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Original Article

The impact of spleen volume on the survival of metastatic pancreatic adenocarcinoma patients receiving nanoliposomal irinotecan

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Abstract: Nanoliposomal irinotecan (nal-IRI) plus 5-fluorouracil and leucovorin (NalFL) comprises the current standard for gemcitabine-failed metastatic pancreatic ductal adenocarcinoma (PDAC). As liposomes generally accumulate in the spleen, we evaluated the impact of spleen volume on prognosis. We enrolled patients with metastatic PDAC who failed gemcitabine-based therapy and were initiated on NalFL between August 2018 and November 2020. The spleen volume before NalFL administration was evaluated. They were stratified into dose subgroups (i.e. low, < 48 mg/m^2; intermediate, 48 - < 64 mg/m^2; high, ≥ 64 mg/m^2) by the average nal-IRI dose during the entire treatment, and multivariate analysis of overall survival (OS) was performed. We included 547 patients with a median age of 63 years (range, 27-89 years) and a median of 1 (range, 0-7) palliative chemotherapy regimen. The median spleen volume was 245 mL (range, 82-817 mL). Among patients with splenomegaly (≥ 245 mL), the low-dose subgroup had the worst median time to treatment failure (TTF, 1.8 months vs. 2.5 months vs. 2.5 months, P = 0.020) and OS (3.3 months vs. 5.9 months vs. 6.6 months, P = 0.018) as against no prognostic impact in patients without splenomegaly. In the multivariate analysis of patients with splenomegaly, performance status (PS) ≥ 2, body surface area (BSA) < 1.6 m^2, prior fluoropyrimidine use, liver metastasis, and low-dose subgroup were independent poor prognostic factors. A low average nal-IRI dose was significantly associated with poor prognosis, especially among patients with splenomegaly. Further pharmacological studies should validate the relevance of spleen volume on the treatment outcomes of nal-IRI.

Keywords: Nanoliposomal irinotecan, pancreatic cancer, dose, spleen

Introduction

Pancreatic cancer is the most challenging malignancy, with steadily increasing trends of incidence and mortality worldwide [1, 2]. The last decade witnessed a therapeutic breakthrough leading to modest prolongation in the survival of patients with pancreatic ductal adenocarcinoma (PDAC). In the first-line setting for metastatic PDAC, gemcitabine plus nab-paclitaxel proved its superiority in terms of overall survival (OS), progression-free survival (PFS), and response rate (RR) comparing to gemcitabine, as much as the FOLFIRINOX regimen [3, 4]. Along with gemcitabine, oral S-1 is an alternative with similar single-agent efficacy for advanced PDAC [5]. Beyond the first-line setting, the poly (ADP)-ribose polymerase inhibitor olaparib has been indicated as maintenance therapy among patients with metastatic pancreatic cancer who carry the germline *BRCA1* or *BRCA2* mutation and at least have stable disease following treatment with frontline platinum-containing regimens [6]. Pembrolizumab has been approved for microsatellite instability-high solid tumors, including PDAC, if cancer progresses despite prior standard treatment [7]. However, for most patients with metastatic PDAC without these rare actionable genetic alterations, nanoliposomal irinotecan (nal-IRI) plus 5-fluorouracil and leucovorin (NalFL) is the only approved therapy if the gemcitabine-based therapy fails [8].

For real-world practice, it is hard to generalize the use of NalFL with standard dose beyond the progression of frontline gemcitabine-based therapy in metastatic PDAC. Most patients enrolled in the NAPOLI-1 trial had a good performance status (PS), and fewer than 10% of the patients had a Karnofsky PS score of less than 80 [8]. Therefore, the clinical trial results in patients with a good condition do not translate into comparable outcomes in clinical settings [9, 10]. The NalFL arm of the NAPOLI-1 trial showed a limited OS benefit of approximately 2 months [8]. Further, patients in this trial need to have preserved liver function [8]. Not only liver is important for irinotecan in metabolism and conversion into its active metabolite, but liver is also the most common metastatic organ of PDAC. Patients with pancreatic head tumors frequently exhibit obstructive jaundice, leading to the subsequent deterioration of liver function. The mean dose of nal-IRI over 6 weeks for patients in the NalFL arm was 167.5 mg/m^2, representing only 70% of the scheduled dose [8]. NalFL had to be discontinued owing to adverse events (AEs) in 11% of the patients [8]. Balancing the risks and benefits of palliative treatment after progression of frontline therapy in advanced PDAC is challenging yet important.

The spleen, a major organ in the reticuloendothelial system (RES), comprises abundant phagocytic cells. Theoretically, liposomes intrinsically tend to accumulate in the spleen [11, 12]. The nal-IRI accumulation within the spleen was identified in the HT29 xenograft model [13]. Splenomegaly remains a common feature of advanced PDAC [14] and may potentially perturb the pharmacokinetics of nanodrugs. Therefore, the liposomal drug accumulation should not be neglected in patients with PDAC with splenomegaly. In this collaborative multicenter retrospective study, we investigated the determinants and prognostic implications of nal-IRI dosing in the real-world context among patients with metastatic PDAC. We further evaluated the effects of spleen volume based on nal-IRI dosing.

Materials and methods

Patient selection and evaluation

This multicenter retrospective study was conducted in compliance with the Declaration of Helsinki and was approved by the research ethics committees of the National Taiwan University Hospital (201911042RINC), Taipei Veterans General Hospital (2021-08-001AC), Tri-Service General Hospital (B202105057), China Medical University Hospital (CMUH109-REC2-176), Chung Shan Medical University Hospital (CS2-21095), National Cheng Kung University Hospital (A-ER-109-477), Chang Gung Memorial Hospital (202100783B0), and Kaohsiung Medical University Hospital (KMUHIRB-E(I)-20210150). The requirement for obtaining informed consent from the patients was waived, considering the study's retrospective nature. As nal-IRI for metastatic PDAC after failure of gemcitabine-based therapy was reimbursed by the National Health Insurance of Taiwan from August 2018 onwards, consecutive patients from these nine medical centers treated with NalFL under the National Health Insurance coverage between August 2018 and November 2020 were selected. After excluding patients receiving other

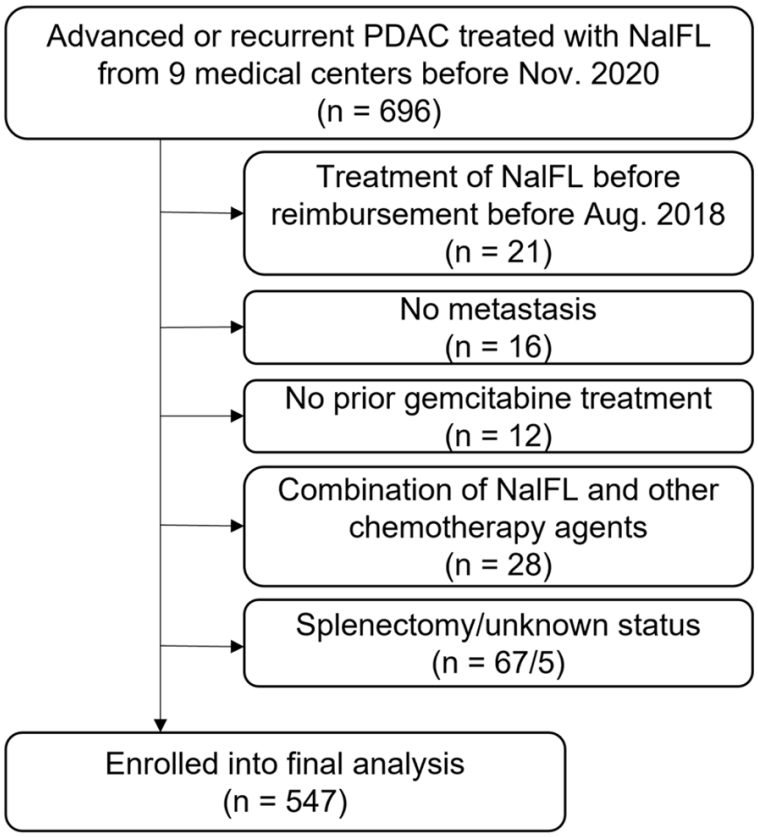

Figure 1. Flow diagram of patient selection.

chemotherapy agents with NalFL (N = 28), receiving NalFL treatment before August 2018 (N = 21), without distant metastasis (N = 16), without prior use of gemcitabine (N = 12), with splenectomy (N = 67) or unknown splenectomy status (N = 5), 547 patients with available medical records and computed tomography (CT) or magnetic resonance imaging (MRI) data were identified for analysis (**Figure 1**). Under the regulations of the National Health Insurance, CT or MRI was performed every 3 months for the dosing of nal-IRI. The Response Evaluation Criteria in Solid Tumors (version 1.1) were used to evaluate the response to NalFL treatment. Spleen volume (mL) based on imaging performed before NalFL treatment was estimated using the following formula:

Spleen volume = 30 + 0.58 × maximal width of spleen (cm) × maximal thickness of spleen (cm) × length of spleen (cm), as previously described [15]. Because of no consensus about the spleen volume as splenomegaly, we used the median spleen volume as the cut-off value [16]. The complete blood count and serum biochemistry were evaluated before the first dose of NalFL. The Common Terminology Criteria for Adverse Events version 4.03 was applied to grade the AEs of NalFL treatment.

Statistical analysis

The data cut-off date was 31 December 2020. The OS after NalFL-based therapy was calculated from day 1 of the first cycle of NalFL until the date of death or the last follow-up date. Time to treatment failure (TTF) after NalFL-based therapy was calculated from day 1 of the first cycle of NalFL until the date of imaging-based progressive disease (PD), clinical PD, treatment termination owing to intolerance to AEs, death, or the final follow-up. The average dose (mg/m^2) of nal-IRI for each patient was calculated as the accumulated dose divided by the total dosing times (cycles), and patients were stratified into three subgroups based on the average dose of nal-IRI with low dose (< 48 mg/m^2), intermediate dose (48 to < 64 mg/m^2), and high dose (≥ 64 mg/m^2), representing 60% (48 mg/m^2) and 80% (64 mg/m^2) of the standard nal-IRI dose (80 mg/m^2) in the NalFL regimen [8]. The theoretical dosing frequency for each patient was determined as the total NalFL treatment duration divided by 2 weeks. The dosing intensity (DI) of nal-IRI for each patient was calculated as the accumulated dose (mg/m^2)/[80 (mg/m^2) × theoretical dosing frequency]. Fisher's exact test or the chi-square test was used to analyze the association between the average dose of nal-IRI and clinical parameters, responses, and AEs. The Kaplan-Meier method was used to compare TTF and OS according to clinical parameters and nal-IRI doses. Variables exhibiting at least borderline significance (i.e., P < 0.1) in the univariate analyses of OS were included in multivariate analyses using Cox proportional hazards regression model. SPSS software (version 20.0; IBM Corp., Armonk, N.Y., USA) was used for all analyses. The significance level was set at P < 0.05.

The prognostic model of risk score

The prognostic model of LISPENADO risk score was constructed and calculated with the coefficient of each factor estimated from the Cox proportional hazards regression model: liver metastasis coefficient (without metastasis = 1, with metastasis = 1.5) × bilirubin level (mg/dL) × spleen volume (mL) × performance status coefficient (PS 0 = 1, PS 1 = 1.5, PS ≥ 2 = 3) to predict the nal-IRI dose-associated OS. The risk score for the whole study group was stratified into low risk (score < 220), intermediate risk (score 220-530), and high risk (score ≥ 530). For patients with splenomegaly (spleen volume ≥ 245 mL), the risk score was stratified into low risk (score < 400), intermediate risk (score 400-800), and high risk (score ≥ 800) based on the score distribution.

Results

Patient characteristics

Data from 547 patients were included in the analysis. **Table 1** shows the baseline characteristics of patients stratified into three subgroups according to the average dose of nal-IRI. The median age of the patients was 63 years (range, 27-89 years). A total of 410 (75%) patients had a good ECOG PS of 0 to 1 before NalFL treatment and 152 (28%) patients had been treated with curative surgery. All patients had received a median of 1 (range, 0-7) prior palliative chemotherapy regimen and 204 (37%) patients had received at least two palliative chemotherapy regimens. All patients had been treated with gemcitabine-based therapy. Fluoropyrimidine-based therapy had been administered to 406 (74%) patients. Only 79 (14%) patients had been exposed to irinotecan. The most common site of metastasis before NalFL treatment was the liver (n = 366, 67%). The median spleen volume was 245 mL (range, 82-817 mL). The two subgroups with high and intermediate doses of nal-IRI had more male patients and included patients with prior use of fluoropyrimidine and platinum, a higher lymphocyte count and albumin level, fewer lines of prior palliative chemotherapy, no prior use of taxane, and smaller spleen volume.

Impacts of spleen volume on prognosis and dosing of nal-IRI

Although spleen volume was significantly different among the three dose subgroups (**Table 1**), it did not have prognostic impacts in the whole study population or patients stratified by nal-IRI dose subgroups. The median TTF (2.4 months vs. 2.3 months, P = 0.517) and OS (5.4 months vs. 5.7 months, P = 0.707) were not significantly different between patients with spleen volume < 245 mL and ≥ 245 mL. Nevertheless, spleen volume was significantly associated with different effects on prognosis among the three dose subgroups (**Table 2**). Overall, the patients in the low-dose subgroup had significantly worse median TTF (1.9 months vs. 2.4 months vs. 2.6 months, P = 0.032) and OS (4.1 months vs. 5.7 months vs. 6.0 months, P = 0.007). The patients with spleen volume ≥ 245 mL in the low-dose subgroup had significantly worse median TTF (1.8 months vs. 2.5 months vs. 2.5 months, P = 0.020, **Figure 2A**) and OS (3.3 months vs. 5.9 months vs. 6.6 months, P = 0.018, **Figure 2B**) than those in the other two higher dose subgroups. In contrast, in the patients with spleen volume < 245 mL, neither the median TTF (**Figure 2C**) nor the median OS (**Figure 2D**) significantly differed among the three dose subgroups. Owing to the similar data regarding TTF and OS between the intermediate- and high-dose subgroups, 48 mg/m^2 was used as the cut-off point for patients with splenomegaly (≥ 245 mL) in univariate and multivariate analyses (**Table 3**). In the multivariate analysis of OS, nal-IRI dose < 48 mg/m^2 (P = 0.013), in addition to ECOG PS ≥ 2 (P < 0.001), BSA < 1.6 m^2 (P = 0.028), prior fluoropyrimidine use (P = 0.016), and liver metastasis (P = 0.030), was an independent poor prognostic factor. Among the significantly different baseline characteristics between the low-dose versus intermediate/high-dose subgroups, BSA < 1.6 m^2 was the only significant, independent, poor prognostic factor in patients with splenomegaly. The nal-IRI dose < 48 mg/m^2 was administered to 29% (36/123) and 17% (25/149) of patients with BSA < 1.6 m^2 and ≥ 1.6 m^2, respectively. In patients with splenomegaly, the median average dose of nal-IRI was 63 mg/m^2. However, the median DI was 0.64 and 0.71 in patients with BSA < 1.6 m^2 and > 1.6 m^2, respectively.

Impact of spleen volume and nal-IRI dose on efficacy and AEs

The dosing, treatment outcomes, and AEs stratified by nal-IRI dose subgroups and spleen volumes are summarized in **Table 4**. The cause of treatment failure was consistent among the

Table 1. Patient characteristics stratified into 3 dose subgroups of nal-IRI (N = 547)

Characteristics	Stratification	All	nal-IRI dose subgroup			P
			< 48 mg/m²	48 to < 64 mg/m²	≥ 64 mg/m²	
		N (%)	105	139	303	
Age	median (range)	63 (27-89)	63 (34-81)	63 (33-89)	64 (27-85)	0.479
	(< 65/≥ 65)	326/221	68/37	82/57	176/127	
Sex	male	318 (58)	51	92	175	0.022
	female	229 (42)	54	47	128	
ECOG PS	0-1	410 (75)	74	100	236	0.204
	2-3	137 (25)	31	39	67	
BSA (m²)	< 1.6	295 (54)	68	51	176	< 0.001
	≥ 1.6	252 (46)	37	88	127	
Primary	head	325 (59)	65	82	178	0.845
	body-tail	222 (41)	40	57	125	
Curative surgery	Yes	152 (28)	32	41	79	0.974
	No	395 (72)	73	98	224	
Prior palliative chemotherapy	0-1	343 (63)	51	81	211	< 0.001
	≥ 2	204 (37)	54	58	92	
Prior chemotherapy	FU +	406 (74)	63	107	236	0.001
	FU -	141 (26)	42	32	67	
	Pt +	234 (43)	26	62	146	< 0.001
	Pt -	313 (57)	79	77	157	
	Tax +	179 (33)	57	44	78	< 0.001
	Tax -	368 (67)	48	95	225	
	Iri +	79 (14)	20	27	32	0.016
	Iri -	468 (86)	85	112	271	
Metastasis at nal-IRI initiation	Liver +	366 (67)	80	92	194	0.072
	Liver -	181 (33)	25	47	109	
	Peritoneum +	170 (31)	31	50	89	0.353
	Peritoneum -	377 (69)	74	89	214	
	Lung +	135 (25)	19	33	83	0.156
	Lung -	412 (75)	86	106	220	
Spleen volume (mL)	Median (range)	245 (82-817)	277 (111-636)	270 (107-817)	232 (82-773)	0.006
	(< 245/≥ 245)	275/272	44/61	60/79	171/132	
WBC (×10³ per mm³)	median/range	6.6 (1.9-107)	6.8 (1.9-107)	6.7 (2.2-31.8)	6.5 (1.9-34.5)	0.649
	(< 6.6/≥ 6.6)	274/272	52/53	65/73	157/146	
Neutrophil (×10³ per mm³)	median/range	4.4 (0.3-91.1)	4.6 (0.9-91.1)	4.7 (1.0-29.0)	4.2 (0.3-28.9)	0.294
	(< 4.4/≥ 4.4)	266/264	49/56	61/71	156/137	
Lymphocyte (×10³ per mm³)	median/range	1.1 (0.1-8.7)	1.1 (0.2-8.7)	1.1 (0.3-3.6)	1.2 (0.1-3.2)	0.007
	(< 1.1/≥ 1.1)	256/274	63/42	68/64	125/168	
Hemoglobin (g/dL)	median/range	10.4 (5.6-14.4)	10.3 (7.4-14.2)	10.4 (6.5-13.7)	10.5 (5.6-14.4)	0.454
	(< 10.5/≥ 10.5)	278/268	57/48	74/64	147/156	
Platelet (×10³ per mm³)	median/range	209 (32-1,420)	206 (35-1,420)	213 (34-880)	207 (32-842)	0.816
	(< 210/≥ 210)	277/269	53/52	67/71	157/146	
Albumin (g/dL)	median/range	3.6 (1.9-5.0)	3.4 (2.0-5.0)	3.6 (1.9-5.0)	3.8 (2.1-4.9)	0.006
	(< 3.6/≥ 3.6)	167/185	60/39	41/49	66/97	
Total bilirubin (mg/dL)	median/range	0.6 (0.2-20.0)	0.7 (0.2-20.0)	0.6 (0.3-4.3)	0.6 (0.2-4.4)	0.058
	(< 0.6/≥ 0.6)	223/263	35/63	58/69	130/131	
CrCl (mL/min)	< 60/≥ 60	135/406	28/77	43/93	64/236	0.064

Abbreviations: BSA, Body surface area; CrCl, Creatinine clearance (Cockcroft and Gault formula); ECOG PS, Eastern Cooperative Oncology Group performance status; FU, 5-FU/5-FU analog; Iri, Irinotecan; Tax, Taxanes; nal-IRI, Nanoliposomal irinotecan; Pt, Platinum; WBC, White blood cell.

dose subgroups, with imaging-based PD being the most common cause. In total, one complete response, 47 partial responses, and 136 stable diseases were observed. In the evaluable patients and the entire study group, the RRs were 11% and 9%, with disease control

Table 2. Different effects of spleen volume on nal-IRI dose-associated prognosis

Survival (month) (95% CI)	N	nal-IRI dose subgroup			P
		< 48 mg/m^2	48 to < 64 mg/m^2	≥ 64 mg/m^2	
All patients					
Median TTF	547	1.9 (1.6-2.1)	2.4 (2.0-2.8)	2.6 (2.3-2.9)	0.032
Median OS		4.1 (3.2-5.0)	5.7 (4.4-7.0)	6.0 (5.3-6.6)	0.007
Patients without splenomegaly (spleen volume < 245 mL)					
Median TTF	275	2.0 (1.4-2.6)	2.3 (1.9-2.7)	2.6 (2.2-3.0)	0.618
Median OS		4.1 (2.5-5.7)	5.4 (2.8-7.9)	5.8 (5.1-6.5)	0.273
Patients with splenomegaly (spleen volume ≥ 245 mL)					
Median TTF	272	1.8 (1.4-2.3)	2.5 (2.0-3.0)	2.5 (2.2-2.8)	0.020
Median OS		3.3 (1.4-5.3)	5.9 (4.5-7.3)	6.6 (5.4-7.8)	0.018

Abbreviations: CI, Confidence interval; nal-IRI, Nanoliposomal irinotecan; OS, overall survival; TTF, Time to treatment failure.

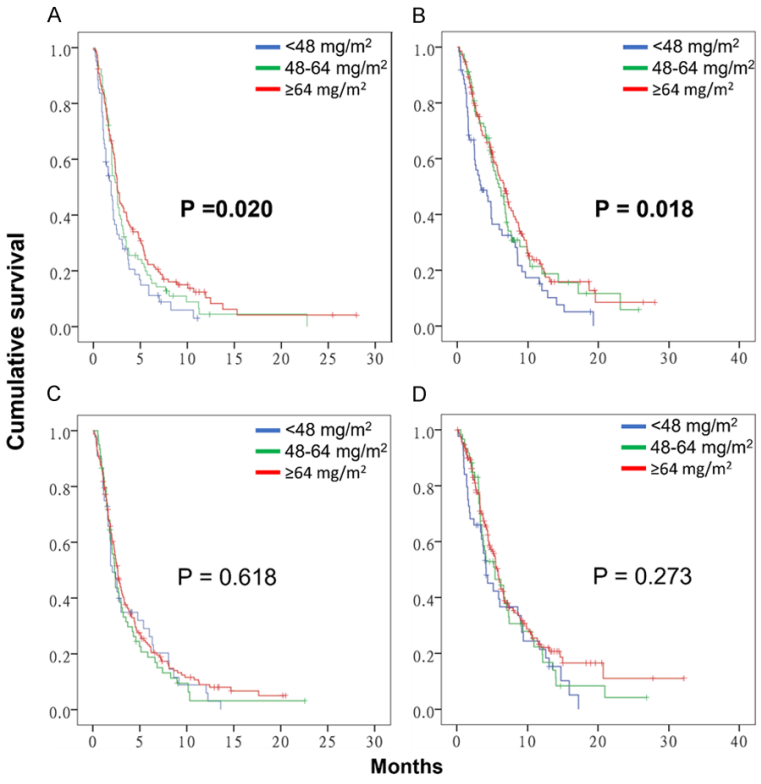

Figure 2. (A) Time to treatment failure (TTF) and (B) overall survival (OS) of patients with splenomegaly after treatment of nanoliposomal irinotecan (nal-IRI) plus 5-fluorouracil and leucovorin (NalFL) stratified into 3 dose subgroups of nal-IRI; (C) TTF and (D) OS of patients without splenomegaly after treatment of NalFL stratified into 3 dose subgroups of nal-IRI.

rates of 41% and 34%, respectively. Irrespective of spleen volume, the dosing pattern of nal-IRI was similar in terms of the cycle, DI, starting dose, and average dose. No significant difference was observed among the dose subgroups in terms of the distribution of the response status, considering the spleen volume (P = 0.682 for spleen volume < 245 mL, P = 0.770 for spleen volume ≥ 245 mL) or not (P = 0.734).

Approximately one-quarter (n = 69) and one-fifth (n = 61) of the patients in the high-dose subgroup (N = 303) had severe (≥ Grade 3) neutropenia and anemia, respectively. Severe thrombocytopenia was rare in all dose subgroups. Overall, severe non-hematological toxicities were rarely observed. However, the incidence of fatigue (P = 0.016), vomiting (P < 0.001), and diarrhea (P = 0.005) significantly increased with increasing doses of nal-IRI and was of grade 1/2 severity in majority. The pattern of nal-IRI dose-related fatigue, vomiting, and diarrhea was consistent between patients with spleen volumes < 245 mL and ≥ 245 mL. However, the increasing trend of fatigue, vomiting, and diarrhea from the intermediate-dose subgroup to the high-dose subgroup seemed smaller in patients with spleen volume ≥ 245 mL compared to < 245 mL.

Balance the benefit and risk in the dosing of nal-IRI considering spleen volume

The association between liver profiles and spleen volume was evaluated because the liver

Table 3. Univariate and multivariate analyses for OS in patients with splenomegaly

Characteristics		N	Univariate			Multivariate		
			HR	95% CI	P	HR	95% CI	P
Age	< 65	195	1.00					
	≥ 65	77	1.09	0.80-1.48	0.581			
Sex	male	179	1.00					
	female	93	1.06	0.79-1.42	0.687			
ECOG PS	0-1	206	1.00			1.00		
	2-3	66	3.26	2.35-4.52	< 0.001	2.56	1.69-3.87	< 0.001
BSA (m^2)	≥ 1.6	149	1.00			1.00		
	< 1.6	123	1.65	1.25-2.18	< 0.001	1.58	1.05-2.37	0.028
Primary	head	154	1.00			1.00		
	body-tail	118	1.45	1.09-1.91	0.010	1.07	0.72-1.60	0.733
Curative surgery	Yes	75	1.00			1.00		
	No	197	1.88	1.35-2.61	< 0.001	1.24	0.78-1.97	0.371
Prior palliative chemotherapy	0-1	162	1.00					
	≥ 2	110	1.26	0.95-1.67	0.109			
Prior chemotherapy	FU -	69	1.00			1.00		
	FU +	203	1.47	1.05-2.07	0.026	1.82	1.12-2.95	0.016
	Pt -	148	1.00			1.00		
	Pt +	124	1.29	0.98-1.70	0.075	1.30	0.81-2.08	0.271
	Tax -	176	1.00					
	Tax +	96	1.04	0.78-1.40	0.787			
	Iri -	221	1.00			1.00		
	Iri +	51	1.56	1.09-2.23	0.015	0.77	0.47-1.26	0.296
Metastasis at nal-IRI initiation	Liver -	75	1.00			1.00		
	Liver +	197	1.45	1.06-1.98	0.020	1.63	1.05-2.52	0.030
	Peritoneum -	185	1.00					
	Peritoneum +	87	1.26	0.94-1.69	0.122			
	Lung -	216	1.00					
	Lung +	56	1.09	0.77-1.53	0.624			
nal-IRI dose (mg/m^2)	≥ 48	61	1.00			1.00		
	< 48	211	1.57	1.14-2.16	0.006	1.70	1.12-2.59	0.013
WBC ($\times 10^3$ per mm^3)	< 6.6	145	1.00			1.00		
	≥ 6.6	127	1.89	1.43-2.50	< 0.001	1.41	0.74-2.70	0.297
Neutrophil ($\times 10^3$ per mm^3)	< 4.4	138	1.00			1.00		
	≥ 4.4	126	1.86	1.40-2.46	< 0.001	1.59	0.83-3.07	0.163
Lymphocyte ($\times 10^3$ per mm^3)	≥ 1.1	123	1.00					
	< 1.1	141	1.13	0.85-1.50	0.401			
Hemoglobin (g/dL)	≥ 10.5	120	1.00			1.00		
	< 10.5	152	1.41	1.06-1.86	0.018	0.83	0.56-1.24	0.367
Platelet ($\times 10^3$ per mm^3)	< 210	160	1.00					
	≥ 210	112	1.16	0.87-1.54	0.308			
Albumin (g/dL)	≥ 3.6	93	1.00			1.00		
	< 3.6	91	1.95	1.40-2.72	< 0.001	1.54	0.99-2.39	0.054
Total bilirubin (mg/dL)	< 0.6	90	1.00			1.00		
	≥ 0.6	156	1.54	1.13-2.10	0.006	0.89	0.60-1.31	0.542
CrCl (mL/min)	≥ 60	211	1.00					
	< 60	57	1.18	0.85-1.65	0.322			

Abbreviations: BSA, Body surface area; CI, Confidence interval; CrCl, Creatinine clearance (Cockcroft and Gault formula); ECOG PS, Eastern Cooperative Oncology Group performance status; FU, 5-FU/5-FU analog; Iri, Irinotecan; NA, Not analyzed; nal-IRI, Nanoliposomal irinotecan; OS, Overall survival; Pt, Platinum; Tax, Taxanes; TTF, Time to treatment failure; WBC, White blood cell.

Table 4. Outcomes and adverse events stratified by nal-IRI dose subgroups and spleen volume

	Spleen volume < 245 mL				Spleen volume ≥ 245 mL			
nal-IRI dose (mg/m^2)	< 48	48 to < 64	≥ 64	P	< 48	48 to < 64	≥ 64	P
N	44	60	171		61	79	132	
Cycle (median, range)	4 (1-26)	4 (1-22)	5 (1-44)	NA	3 (1-22)	4 (1-18)	5 (1-28)	NA
DI (median, range)	0.44 (0.27-0.59)	0.68 (0.37-1.43)	0.85 (0.31-1.87)	NA	0.41 (0.20-0.64)	0.66 (0.15-1.02)	0.82 (0.35-1.69)	NA
Starting dose (median, range)	36 (26-77)	60 (31-81)	73 (46-107)	NA	33 (26-80)	60 (31-82)	74 (46-85)	NA
Average dose (median, range)	36 (26-47)	60 (49-64)	73 (64-92)	NA	34 (24-48)	59 (48-64)	71 (64-90)	NA
			Efficacy					
Response (CR/PR/SD/PD)	0/4/14/19	0/6/11/33	1/13/50/86	0.682	0/5/10/29	0/6/16/40	0/13/35/63	0.770
Disease control rate	41% (18/44)	28% (17/60)	37% (64/171)		25% (15/61)	28% (22/79)	36% (48/132)	
Cause of treatment failure				0.293				0.301
Imaging PD	29	37	83		31	43	67	
Clinical PD	6	10	29		10	12	30	
Intolerance to AEs	2	2	20		6	7	11	
Death	3	5	13		8	10	6	
Treatment-emergent adverse events	0/Grade 1-2/≥ 3			P	0/Grade 1-2/≥ 3			P
Neutropenia	22/10/12	36/8/15	98/35/35	0.579	35/15/11	52/12/12	67/28/34	0.161
Anemia	18/17/9	16/28/15	60/78/31	0.540	21/25/15	24/39/16	36/62/30	0.827
Thrombocytopenia	39/4/1	39/16/4	126/33/10	0.137	40/9/12	54/18/6	79/37/13	0.072
Total bilirubin	33/6/2	42/12/2	129/15/12	0.194	37/13/7	51/16/9	82/28/9	0.828
Creatinine	37/4/1	47/11/1	136/25/3	0.802	45/11/1	61/15/1	101/20/0	0.675
Fatigue (% of ≥ Grade 1)	28/15/1 (36%)	30/24/2 (46%)	60/84/2 (59%)	0.050	37/22/2 (39%)	44/33/1 (44%)	57/58/2 (51%)	0.449
Vomiting (% of ≥ Grade 1)	30/11/3 (32%)	39/15/5 (34%)	85/80/2 (49%)	0.001	42/14/5 (31%)	47/27/5 (41%)	72/56/0 (44%)	0.004
Diarrhea (% of ≥ Grade 1)	30/11/3 (32%)	43/13/3 (27%)	111/54/2 (34%)	0.136	44/12/5 (28%)	51/24/3 (35%)	84/42/1 (34%)	0.047

Abbreviations: AE, Adverse event; ALT, Alanine aminotransferase; CI, Confidence interval; CR, Complete response; DI, Dosing intensity; NA, Not analyzed; nal-IRI, Nanoliposomal irinotecan; OS, Overall survival; PD, Progressive disease; PR, Partial response; SD, Stable disease; TTF, Time to treatment failure.

Table 5. LISPENADO risk score and prognosis

		Low risk	Intermediate risk	High risk	P1
All patients (N = 486)					
Dose	Score	< 220	220 to < 530	≥ 530	
< 48 mg/m^2	N	26	28	44	
	Median OS (95% CI)	9.1 (7.1-11.1)	3.1 (1.0-5.2)	2.4 (1.2-3.6)	0.034
48 to < 64 mg/m^2	N	34	44	49	
	Median OS (95% CI)	7.4 (3.4-11.4)	6.2 (4.0-8.4)	4.8 (3.6-6.0)	0.038
≥ 64 mg/m^2	N	101	91	69	
	Median OS (95% CI)	6.2 (5.0-7.4)	6.6 (5.1-8.1)	4.2 (2.6-5.8)	0.007
P2		0.946	0.060	0.248	
Patients with spleen volume ≥ 245 mL (N = 246)					
Dose	Score	< 400	400 to < 800	≥ 800	
< 48 mg/m^2	N	13	20	24	
	Median OS (95% CI)	4.2 (2.4-6.0)	4.8 (0-17.3)	1.5 (0.2-2.9)	0.003
48 to < 64 mg/m^2	N	19	24	32	
	Median OS (95% CI)	7.1 (0.5-13.7)	6.8 (3.1-10.5)	4.5 (1.7-7.4)	0.009
≥ 64 mg/m^2	N	51	37	26	
	Median OS (95% CI)	8.4 (7.0-9.7)	5.4 (3.1-7.8)	2.5 (0-5.5)	0.015
P2		0.142	0.913	0.046	

Abbreviations: CI, Confidence interval; OS, Overall survival (month). P1: comparison among three risk subgroups; P2: comparison among three nal-IRI dose subgroups.

is the primary site of irinotecan metabolism and metastasis. Liver metastasis (P = 0.006) and bilirubin level (P < 0.001) but not albumin level (P = 0.429) and ALT level (P = 0.135) were significantly associated with spleen volume. The LISPENADO risk score (**Table 5**) with concomitant incorporation of liver metastasis status, bilirubin level, spleen volume, and PS was derived to predict the nal-IRI dose subgroup-associated OS. The median OS differed significantly among the three risk subgroups in all dose subgroups. Notably, for patients with spleen volume ≥ 245 mL and in the high-risk subgroup, treatment with nal-IRI of < 48 mg/m^2 showed a significantly shorter median OS compared to ≥ 48 mg/m^2 (P = 0.046). The receiver operating characteristic (ROC) analysis of the LISPENADO risk score at different time points is summarized in **Figure 3**.

Vomiting was selected as the representative adverse event because of its significant correlation with the nal-IRI dose subgroup, especially in patients with bilirubin < 0.6 mg/dL (**Table 6**), and its significant correlation with fatigue (P < 0.001) and diarrhea (P < 0.001). In addition to the nal-IRI dose subgroup, PS (P = 0.024), primary head tumor (P = 0.017), no liver metastasis (P < 0.001), and peritoneal metastasis (P = 0.004) were significantly associated with the occurrence of vomiting. To evaluate the factors associated with vomiting, a logistic regression model incorporating components of the LISPENADO risk score (PS, liver metastasis, bilirubin, and spleen volume), peritoneal metastasis, primary head tumor, and dose subgroup of nal-IRI was constructed with the occurrence of vomiting as the dependent variable. As **Table 7** demonstrates, a PS of 1 (OR 1.762, 95% CI 1.034-3.002, P = 0.037), nal-IRI dose subgroup ≥ 64 mg/m^2 (OR 1.708, 95% CI 1.002-2.910, P = 0.049), and liver metastasis status (OR 0.534, 95% CI 0.349-0.816, P = 0.004) were significantly associated with vomiting. The probability of vomiting increased with increasing doses of nal-IRI but decreased with liver metastasis. However, the relationship between spleen volume (per mL) and the probability of vomiting was not significant (OR 0.999, 95% CI 0.997-1.000, P = 0.149).

Discussion

Real-world single- or multicenter experience in nal-IRI dosing for advanced or recurrent PDAC has been reported previously; however, these studies did not analyze the role of spleen [17-

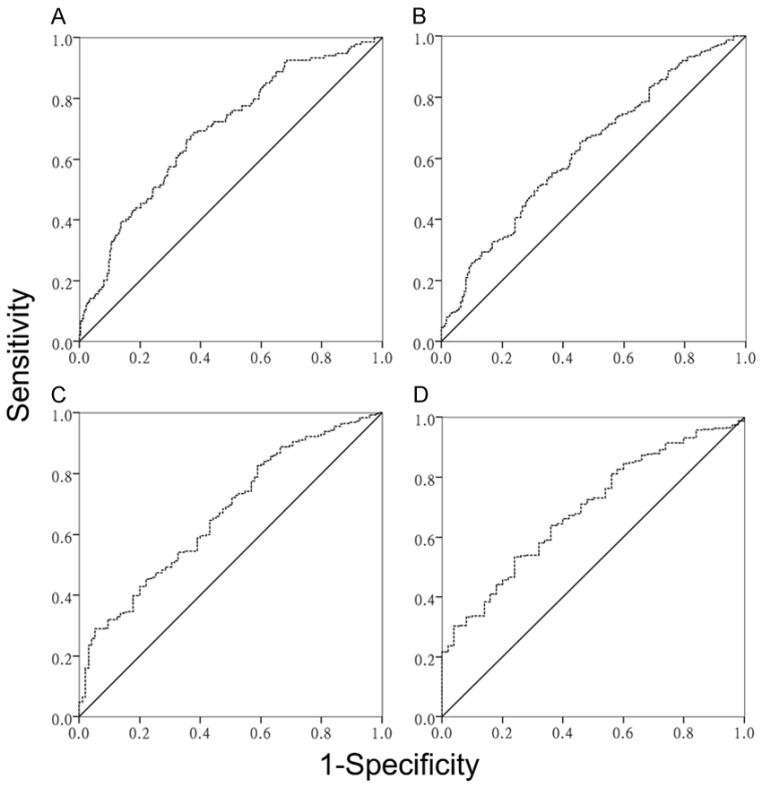

Figure 3. ROC analysis of LISPENADO risk score for prediction of survival status at time points of (A) 3 months, (B) 6 months, (C) 9 months, and (D) 12 months. The area under curves is 0.691 (3 months, N = 434), 0.627 (6 months, N = 412), 0.668 (9 months, N = 389), and 0.691 (12 months, N = 374).

22]. A majority (> 70%) of patients had metastatic diseases [17, 18, 20-22], and the liver was the most common metastatic site [17, 20-22]. These studies reported variable survival data, with OS between 4.3 and 9.4 months and PFS/TTF between 1.9 and 3.84 months. The RR ranged from 5% to 19%, with disease control rates between 43% and 55% [17, 18, 20-22]. Anemia was the most common hematological AE, with lower incidences of neutropenia and thrombocytopenia [17-21]. Gastrointestinal AEs and fatigue were the most common non-hematological toxicities [17-22]. These outcomes were within acceptable ranges in the NAPOLI-1 trial [8]. All patients in our study had recurrence or progression after gemcitabine-based therapy and metastatic diseases. Liver metastasis was observed in 67% of the patients, which was in line with the characteristics of patients from the NAPOLI-1 trial [8]. The prior treatment line was also like that in the NAPOLI-1 trial; the median time from initial metastasis to NalFL was 6.1 months, which was in the range of the PFS data from the gemcitabine plus nab-paclitaxel and FOLFIRINOX regimens [3, 4]. Similarly, anemia was the most common hematological AE in our study population, and fatigue and vomiting were the most common non-hematological AEs. As against the population in the NAPOLI-1 trial, our study cohort had more patients with ECOG PS ≥ 2, primary non-pancreatic head tumor, and prior fluoropyrimidine and platinum use. However, the median TTF of 2.4 (95% CI, 2.2-2.6) months and the median OS of 5.6 (95% CI, 5.0-6.2) months were still comparable with those in the NAPOLI-1 trial with a lower RR in our study cohort.

In addition to baseline patient characteristics, the dose of nal-IRI may be associated with survival. In the NAPOLI-1 trial, the mean dose of nal-IRI was 167.5 mg/m^2 over 6 weeks, representing 70% of the DI of the standard nal-IRI dose (80 mg/m^2 or equivalent to 70 mg/m^2 of irinotecan free base) [8]. Based on real-world experiences, the main reason for dose modification was fatigue or hematological or gastrointestinal toxicities [17, 18, 20, 22]. Considering the dose of nal-IRI delivered, the percentages of dose modifications (reduction or delay) varied initially or subsequently in all these studies, with at least one-third of patients initiated from the standard dose [17, 19, 21]. The DI of nal-IRI ranged from 61% to 85% [17, 19, 21]. To investigate the prognostic impact of the nal-IRI dose, our study cohort was stratified into three subgroups based on the average dose of each patient. The average dose in our study, calculated based on all doses administered to the patients, was theoretically more comprehensive than the doses in other retrospective studies and in the post hoc analysis of the NAPOLI-1 trial, which reported 6-week cumulative doses for analyzing the association of the nal-IRI dose with TTF, OS, and AEs [19, 21, 23]. The OS of patients with early dose modifications of nal-IRI

Table 6. Liver profiles versus adverse events

Liver Mets	Bilirubin (mg/dL)	Dose of nal-IRI (mg/m^2)	N	Vomiting	P	Diarrhea	P	Neutropenia	P
				0/Gr 1-2/Gr ≥ 3		0/Gr 1-2/Gr ≥ 3		0/Gr 1-2/Gr ≥ 3	
+	≥ 0.6	< 48	51	41/8/2	0.157	41/8/2	0.316	24/12/15	0.531
		48 to < 64	52	33/18/1		37/13/1		32/9/10	
		≥ 64	93	59/29/1		57/28/3		51/15/25	
	< 0.6	< 48	24	15/6/3	0.002	14/6/4	0.011	20/3/1	0.353
		48 to < 64	37	25/8/4		26/8/3		27/5/5	
		≥ 64	81	41/40/0		54/27/0		50/14/15	
-	≥ 0.6	< 48	12	4/6/2	0.479	5/6/1	0.134	3/6/3	0.177
		48 to < 64	17	8/8/1		11/6/0		10/2/5	
		≥ 64	38	14/21/1		26/10/0		16/9/13	
	< 0.6	< 48	11	7/4/0	0.002	9/2/0	0.137	4/3/4	0.203
		48 to < 64	21	12/5/4		12/7/2		14/2/5	
		≥ 64	49	20/28/0		32/16/0		27/14/7	

Abbreviations: Gr, Grade; Mets, Metastasis; nal-IRI, Nanoliposomal irinotecan.

Table 7. Logistic regression model of vomiting

Factor	Wald	Significance	OR (95% CI)
PS*			
PS 1	4.331	0.037	1.762 (1.034-3.002)
PS 2	2.508	0.113	1.647 (0.888-3.055)
PS 3	0.989	0.320	1.613 (0.629-4.137)
Bilirubin (mg/dL)	0.751	0.386	1.071 (0.917-1.251)
Liver metastasis	8.402	0.004	0.534 (0.349-0.816)
Spleen volume (mL)	2.079	0.149	0.999 (0.997-1.000)
Peritoneal metastasis	2.302	0.129	1.406 (0.905-2.182)
Primary head tumor	3.499	0.061	1.454 (0.982-2.152)
Dose of nal-IRI (mg/m^2)†			
48 to < 64	0.576	0.448	1.255 (0.698-2.255)
≥ 64	3.873	0.049	1.708 (1.002-2.910)
Constant	3.226	0.072	0.458

*Comparing to PS 0; †Comparing to < 48 mg/m^2. Abbreviations: CI, Confidence interval; nal-IRI, Nanoliposomal irinotecan; OR, Odds ratio; PS, Performance status.

was not worse than patients without such modifications in these studies [19, 21, 23]. In fact, gradual and stepwise dose reduction of nal-IRI with intermittent dose interruption was common in real-world studies and clinical trials, which was in line with the overlap in the ranges of DI between the dose subgroups in our study.

In this study, we stratified patients into three subgroups based on the average dose of nal-IRI for each patient. In the two higher dose subgroups, TTF and OS significantly improved, with concomitant increases in the incidence of fatigue, vomiting, and diarrhea, mainly of mild severity. However, patients in the low-dose subgroup with poor TTF and OS had more unfavorable characteristics, such as lower BSA and albumin levels and more prior lines of chemotherapy. This phenomenon is compatible with daily oncology practice, i.e., patients with unfavorable conditions usually have a high probability of drug intolerance, receive lower chemotherapy doses in the first or subsequent cycles, and have a worse prognosis. The median cycle was lower in the low-dose subgroup, especially among patients with splenomegaly. The median DI in the low-dose subgroup was smaller, but with the same median average dose than the intermediate/high-dose subgroups. This may indicate more frequent dose interruptions in the low-dose subgroup. The negative effect of low dose on patient prognosis may also be confounded by other key factors such as comorbidities, cachexia, multiple prior chemotherapy lines, chemotherapy-induced toxicities, and cancer-related complications [24, 25]. However, the lower BSA noted in the low-dose subgroup may still reflect the potential risk of nal-IRI underdose at prognosis.

Specifically, nal-IRI dose was positively correlated with longer median TTF and OS only in patients with splenomegaly (spleen volume ≥ 245 mL) with the worst prognosis in the low-dose subgroup. In patients with splenomegaly,

nal-IRI dose < 48 mg/m^2 and BSA < 1.6 m^2 were independent poor prognostic factors. Notably, spleen volume was significantly larger in the intermediate- and low-dose subgroups than in the high-dose subgroup and was significantly associated with a low lymphocyte count in the peripheral blood (Pearson's r = -0.143, P = 0.001). Indirectly, splenomegaly may be associated with massive infiltration of immunosuppressive myeloid and phagocytic cells due to extramedullary hematopoiesis in the spleen [26-28]. Although the nanoliposomal formulation of irinotecan could be metabolized by macrophages at a slower rate [29], the clinical impact of splenomegaly on nal-IRI pharmacokinetics and treatment outcomes has not been evaluated in early phase studies of nal-IRI. In addition to spleen volume, immune reactions within the spleen may play vital roles in nal-IRI pharmacokinetics. Previous studies have demonstrated that anti-polyethylene glycol (PEG) antibodies are detectable in healthy individuals [30]. With complement activation, these pre-existing anti-PEG antibodies derived from splenic marginal zone B cells may accelerate the clearance of PEGylated liposomes [31], such as nal-IRI, through the RES and consequently alter the pharmacokinetics and reduce efficacy [32]. Therefore, based on our results, a nal-IRI dose of ≥ 48 mg/m^2 is highly recommended for patients with splenomegaly. Our study is the first to discuss the impact of splenomegaly on prognosis in terms of nal-IRI dose.

Liver metastasis was an independent poor prognostic factor in the NAPOLI-1 trial [33] and our study. It may also have had negative effects on the pharmacokinetics and efficacy of nal-IRI. A previous study demonstrated that two patients with chronic hepatitis and hepatocellular carcinoma showed significantly reduced liver uptake of liposomes [12]. The intratumor uptake of nal-IRI and duration of exposure to SN-38 also highly varied within or across cancer types [13]. Patients with hepatic dysfunction showed increased exposure to SN-38 irrespective of treatment with irinotecan or nal-IRI [34, 35]. Hepatic dysfunction is multifactorial in PDAC and may be attributable to biliary tract obstruction, underlying chronic liver disease, drug-related toxicities, and liver metastasis. Therefore, in patients with hepatic dysfunction and multiple space-occupying liver metastases, a reduced nal-IRI dose due to AE or the physician's preference may offset the increased exposure to SN-38. Moreover, in theory, spleen-associated effects on pharmacokinetics may further aggravate the negative impacts of the nal-IRI underdose, which is in line with the negative prognosis of our patients with spleen volume ≥ 245 mL, those with liver metastasis, and those receiving low-dose nal-IRI and compatible with the worst prognosis in patients with splenomegaly and the high-risk subgroup of the LISPENADO risk score model. Lower risk of vomiting may also indirectly reflect the potential perturbation of pharmacokinetics of nal-IRI in patients with liver metastasis.

This study has several limitations. We included a retrospective heterogeneous population treated at different hospitals. The patients received non-fixed 5-fluorouracil doses and schedules. There was a lack of consensus on splenomegaly to be followed. Moreover, only initial data on spleen volume and laboratory profiles were available, and only the worst grade of AE during the whole treatment course was recorded. Although low baseline level of carbohydrate antigen 19-9 (CA 19-9) was a good prognostic marker in the NAPOLI-1 trial [33], the level of CA 19-9 before NalFL was not obtained in routine practice. Apart from these, any inherent biases of a retrospective study were also applicable to our study. Pharmacokinetic data of nal-IRI in patients with and without splenomegaly were not available.

In conclusion, a higher dose of nal-IRI was significantly associated with a better prognosis but a concomitant increase in the incidence of AE. For patients with splenomegaly, an adequate dose of nal-IRI of > 48 mg/m^2 is recommended. Further clinical and pharmacological studies are warranted to validate the findings of this hypothesis-generating study.

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Disclosure of conflict of interest

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