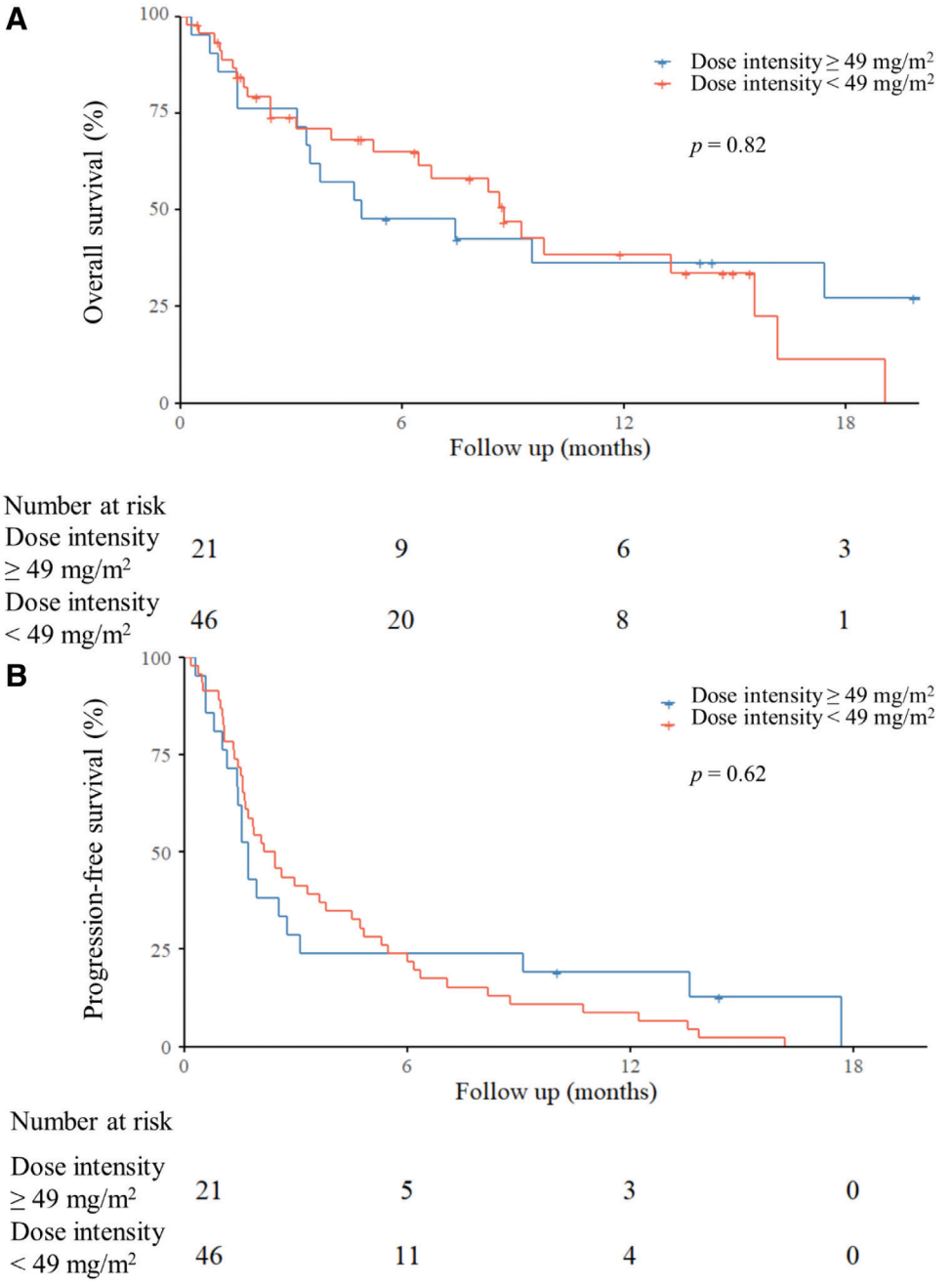

Fig. 5 Kaplan–Meier survival analyses of overall survival (A) and progression-free survival (B) in all patients between higher dose intensity group and lower dose intensity group.

This might be due to the relatively small sample size in this study. Therefore, there is still no conclusion about the relationship between ECOG and OS.

Reduced dose intensity of nal-IRI is prescribed in most elderly patients with impaired organ function, and/or poor performance status, due to higher rates of neutropenia. In the Asian subgroup analysis of NAPOLI-1, the ≥grade 3 neutropenia rate was higher (54.5%) than that in NAPOLI-1 (27%).[7,8] Unencapsulated SN-38 concentration was higher in Asian patients during the treatment of nal-IRI,[16] which may result in more frequent neutropenia. Comparable outcomes were observed between the lower and higher dose intensity groups, such as objective response rate, OS, and PFS. In addition, there was a similar duration of treatment. In a real-world study, dose reduction was common due to fatigue or other adverse effects.[15] Glassman et al[10] reported a lower starting dose with a median dose of 55 mg/m^2, and lower serious adverse event rates were recorded. The study also concluded that starting dose and dose reduction were not associated with worse outcomes, including PFS and OS.

Among patients with a starting dose above 49 mg/m^2, nine patients (29%) had a reduced dose in the first three times they received chemotherapy. There were also nine patients (29%) who received <3 doses of chemotherapy due to poor condition or adverse effects. Only 13 patients (42%) could tolerate

Table 6

Univariate and multivariate analyses of overall survival

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*	HR	95% CI	*p*
Sex (male vs female)	1.41	0.75–2.64	0.29	1.10	0.49–2.47	0.82
Age (≥65 vs <65 y)	1.14	0.60–2.15	0.69	1.11	0.53–2.33	0.78
BMI (<17 vs ≥17)	1.74	0.67–4.53	0.26	1.06	0.42–2.64	0.91
ECOG (2–4 vs 0–1)	2.93	1.47–5.83	0.002	1.99	0.71–5.61	0.19
T. bilirubin (≥1.2 vs <1.2 mg/dL)	1.92	0.83–4.44	0.13	4.46	1.21–16.44	0.03
Albumin (<3 vs ≥3 mg/dL)	1.10	0.46–2.63	0.84	1.65	0.60–4.56	0.33
Creatinine (≥1.2 vs <1.2 mg/dL)	0.67	0.16–2.79	0.58	0.66	0.11–4.15	0.66
Liver metastases	2.15	1.09–4.24	0.027	1.67	0.70–4.02	0.25
Carcinomatosis	1.55	0.82–2.92	0.17	4.18	1.58–11.05	0.004
Previous treatment with irinotecan	4.20	1.83–9.60	0.001	5.36	1.84–15.61	0.002
Previous lines of treatment (3rd line or later versus 2nd line)	1.71	0.87–3.38	0.12	2.07	0.84–5.14	0.12
Starting dose (≥49 vs <49 mg/m^2)	1.03	0.55–1.91	0.94	0.51	0.18–1.51	0.23
Dose intensity (≥49 vs <49 mg/m^2)	1.01	0.34–1.91	0.97	3.18	0.94–10.83	0.06

95% CI = 95% confidence interval; BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio.

Table 7

Univariate and multivariate analyses of progression-free survival

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*	HR	95% CI	*p*
Sex (male vs female)	0.67	0.41–1.10	0.11	1.41	0.75–2.66	0.29
Age (≥65 vs <65 y)	1.09	0.66–1.82	0.73	1.21	0.68–2.17	0.52
BMI (<17 vs ≥17)	1.55	0.70–3.44	0.28	1.32	0.61–2.83	0.48
ECOG (2–4 vs 0–1)	1.82	0.16–3.13	0.03	2.07	0.97–4.43	0.06
T. bilirubin (≥1.2 vs <1.2 mg/dL)	1.86	1.00–3.45	0.05	2.05	0.87–4.82	0.10
Albumin (<3 vs ≥3 mg/dL)	1.08	0.58–2.04	0.80	0.71	0.34–1.52	0.38
Creatinine (≥1.2 vs <1.2 mg/dL)	1.29	0.51–3.25	0.59	0.89	0.25–3.15	0.86
Liver metastases	1.72	1.03–2.86	0.04	1.04	0.54–2.00	0.90
Carcinomatosis	1.24	0.75–2.04	0.40	0.72	0.37–1.40	0.33
Previous treatment with irinotecan	3.16	1.45–6.86	0.004	3.41	1.37–8.46	0.01
Previous lines of treatment (3rd line or later versus 2nd line)	1.09	0.66–1.82	0.73	1.09	0.56–2.11	0.80
Starting dose (≥49 vs <49 mg/m^2)	0.83	0.51–1.36	0.46	0.54	0.24–1.24	0.15
Dose intensity (≥49 vs <49 mg/m^2)	0.99	0.59–1.66	0.97	2.12	0.91–4.96	0.08

95% CI = 95% confidence interval; BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio.

Table 8

Adverse events

Adverse events for any grade and grades 3–4

	Any grade	%	Grades 3–4	%
Total	66	99	31	46
Diarrhea	39	58	10	15
Vomiting	40	60	4	6
Nausea	51	76	7	10
Fatigue	44	66	4	6
Neutropenia	44	66	14	21
Anemia	62	93	13	19

>3 doses of chemotherapy. On the other hand, in patients with a starting dose of <49 mg/m^2, 23 patients (64%) were able to tolerate the nal-IRI regimen. There were 13 patients (36%) that did not receive at least three doses of chemotherapy due to poor condition or severe adverse effects such as neutropenic fever with septic shock, even under a lower starting dose of nal-IRI.

The safety profiles in the current study were manageable, with a total of 44% patients experiencing ≥grade 3 adverse effects, including neutropenia (22%), anemia (18%), and diarrhea (15%). In the current study, similar efficacy (tumor response, OS, and PFS) but less ≥grade 3 neutropenia (22%) occurred compared to the Asian subgroup analysis of NAPOLI-1 (54.5%), and this difference may have resulted from a reduced dosage of nal-IRI.

This study had several limitations. First, this was a retrospective study, which could have resulted in some selection bias and recall bias. Second, this was a tertiary medical center-based study, and a relatively small sample size was included, which might not represent the entire population. Therefore, further multi-center studies may be needed to evaluate its efficacy and safety of the regimen. Third, in our study, we did not perform UGT1A1 genotype testing, which may cause irinotecan overdose and more adverse effects. In the FDA recommendations, the recommended dose for patients who are known to be homozygous for the UGT1A1*28 allele is 50 mg/m^2. In addition, the UGT1A1*6 allele can also increase the incidence of neutropenia, which occurs more frequently in Asian populations.[8] In our study, only 31 patients (46.3%) received first doses of nal-IRI above 50 mg/m^2. Further investigation of the relationship between effectiveness, adverse effects, and the pattern of the UGT1A1 allele is needed.

In conclusion, nal-IRI with the 5-FU/LV regimen at reduced doses is an effective and tolerable second-line chemotherapy for gemcitabine-based treatment failure of metastatic pancreatic adenocarcinoma in a real-world context. In patients with relatively poor ECOG or impaired organ function, it is reasonable to reduce the dose intensity of nal-IRI with noninferior outcomes and more tolerable adverse effects.

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