CANCER DIAGNOSIS & PROGNOSIS *5*: 198-206 (2025)
doi: 10.21873/cdp.10430

Outcomes of Liposomal Irinotecan With 5-FU and Leucovorin in Patients With Metastatic Pancreatic Cancer and Borderline Performance Status

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Abstract

Background/Aim: This study investigated the effectiveness and safety of liposomal irinotecan plus 5-fluorouracil (5-FU) and leucovorin (LV) as a second-line treatment for patients with pancreatic ductal adenocarcinoma (PDAC) and borderline performance status. These patients are often excluded from clinical trials, but may still receive this therapy due to limited alternatives.

Patients and Methods: A retrospective analysis was conducted on 31 patients with metastatic PDAC and a Karnofsky Performance Status (KPS) of 40-60, who received liposomal irinotecan plus 5-FU/LV at two institutions between 2018 and 2019 in Taiwan. The NAPOLI nomogram was utilized to stratify patients into prognostic groups for survival comparison, with the good prognostic group defined as having total NAPOLI nomogram points ≥ the median value, and the poor prognostic group defined as having total NAPOLI nomogram points < the median value.

Results: The median overall survival (OS) for the entire cohort was 4.2 months [95% confidence interval (CI)=3.0-5.3 months]. Patients in the NAPOLI nomogram's good prognostic group had a median OS of 4.9 months (95%CI=3.7-6.1 months), compared to 2.0 months (95%CI=1.5-2.4 months) in the poor prognostic group (p=0.014). Tumor response rates to liposomal irinotecan + 5-FU/LV were partial response in 3%, stable disease in 23%, and progressive disease in 74%, with significant differences in disease progression rates between good (56%) and poor (93%) prognostic groups (p=0.011). The most common grade 3 or 4 chemotherapy-related adverse events included anemia (26%), neutropenia (23%), non-neutropenic infection (19%), mucositis (13%), diarrhea (10%), and fatigue (3%).

Conclusion: Liposomal irinotecan plus 5-FU/LV regimen is a feasible second-line treatment option for PDAC patients with borderline performance status, with a safety profile consistent with clinical trial findings.

Keywords: Nanoliposomal irinotecan, pancreatic cancer, real-world data, safety profile.

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Received January 8, 2025 | Revised January 23, 2025 | Accepted February 4, 2025

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive malignancy with a poor prognosis, especially for patients with metastatic disease (1, 2). Gemcitabine-based therapy has been the standard of care as the first-line treatment for patients with metastatic PDAC (3), but many patients eventually develop resistance or experience disease progression (4). In recent years, liposomal irinotecan in combination with 5-fluorouracil (5-FU) and leucovorin (LV) has emerged as a viable treatment option for patients with metastatic PDAC who have previously received gemcitabine-based therapy (5, 6).

The NAPOLI-1 trial, a phase 3 study, demonstrated the efficacy and safety of liposomal irinotecan in this patient population, leading to its approval for use in the second-line setting after progression on gemcitabine-based treatment (5). The NAPOLI-1 trial included patients with a Karnofsky Performance Status (KPS) of 70 or higher, which is considered a relatively good performance status (5). In this study, the median overall survival (OS) was significantly longer in the liposomal irinotecan plus 5-FU/LV group compared to the 5-FU/LV group (6.1 months *vs.* 4.2 months, respectively) (5). While the NAPOLI-1 trial did not specifically focus on patients with borderline performance status, a post-hoc analysis of the trial suggested that better performance status was associated with longer OS (7).

The NAPOLI nomogram is a predictive tool developed to estimate OS in patients with metastatic mPDAC who participated in the NAPOLI-1 trial (8). The nomogram integrates eight baseline factors associated with OS: Karnofsky Performance Status (KPS), presence of liver metastases, albumin levels, neutrophil-to-lymphocyte ratio (NLR), cancer antigen 19-9 (CA19-9) levels, disease stage at diagnosis, body mass index (BMI), and treatment arm (*e.g.*, liposomal irinotecan plus 5-FU/LV). The NAPOLI nomogram provides a quantitative method to stratify patients into prognostic groups (good, intermediate, poor) based on their calculated total score from these variables. Higher scores correlate with improved survival probabilities at six and 12 months. This stratification supports clinicians in making personalized treatment decisions by identifying patients most likely to benefit from therapies like liposomal irinotecan plus 5-FU/LV. The NAPOLI nomogram has been externally validated in real-world clinical practice to demonstrate its robust prognostic performance (9).

Although the efficacy of liposomal irinotecan in patients with borderline performance status (defined as a KPS of 40-60, equal to an Eastern Cancer Cooperative Group performance status of 2 to 3) was not specifically evaluated in clinical trials, real-world analyses have included these patients to assess its effectiveness in clinical practice (10-16).

Patients with borderline performance status are often excluded from clinical trials (10, 11). However, these patients may still receive liposomal irinotecan as a second-line treatment for PDAC in real-world practice due to the limited availability of alternatives (12-17). This study aimed to evaluate the efficacy and safety profile of liposomal irinotecan in this underrepresented patient population. Furthermore, this study further evaluates the prognostic value of the NAPOLI nomogram specifically in patients with borderline performance status.

Patients and Methods

Patient selection. This retrospective study included 31 consecutive patients who received liposomal irinotecan plus 5-FU/LV as second-line palliative chemotherapy for metastatic PDAC. The study was conducted between November 2018 and December 2019 at two affiliated branches of the Chang Gung Memorial Hospital after the reimbursement of liposomal irinotecan in Taiwan. All patients had a histologically or radiographically confirmed diagnosis of locally advanced or metastatic PDAC, had a KPS of 40 to 60, and received liposomal irinotecan plus 5-FU/LV according to the NAPOLI-1 protocol for the second-line treatment of metastatic PDAC (5). Patients were excluded if they had not received gemcitabine-based therapy as first-line treatment, had insufficient follow-up data, or had received concurrent radiotherapy during

Table I. *Patient characteristics.*

Variable	Category	N	Percentage or range
Sex	Male	16	52
	Female	15	48
Age, years	Median	66	50-89
Tumor stage at initial diagnosis	1-3	10	32
	4	21	68
Tumor site	Head	16	52
	Body	8	26
	Tail	7	22
First-line treatment			
Regimen	Gemcitabine + nab-paclitaxel	11	35
	Gemcitabine + TS-1	16	52
	Gemcitabine	4	13
Treatment duration, months	Median	6.5	2.0-36.1
Best tumor response	Partial response	5	16
	Stable disease	12	39
	Progressive disease	14	45
Characteristics at initiation of second-line treatment			
Metastatic organ site	Median	2	1-5
	Liver	16	52
	Peritoneum	20	65
	Distal lymph nodes	22	71
	Lung	9	29
	Bone	3	10
Karnofsky Performance Status	60	18	58
	50	10	32
	40	3	10
Cancer antigen 19-9, U/ml	Median	916	2-50,000
Body mass index, Kg/m^2	Median, range	20.8	15.1-29
Neutrophil-to-lymphocyte ratio	Median, range	3.7	1.2-12.6
Albumin (g/dl)	Median, range	3.4	2.1-4.3

second-line treatment. Given the retrospective nature of the study, informed consent was waived. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital and conducted in accordance with the principles of the Declaration of Helsinki.

Data collection. Demographic and clinicopathological characteristics (Table I) were retrospectively collected through a chart review. Primary care physicians determined the first-line chemotherapeutic regimens and treatment schedules. OS was measured from the initiation of second-line chemotherapy until the date of death from any cause. Patients were closely monitored until death or the data cutoff date (December 31, 2021). Chemotherapy toxicity was graded according to CTCAE 5.0 and RECIST 1.1 criteria were used to evaluate tumor response (18, 19).

Statistical analysis. Baseline demographic data are presented as frequencies and percentages for categorical variables and as medians with ranges for continuous variables. To determine prognostic scores, each patient's values for the eight independent factors in the NAPOLI nomogram were assigned corresponding points, aligning with the "points" scale (8). The total score for each patient was calculated by summing the individual points assigned based on the NAPOLI nomogram variables, and then mapping to the "total points" scale to obtain predictions for OS. Patients were subsequently stratified into two

Table II. *Grade 3 or higher chemotherapy-related toxicity (n=31).*

Toxicity	N	Percentage
Hematological toxicity		
Anemia	8	26%
Neutropenia	7	23%
Thrombocytopenia	3	10%
Febrile neutropenia	1	3%
Non-hematological toxicity		
Infection	6	19%
Mucositis	4	13%
Diarrhea	3	10%
Vomiting	2	6%
AST or ALT elevation	2	6%
Hypokalemia	2	6%
Fatigue	1	3%
Creatinine elevation	1	3%

AST: Aspartate aminotransferase; ALT: alanine transaminase.

prognostic groups using the median value from the NAPOLI nomogram (8). OS was estimated using the Kaplan-Meier method, and differences in OS between the prognostic groups were compared using the log-rank test. All statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 29.0.2.0, IBM Corp, Armonk, NY, USA). A *p*-value of less than 0.05 was considered statistically significant for all tests.

Results

The study included 31 patients with a median age of 66 years (range=50-89 years). Among these, 52% were male. The majority of patients (68%) had stage IV tumors at initial diagnosis, with tumor sites predominantly in the head of the pancreas (52%). First-line treatments were varied, with 52% receiving Gemcitabine + TS-1, 35% receiving Gemcitabine + nab-paclitaxel, and 13% receiving gemcitabine alone (3, 20, 21). The median treatment duration of the first-line regimen was 6.5 months (range=2.0-36.1 months). At the initiation of second-line treatment, patients presented with a median of two metastatic sites, most commonly in distal lymph nodes (71%), peritoneum (65%), and liver (52%). The median CA 19-9 level was 916 U/ml (range=2-50,000 U/ml). Baseline performance characteristics indicated that 58% of patients had a KPS of 60, 32% had a KPS of 50, and 10% had a KPS of 40. The median BMI was 20.8 Kg/m^2 (range=15.1-29 Kg/m^2). Median albumin levels and NLR were 3.4 g/dl and 3.7, respectively,

Table II summarizes the incidence of grade 3 or 4 chemotherapy-related toxicities observed in the study cohort. Hematological toxicities were the most prevalent, with anemia affecting 26% of patients, followed by neutropenia (23%), thrombocytopenia (10%), and febrile neutropenia (3%). Non-hematological toxicities included infection in 19% of patients, mucositis in 13%, and diarrhea in 10%. Less frequently reported adverse events included vomiting (6%), elevated aspartate amino-transferase or alanine transaminase levels (6%), hypokalemia (6%), fatigue (3%), and elevated creatinine levels (3%).

Table III outlines the patient percentage for each variable within the NAPOLI nomogram. All our patients had a KPS of 40-60. Albumin levels were below 4 g/dl in 87% of patients and the NLR exceeded 5 in 32% of patients. Liver metastases were present in 52% of the cohort, while 48% were without. At diagnosis, 68% of patients had stage IV disease and 94% of our patients had a BMI ≤25 kg/m^2. All participants received the liposomal irinotecan plus 5-FU/LV treatment arm, reflecting a uniform intervention strategy for this study.

By the end of the study, 24 patients (77%) had died, and the median OS was 4.2 months [95% confidence interval (CI)=3.0-5.3 months]. The median OS times for patients with NAPOLI nomogram good and poor prognostic scores were 4.9 months (95%CI=3.7-6.1) and 2.0 months (95%CI=1.5-2.4), respectively (Figure 1). A statistically significant difference in OS between the groups is indicated by a log-rank *p*-value of 0.014. The tumor response rates to liposomal irinotecan plus 5-FU/LV treatment were as follows: partial response, 3%; stable disease, 23%; and progressive disease, 74%. Patients in the good prognostic group had a lower rate of progressive disease than those in the poor prognostic group (56% *vs.* 93%) (Figure 2). Differences in tumor

Table III. *Variable within the NAPOLI nomogram.*

Variable	Category	No	Percentage
Karnofsky Performance Score	90-100	0	0%
	60-80	0	0%
	40-60	31	100%
Albumin (g/dl)	≥4	4	13%
	<4	27	87%
Neutrophil/Lymphocyte ratio	≤5	21	68%
	>5	10	32%
Liver metastases	No	15	48%
	Yes	16	52%
Baseline CA19-9 (U/ml)	≤1,542	17	55%
	>1,542	14	45%
Disease stage at diagnosis	1-3	10	32%
	4	21	68%
Body mass index (kg/m^2)	≤25	29	94%
	>25	2	6%
Treatment arm	Liposomal irinotecan + 5-FU/LV	31	100%
Liposomal irinotecan or 5-FU/LV		0	0%

response rates between the two prognostic groups were statistically significant (p=0.011).

Discussion

This real-world study examined the effectiveness and safety of second-line treatment with liposomal irinotecan plus 5-FU/LV in PDAC patients with borderline performance status. The median OS of 4.2 months observed in this study was shorter than the results from the NAPOLI-1 trial, which reported a median OS of 6.1 months in the liposomal irinotecan plus 5-FU/LV arm (5). This is likely due to the inclusion of patients with poorer performance status, making the study population more representative of real-world clinical practice (12-17). The safety profile of liposomal irinotecan plus 5-FU/LV in our patient cohort was consistent with the NAPOLI-1 trial, with hematological toxicities being the most common grade 3 or higher adverse events (5). Furthermore, our findings indicate that the NAPOLI nomogram can effectively stratify pancreatic cancer patients receiving second-line liposomal irinotecan plus 5-FU/LV treatment into good and poor prognostic groups (8).

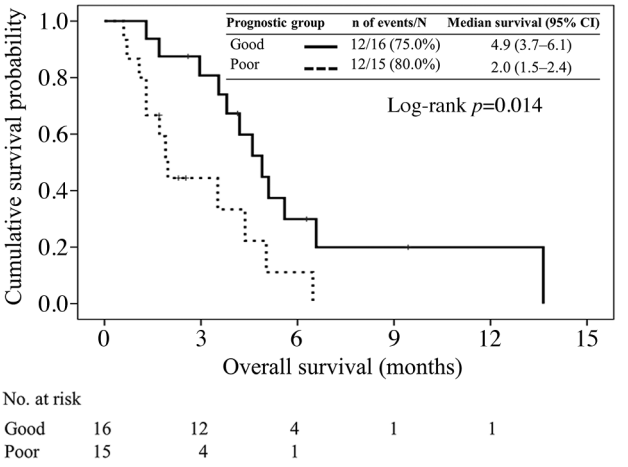

Figure 1. *Survival outcomes according to patients stratified by the NAPOLI nomogram.*

Identifying patients suitable for further treatment is critical to patient prognosis, and may include methods ranging from performance status to lymphocyte-albumin scores (22). The performance status is a well-established tool for assessing the functional ability of cancer patients and guiding treatment decisions (10). Patients with a borderline performance status are typically capable of self-care but cannot engage in strenuous activity, which

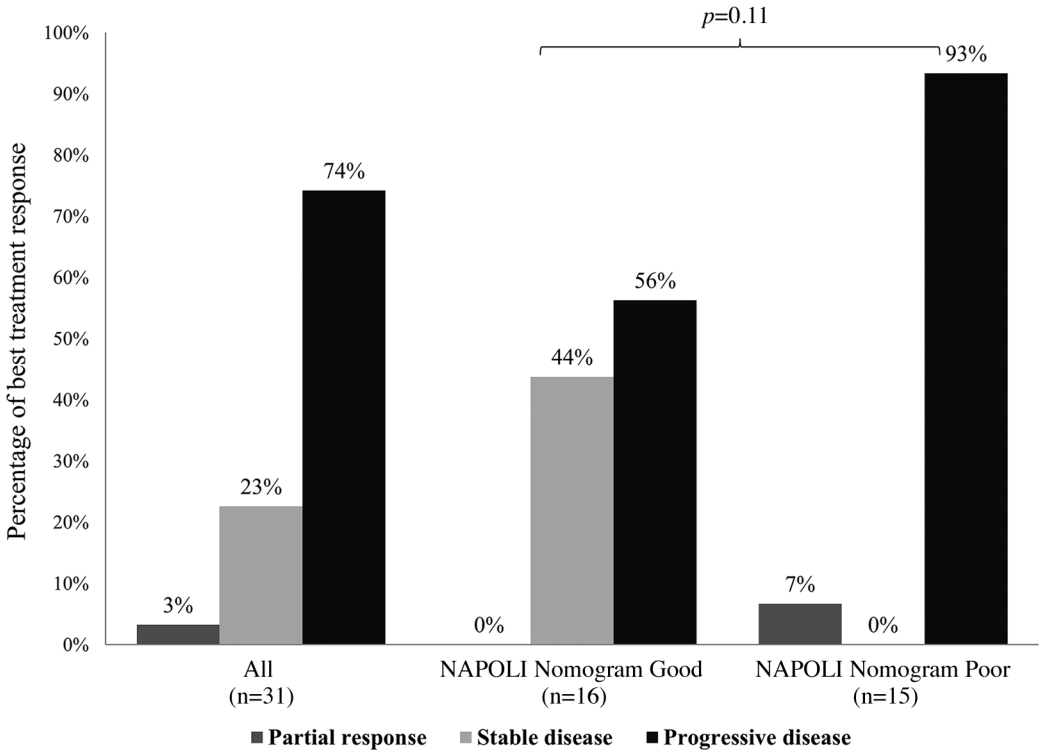

Figure 2. *Best tumor responses according to patients stratified by the NAPOLI nomogram.*

places them in a gray area regarding treatment decisions due to concerns about treatment-related toxicities. These patients present a unique challenge when undergoing chemotherapy due to a delicate balance of potential benefits and risks (23). On the positive side, chemotherapy can provide meaningful clinical benefits, including symptom relief, improved quality of life, and modest survival extension, even for patients with compromised functional status (23). Advanced therapies like liposomal irinotecan might show efficacy in such populations, offering a viable treatment option where few alternatives exist (17). However, the risks are significant; patients with borderline performance often face higher rates of severe treatment-related toxicities due to their limited physiological reserve. This can lead to treatment interruptions, dose reductions, or even treatment discontinuation, potentially undermining the intended therapeutic benefits (24, 25). Additionally, the aggressive nature of chemotherapy can further diminish quality of life in these already vulnerable patients (26). Consequently, careful patient selection, personalized treatment planning, and vigilant toxicity management are essential to maximize benefits while minimizing harm, emphasizing the importance of prognostic tools like the NAPOLI nomogram or frailty assessment to guide decision-making (8, 23).

The suboptimal OS observed in this study of patients with borderline performance status underscores the urgent need to develop more effective treatment approaches for this challenging patient population. The median OS of 4.2 months was comparable to the 4.1 months reported for the 5-FU/LV arm in the NAPOLI-1 trial, reflecting the limited benefit of the current second-line treatment options for these patients (5). Tumor response rates were also lower in our cohort (3%) compared to the liposomal irinotecan + 5-FU/LV arm

(16%) in NAPOLI-1 trial, further reflecting the poorer prognosis of patients with borderline performance (5). These findings emphasize the importance of selecting appropriate patients for liposomal irinotecan plus 5-FU/LV therapy based on individual risk factors and performance status to optimize outcomes.

The survival and response discrimination provided by the NAPOLI nomogram in our study population supports its potential utility in guiding treatment decisions for second-line liposomal irinotecan plus 5-FU/LV therapy in PDAC (8). Given the median OS of 2.0 months and 93% progressive disease rate, patients identified as having a poor prognosis based on the NAPOLI nomogram may be better served by palliative care approaches or investigational therapies, rather than pursuing marginally beneficial second-line chemotherapy.

The most common grade 3-4 treatment-related adverse events observed in the liposomal irinotecan arm of the NAPOLI-1 trial were neutropenia (27%), diarrhea (13%), and fatigue (14%) (5). Similarly, our study found hematological toxicities, including anemia, neutropenia, and thrombocytopenia, to be the most prevalent severe adverse events, affecting over a quarter of patients. Previous study had indicated that patients with UGT1A1*6 or *28 (+/+) genotypes and elevated liver function test should be particularly cautious about the risk of neutropenia and leukopenia during liposomal irinotecan treatment (27). The management of these toxicities, including prophylactic use of growth factors and dose modifications, is crucial to enable patients to complete the prescribed treatment regimen and potentially derive clinical benefit.

This study is strengthened by its real-world design, which provides additional context on the use of liposomal irinotecan plus 5-FU/LV in a broader population of patients with PDAC, including those with borderline performance status. However, the relatively small sample size and two-institution nature of this analysis are limitations. Additionally, the retrospective nature of the data collection introduces potential biases, and the lack of a comparator group prevents direct efficacy comparisons (28). Larger real-world studies are needed to further validate the findings and provide more robust data on the efficacy and safety of liposomal irinotecan plus 5-FU/LV in patients with advanced pancreatic cancer and borderline performance status.

Conclusion

This real-world study demonstrates that the liposomal irinotecan plus 5-FU/LV regimen is a feasible second-line treatment option for PDAC patients with borderline performance status, with a safety profile consistent with clinical trial findings. The NAPOLI nomogram effectively stratified patients into good and poor prognostic groups, emphasizing its potential to identify those most likely to benefit from this treatment regimen in real-world clinical practice.

Conflicts of Interest

The Authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contributions

Conception and design of study: CYC, TJC, YYC, JSC, WCC; Acquisition of data: WCC, TJC, YYC; Analysis and interpretation of data: CYC, TJC, YYC, WCC; Drafting of the manuscript: CYC, TJC, YYC, JSC, WCC.

Acknowledgements

The Authors gratefully acknowledge the assistance of the patients who participated in this study.

Funding

The Authors received no financial support for the research, authorship, and/or publication of this article.

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