의학석사 학위논문

이리노테칸 항암 요법 시행 후 진행한 전이성 췌장암 환자에서 리포좀 이리노테칸 및 플루오로우라실/류코보린 병합 요법에 대한 연구

Clinical outcomes of liposomal irinotecan plus fluorouracil/leucovorin therapy after progression on conventional irinotecan-containing chemotherapy in metastatic pancreatic adenocarcinoma patients

울 산 대 학 교 대 학 원

의 학 과

방 경 혜

이리노테칸 항암 요법 시행 후 진행한 전이성 췌장암 환자에서 리포좀 이리노테칸 및 플루오로우라실/류코보린 병합 요법에 대한 연구

지 도 교 수　　류 백 렬

이 논문을 의학석사 학위 논문으로 제출함

2021년 2월

울 산 대 학 교 대 학 원

의　　학　　과

방 경 혜

방경혜의 의학석사학위 논문을 인준함

심사위원장　　김　규　표　(인)

심사위원　　류　백　렬　(인)

심사위원　　유　창　훈　(인)

울 산 대 학 교 대 학 원

2021년 2월

Master's degree

Clinical outcomes of liposomal irinotecan plus fluorouracil/leucovorin therapy after progression on conventional irinotecan-containing chemotherapy in metastatic pancreatic adenocarcinoma patients

The Graduate School of the University of Ulsan

Department of Oncology

Bang, Kyung Hye

Clinical outcomes of liposomal irinotecan plus fluorouracil/leucovorin therapy after progression on conventional irinotecan-containing chemotherapy in metastatic pancreatic adenocarcinoma patients

Supervisor : Ryoo, Baek-Yeol

A Master's Thesis

Submitted to

the Graduate School of the University of Ulsan

In partial Fulfilment of the Requirements

for the Degree of

Master's degree

by

Bang, Kyung Hye

Department of Oncology

Ulsan, Korea

February 2021

Abstract

Background: Liposomal irinotecan (nal-IRI) plus fluorouracil/leucovorin (5-FU/LV) therapy has shown clinical benefit in metastatic pancreatic adenocarcinoma (mPAC) patients who progressed after gemcitabine-based chemotherapy. However, its role in mPAC patients previously treated with conventional irinotecan-containing chemotherapy has not been appropriately investigated.

Methods: In this retrospective analysis, mPAC patients who received nal-IRI plus 5-FU/LV after progression on conventional irinotecan-containing regimen between January 2017 and March 2020, were identified from two referral cancer centers in South Korea. The ratio of time to progression (TTP) with nal-IRI plus 5-FU/LV to TTP with conventional irinotecan (TTPr) was analyzed with respect to the duration and cumulative dose of conventional irinotecan treatment.

Results: In total, 35 patients treated with nal-IRI plus 5-FU/LV after progression on irinotecan-containing regimen were analyzed. The median age was 58 years and 16 (46%) patients were male. The median duration of conventional irinotecan therapy was 4.6 months at a median cumulative dose of 1230 mg. The objective response rate of nal-IRI plus 5-FU/LV was 2.9%, and stable disease was achieved in 11 (31.4%) patients. During the median follow-up of 9.2 (95% confidence interval [CI]: 7.8-10.5) months, the median progression-free survival (PFS) and overall survival (OS) were 2.0 (95% CI: 1.4-2.6) months and 4.4 (95% CI: 3.6-5.7) months, respectively. The 6-month PFS and OS rates were 16.3% and 37.5%, respectively. The median TTPr was 0.41 (range, 0.07-2.07), showing a negative correlation with the cumulative dose of prior irinotecan therapy (R=-0.37, p=0.041). A tentative negative correlation between TTPr and duration of prior irinotecan therapy was observed (R=-0.35, p=0.062). The most common grade 3-4 toxicities were neutropenia (20%) and fatigue (8.6%).

Conclusions: Nal-IRI plus 5-FU/LV showed modest effectiveness and manageable toxicities for mPAC patients who progressed after conventional irinotecan-containing chemotherapy. The cumulative dose and duration of prior conventional irinotecan therapy have tendency of negative correlation with the effectiveness of nal-IRI plus 5-FU/LV.

Keywords: metastatic pancreatic adenocarcinoma, liposomal irinotecan, fluorouracil/leucovorin, irinotecan

목 차

표 및 그림 목차

Introduction

Pancreatic adenocarcinoma (PAC) is a leading cause of cancer-related deaths worldwide as well as in South Korea.[1] [2] It is usually diagnosed at an advanced stage and has a high recurrence rate despite curative resection, with a 5-year survival rate of approximately 9%.

In the late 1990s, gemcitabine monotherapy showed significant improvement in overall survival (OS) compared with the fluorouracil (5-FU) treatment. Since then, it has been the standard first-line regimen for patients with advanced PAC.[3] However, there had been limited progress in systemic treatment strategies for advanced PAC until 2010. As first-line treatment, new chemotherapy regimens such as FOLFIRINOX (5-FU, leucovorin [LV], irinotecan, and oxaliplatin) and gemcitabine plus albumin-bound paclitaxel (nab-paclitaxel) have significantly improved survival outcomes in patients with advanced PAC.[4] [5] [6] [7] [8]

Liposomal irinotecan (nal-IRI) is an intravenous liposomal formulation of irinotecan that consists of irinotecan sucrosofate salt encapsulated in a liposome particle. Preclinical studies have shown that the active metabolite of irinotecan, SN-38, in both nal-IRI and conventional irinotecan therapy cause similar tumor exposure, except that much lower doses of the former are needed.[9] Driven by the promising efficacy of nal-IRI reported by a phase II study, NAPOLI-1, a phase III trial, investigated the effects of nal-IRI in patients with metastatic PAC (mPAC) who previously underwent gemcitabine-based treatment.[10] [11] This trial demonstrated that nal-IRI plus 5-FU/LV improved the OS, progression-free survival (PFS), and objective response rate (ORR) in patients with mPAC who progressed after prior gemcitabine-based therapy.[11] Although the NAPOLI-1 trial included patients who previously received conventional irinotecan-containing chemotherapy, the small sample size (approximately 10% patients) was not enough to avoid skepticism about the efficacy of nal-IRI for these patients.

Therefore, we performed a multicenter retrospective analysis to evaluate the effectiveness and safety of nal-IRI plus 5-FU/LV in patients with mPAC who progressed after conventional irinotecan-containing chemotherapy.

Subjects and Methods

1. Study population

This retrospective study aimed to evaluate the effectiveness and safety of nal-IRI plus 5-FU/LV regimen in patients with mPAC who progressed after conventional irinotecan-containing chemotherapy. Patients with histologically confirmed mPAC treated with nal-IRI plus 5-FU/LV were eligible for this study if they had previously received conventional irinotecan-containing chemotherapy as a neoadjuvant, adjuvant, or palliative therapy. The patients were enrolled from two referral cancer centers (Asan Medical Center and Ulsan University Hospital) in South Korea. Clinical data on patient characteristics, treatment history, and survival outcomes were retrospectively obtained by reviewing patient medical records.

This study was approved by the Institutional Review Board of each participating center (Asan Medical Center, 2018-0492; Ulsan University Hospital, 2019-11-037) and was performed in accordance with the ethical standards of institutional research and the Declaration of Helsinki. The need for informed consent for this study was waived, as retrospective analyses do not require consent per the Korean regulations.

2. Treatment

The dosing schedule of nal-IRI plus 5-FU/LV described in the NAPOLI-1 trial (80 mg/m^2 irinotecan hydrochloride trihydrate salt equivalent to 70 mg/m^2 irinotecan free base over 90 minutes, followed by 400 mg/m^2 LV over 30 minutes and 2400 mg/m^2 5-FU over 46 hours, every 2 weeks) was considered standard in this analysis.[11] Dose modification was allowed at the discretion of the attending physicians. Nal-IRI plus 5-FU/LV treatment continued until patients experienced intolerable toxicity or disease progression.

3. Evaluation

Patients were examined every 6-8 weeks using computed tomography (CT) or magnetic resonance imaging (MRI). Tumor response was graded using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. All treatment-related adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

4. Statistical analysis

The ORR and disease control rate (DCR) were evaluated according to RECIST version 1.1. PFS was defined as the time from the initiation of nal-IRI plus 5-FU/LV to the time of disease progression or death, whichever occurred first. OS was defined as the time from the initiation of nal-IRI plus 5-FU/LV to death from any cause. The time to progression (TTP) was defined as the time between the initiation of specific chemotherapy and tumor progression. The ratio of TTP with nal-IRI plus 5-FU/LV to TTP with conventional irinotecan (TTPr) was calculated. Survival outcomes were estimated using Kaplan-Meier curves. A two-sided p-value <0.05 was considered statistically significant. All statistical analyses were performed using Statistical Package for the Social Sciences version 22.0 (IBM, Armonk, NY, USA).

Results

1. Characteristics of study subjects

A total of 35 patients who received nal-IRI plus 5-FU/LV after disease progression following prior conventional irinotecan-containing chemotherapy at Asan Medical Center and Ulsan University Hospital between January 2017 and March 2020 were included. Baseline characteristics of the patients are summarized in Table 1.

Table 1. Patient baseline characteristics

Variables	Total N=35
Sex	
Male	16 (45.7%)
Female	19 (54.3%)
Age, years, median (range)	58 (35–73)
<65	27 (77.1%)
≥65	8 (22.9%)
Primary tumour site	
Head	22 (62.9%)
Body	7 (20.0%)
Tail	6 (17.1%)
Site of metastasis	
Liver	23 (65.7%)
Lymph node	16 (45.7%)
Peritoneum	12 (34.3%)
Lung	7 (20.0%)
Bone	3 (8.6%)
Adrenal gland	1 (2.9%)
Baseline CA19-9 level (U/ml)	
Within normal range	1 (2.9%)
> UNL	22 (62.9%)
N/A	12 (34.3%)
Prior surgery	12 (34.3%)
Prior radiotherapy	14 (40.0%)
Number of prior lines of chemotherapy	
2	26 (74.3%)
3	9 (25.7%)
Prior irinotecan-containing chemotherapy*	35 (100.0%)
Interval between the last dose of prior conventional irinotecan and the start of nal-IRI+5-FU/LV, months, median (range)	7.0 (0.6-30.8)

All patients received conventional irinotecan as a component of FOLFIRINOX.
Abbreviations: CA19-9, Carbohydrate Antigen 19-9; UNL, upper normal limit; N/A, not available

The median age was 58 years (range, 35-73 years) and 16 (45.7%) patients were male. Majority of the patients (n=28, 80.0%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Most common location of the primary tumor was the pancreatic head (n=22, 62.9%), followed by the body (n=7, 20.0%) and the tail (n=6, 17.1%). All patients had metastatic disease, and the most common metastatic sites were the liver (n=23, 65.7%), lymph nodes (n=16, 45.7%), peritoneum (n=12, 34.3%), and lungs (n=7, 20.0%). Furthermore, 12 (34.3%) patients underwent prior surgery and 14 (40%) patients received prior radiotherapy. The number of lines of prior systemic chemotherapy were two (n=26, 74.3%) and three (n=9, 25.7%). The median interval between the last dose of prior conventional irinotecan therapy and the initiation of nal-IRI plus 5-FU/LV was 7.0 months (range, 0.6-30.8 months).

2. Prior conventional irinotecan therapy

Prior to nal-IRI plus 5-FU/LV, all patients had received conventional irinotecan as a component of FOLFIRINOX (Table 2). Majority of the patients (n=29, 82.9%) were treated with FOLFIRINOX as first-line therapy for either locally advanced or metastatic diseases.

Table 2. Details of prior conventional irinotecan chemotherapy

Variables	Total N=35
Chemotherapy regimen including prior irinotecan	
FOLFIRINOX	35 (100%)
Disease extent at the time of irinotecan initiation	
Locally advanced, non-metastatic	23 (62.1%)
Metastatic	12 (32.4%)
Treatment line of irinotecan	
First	29 (82.9%)
Second	5 (14.3%)
Third	1 (2.9%)
Duration of administration of irinotecan therapy, months, median (range)	4.6 (0.5-16.8)
Cumulative dose of irinotecan therapy, mg, median (range)	1230 (150-4650)
Reason of discontinuation of irinotecan	
Disease progression	28 (80.0%)
Conversion surgery	6 (17.1%)
Adverse event	1 (2.9%)
TTP with irinotecan-containing chemotherapy, months, median (95% CI)	5.7 (4.9-6.4)

Abbreviations: TTP, time to progression; CI, confidence interval.

At the time of FOLFIRINOX treatment, the extent of disease stage was locally advanced in 23 (62.1%) patients and metastatic disease in 12 (32.4%) patients. The median duration of prior conventional irinotecan treatment was 4.6 months (range, 0.5-16.8 months), and the median cumulative dose of conventional irinotecan therapy was 1230 mg (range, 150-4650 mg). The best responses to prior conventional irinotecan-containing regimen were partial response (PR), stable disease (SD), and progressive disease (PD) in 6 (17.1%), 20 (57.1%), and 7 (20.0%) patients, respectively. The most common reasons for discontinuation of conventional irinotecan-containing therapy were tumor progression (n=28, 80.0%) and completion of scheduled chemotherapy (n=6, 17.1%).

3. Effectiveness of nal-IRI plus 5-FU/LV

Effectiveness outcomes of nal-IRI plus 5-FU/LV treatment after prior irinotecan-containing chemotherapy are summarized in Table 3.

Table 3. Effectiveness outcomes of liposomal irinotecan plus fluorouracil/leucovorin therapy

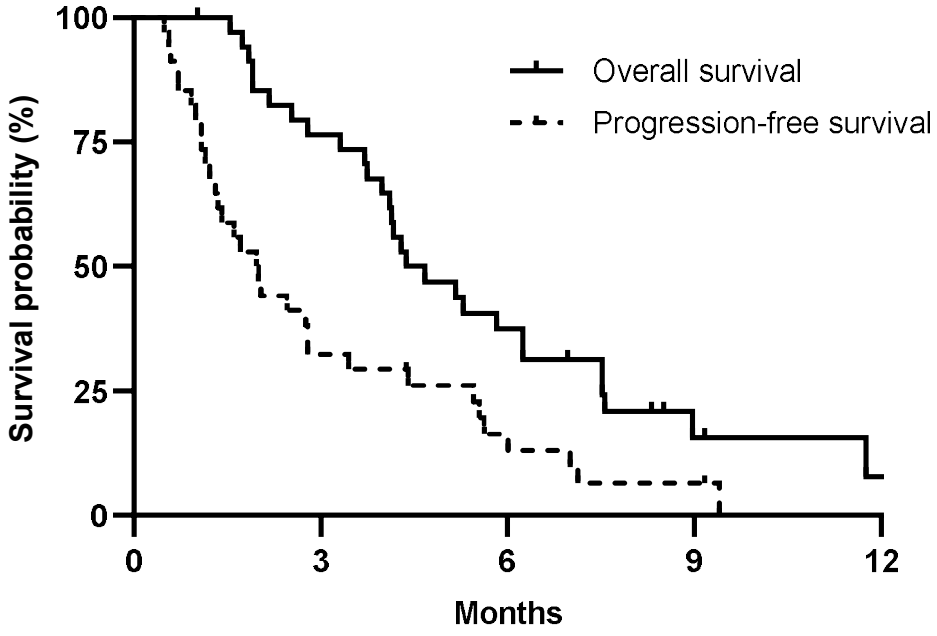
Variables	nal-IRI+5-FU/LV (N=35)
Best response	
CR	0 (0.0%)
PR	1 (2.9%)
SD	11 (31.4%)
PD	21 (60.0%)
Not evaluable	1 (2.9%)
Median PFS, months (95% CI)	2.0 (1.4–2.6)
6-month PFS rate (95% CI)	16.5% (7.5-36.0%)
Median OS, months (95% CI)	4.4 (3.0-5.7)
6-month OS rate (95% CI)	37.5% (24.2-58.2%)

Abbreviations: nal-IRI+5-FU/LV, liposomal irinotecan plus fluorouracil/leucovorin; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival; CI, confidence interval; OS, overall survival.

According to RECIST v1.1, one (2.9%) patient achieved PR and none achieved CR, revealing an ORR of 2.9%. SD and PD was best response in 11 (31.4%) and 21 (60.0%) patients, respectively, and the DCR was 34.3%.

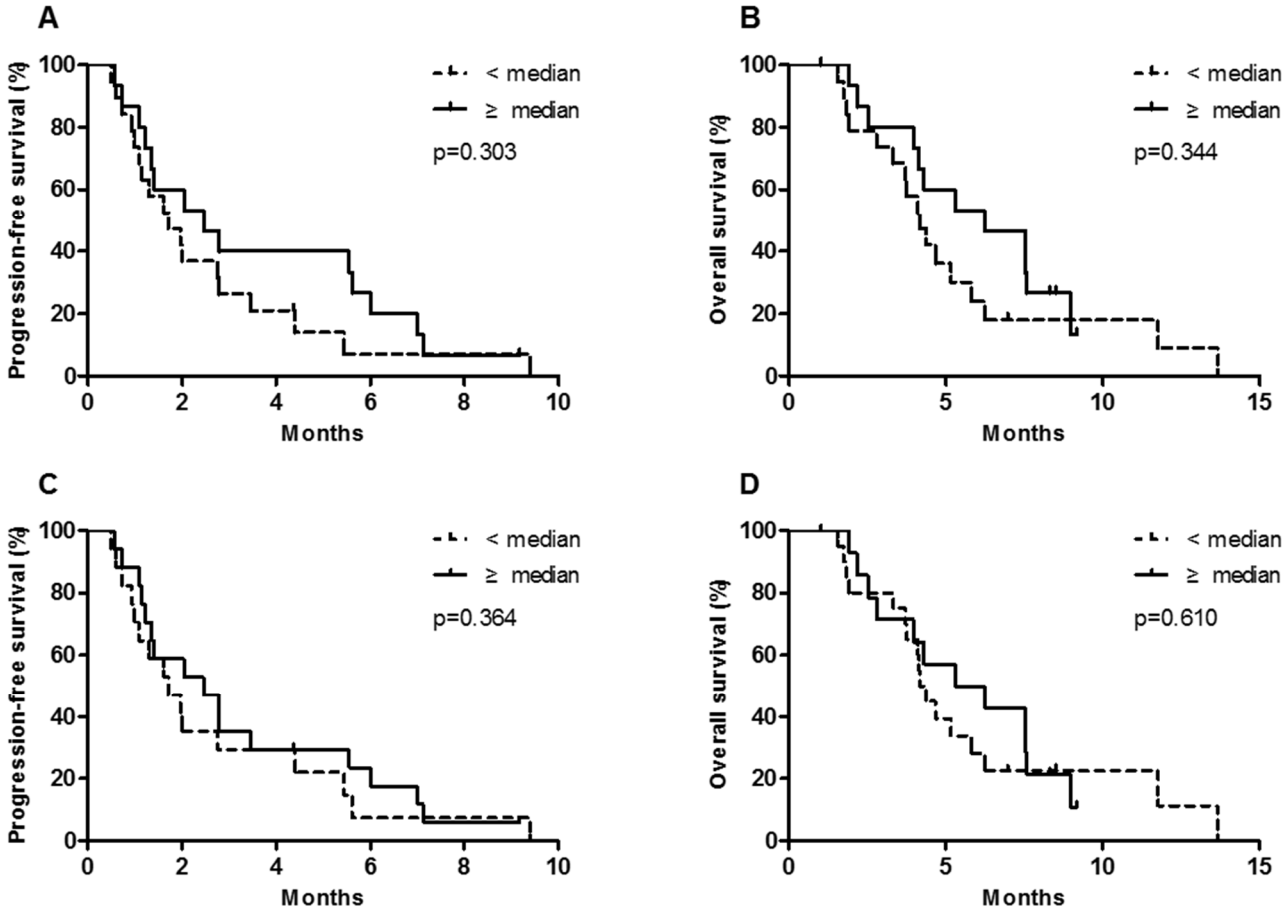
During a median follow-up of 9.2 months (95% confidence interval [CI]: 7.8-10.5 months), the median PFS and OS were 2.0 months (95% CI: 1.4-2.6 months) and 4.4 months (95% CI: 3.0-5.7 months), respectively. The 6-month PFS and OS rates were 16.5% (95% CI: 7.5%-36.0%) and 37.5% (95% CI: 24.2%-58.2%), respectively (Figure 1).

Figure 1. Survival outcomes with liposomal irinotecan plus fluorouracil/leucovorin



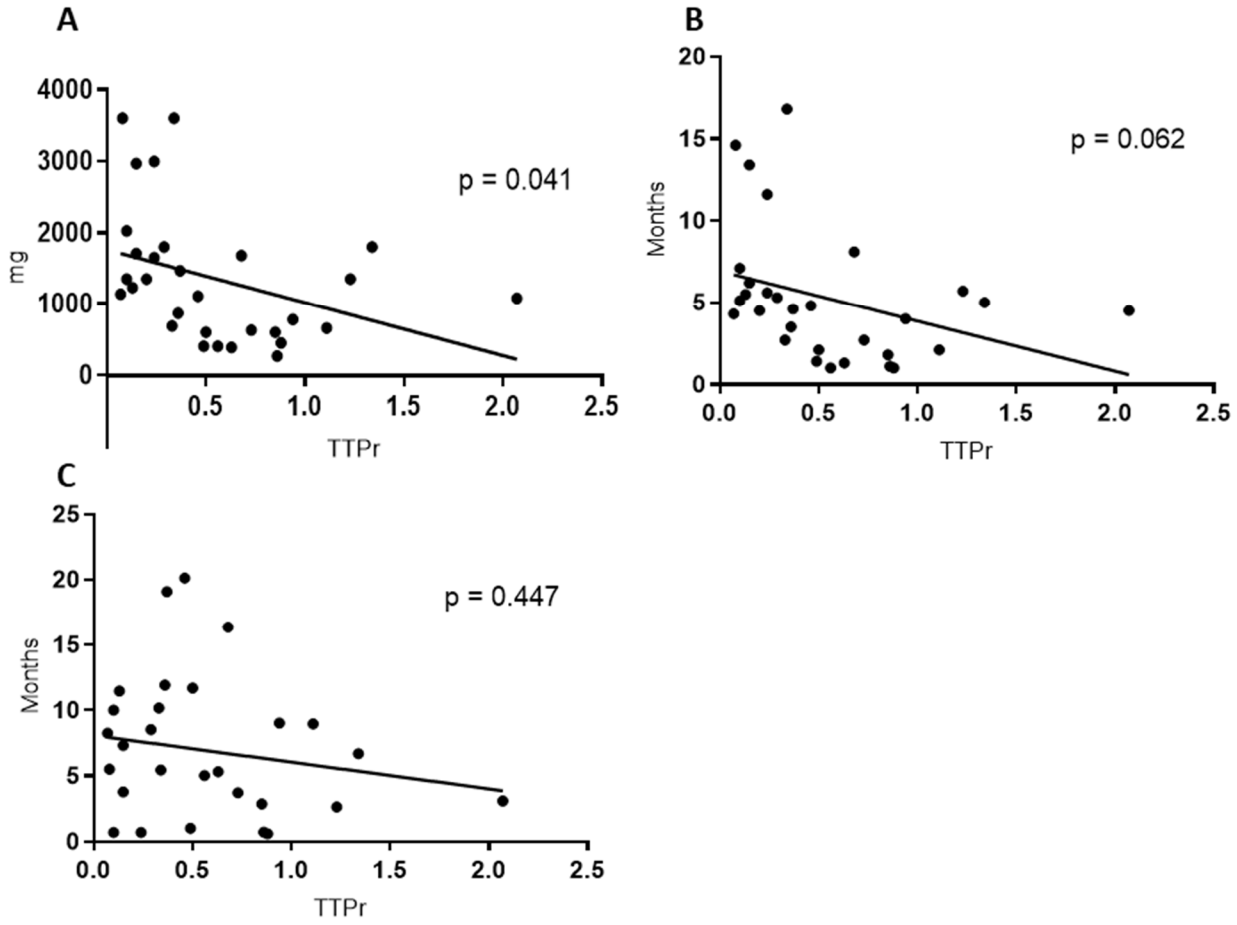
Correlation analysis between nal-IRI plus 5-FU/LV survival outcomes and prior exposure to conventional irinotecan (based on duration and cumulative dose) was performed. When patients were stratified according to the median duration of prior irinotecan therapy (<4.6 vs. ≥4.6 months), the median PFS and OS with nal-IRI plus 5-FU/LV were quantitatively better in patients with longer irinotecan exposure than in those with shorter irinotecan exposure; however, the differences were not statistically significant (PFS, 1.7 months [95% CI: 1.0-2.5] vs. 2.5 months [95% CI: 0.7-4.2], p=0.303; OS, 4.2 months [95% CI: 3.6-4.7] vs. 6.2 months [95% CI: 3.2-9.3], p=0.344; Figure 2A and 2B). When stratified according to the median cumulative dose of prior irinotecan therapy (<1230 mg vs. ≥1230 mg), patients administered a higher cumulative dose showed quantitatively better median PFS (1.6 months [95% CI: 0.9-2.4 months] vs. 2.5 months [95% CI: 1.5-3.5 months]; p=0.364) and OS (4.2 months [95% CI: 3.7-4.7 months] vs. 5.3 months [95% CI: 1.5-9.1 months]; p=0.610) than those administered a lower cumulative dose, but the difference was not statistically significant (Figure 2C and 2D).

Figure 2. Progression-free survival and overall survival with liposomal irinotecan plus fluorouracil/leucovorin according to the duration of prior conventional irinotecan therapy (A, B) and the cumulative dose of prior conventional irinotecan therapy (C, D)



The median TTPr was 0.41 (range, 0.07-2.07), and the correlation analysis showed that the TTPr was significantly inversely correlated with the cumulative dose of prior conventional irinotecan therapy (R =-0.37, p=0.041; Figure 3A). The TTPr showed tendency of negative correlation with the duration of prior irinotecan therapy (R=-0.35, p=0.062) and the interval between the last dose of prior irinotecan and the initiation of nal-IRI plus 5-FU/LV (R=-0.17, p=0.447; Figure 3B and 3C).

Figure 3. Lineal regression between the time to progression ratio and A) the cumulative dose of prior conventional irinotecan therapy, B) duration of prior conventional irinotecan therapy, and C) interval between the last dose of prior conventional irinotecan therapy and the initiation of liposomal irinotecan plus fluorouracil/leucovorin therapy.



4. Safety profiles

AEs that occurred in >10% patients are listed in Table 4.

Table 4. Adverse events occurring in >10% patients

	Adverse Events (Total N=35)	
	Any grade	**Grade 3–4**
All, n (%)	31 (88.6%)	11 (31.4%)
Neutropenia, n (%)	16 (45.7%)	7 (20.0%)
Febrile neutropenia, n (%)	2 (5.7%)	2 (5.7%)
Anemia, n (%)	12 (34.3%)	0 (0.0%)
Thrombocytopenia, n (%)	6 (17.1%)	1 (2.9%)
AST/ALT elevation, n (%)	7 (20.0%)	0 (0.0%)
Fatigue, n (%)	11 (31.4%)	3 (8.6%)
Nausea, n (%)	15 (42.9%)	1 (2.9%)
Vomiting, n (%)	8 (22.9%)	1 (2.9%)
Diarrhea, n (%)	6 (17.2%)	0 (0.0%)

Abbreviations: AST, aspartate aminotransferase; ALT, alanine transaminase.

Any-grade AEs were observed in majority of the patients (n=31, 88.6%); the most common AEs were neutropenia (n=16, 45.7%) and nausea (n=15, 42.9%). Precisely, 11 patients (31.4%) had grade 3-4 toxicities, and the most common grade 3-4 AEs were neutropenia (n=7, 20.0%) and fatigue (n=3, 8.6%). Additionally, febrile neutropenia occurred in two (5.7%) patients.

Discussion

In this retrospective analysis, we evaluated the effectiveness and toxicities of nal-IRI plus 5-FU/LV therapy in 35 Korean patients with mPAC who progressed after conventional irinotecan-containing chemotherapy. In our study, the median PFS and OS were 2.0 months and 4.4 months, respectively; these outcomes appear to be numerically worse than those reported by the NAPOLI-1 trial and other previous real-world analyses, which showed a median PFS and OS of 2.9-3.5 and 5.3-9.4 months, respectively.[12] [13] Current findings are in line with our earlier retrospective studies which have reported reduced survival outcomes with nal-IRI plus 5-FU/LV in the patient subgroup that was previously treated with irinotecan-based chemotherapy, with a median PFS of 1.7-2.2 months and a median OS of 3.9-4.4 months. It can be speculated that these survival outcomes might be a result of the resistance developed against irinotecan or SN-38 during prior conventional irinotecan-containing chemotherapy. The impact of nal-IRI treatment on the improvement of pharmacological properties such as biodistribution, extension of the circulation time, and tumor accumulation time, might not be sufficient to overcome the resistance against irinotecan or SN-38.[14] [15] However, the modest effectiveness outcomes with nal-IRI plus 5-FU/LV in the current study might be also related with its use in the later lines itself,[12] as all patients in the current analysis received nal-IRI plus 5-FU/LV as at least third-line therapy.

In the correlation analysis between survival outcomes with nal-IRI plus 5-FU/LV and prior exposure to conventional irinotecan (based on duration and cumulative dose), significant relationships were not noted. However, the TTPr, effectiveness indicator of nal-IRI plus 5-FU/LV in comparison with prior FOLFIRINOX, was significantly inversely correlated with the cumulative dose of prior conventional irinotecan therapy (R=-0.37, p=0.041). This may suggest the efficacy of nal-IRI plus 5-FU/LV appears to be decreased in patients who have received irinotecan-containing therapy with higher cumulative doses. Although the effectiveness outcomes shown in our patient

population are modest and not justifiable to recommend nal-IRI plus 5-FU/LV for all patients who progressed on FOLFIRINOX and gemcitabine-based chemotherapy, our findings indicate that nal-IRI plus 5-FU/LV may provide clinically meaningful outcomes in some subgroups of patients (i.e., less exposure to conventional irinotecan in terms of cumulative dose). Further studies with larger sample sizes are needed to find the subgroups who would be benefited with nal-IRI after progression on conventional irinotecan, considering the dismal prognosis and limited therapeutic options of those patients.

The safety profile of nal-IRI plus 5-FU/LV reported in this real-world study was consistent with the results of the NAPOLI-1 trial and previous trials.[11] The most common grade 3-4 toxicities were neutropenia (20%) and fatigue (8.6%). The incidence of non-hematological toxicities including diarrhea was lower than that reported in the NAPOLI-1 trial, which can be explained by the ethnic differences in the pharmacokinetics of nal-IRI in the East Asian population or a potential underestimation considering the retrospective nature of our study.[16]

Our study has several limitations. First, the retrospective design subjects this study to unintentional biases. Second, although our study included patients from two cancer referral centers, the number of analyzed patients was the relatively small. However, our data are clinically applicable as this study provides the outcomes of the largest real-world analysis of patients with mPAC who received nal-IRI plus 5-FU/LV after failure of conventional irinotecan-containing therapy. Third, our study included an ethnically homogeneous East Asian population of South Korea; therefore, the results are not generalizable to other populations.

Conclusion

Nal-IRI plus 5-FU/LV showed modest effectiveness and manageable toxicities for mPAC patients who progressed after conventional irinotecan-containing chemotherapy. The survival outcomes appear to be numerically worse than those reported by previous studies, and it might be a result of the resistance developed against irinotecan and use in later lines. The cumulative dose and duration of prior conventional irinotecan therapy have tendency of negative correlation with the effectiveness of nal-IRI plus 5-FU/LV.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69(1):7-34.

2. Hong S, Won YJ, Park YR, Jung KW, Kong HJ, Lee ES, et al. Cancer Statistics in Korea: Incidence, Mortality, Survival, and Prevalence in 2017. Cancer Res Treat. 2020;52(2):335-50.

3. Burris Hr, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. Journal of clinical oncology. 1997;15(6):2403-13.

4. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. New England Journal of Medicine. 2011;364(19):1817-25.

5. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. New England Journal of Medicine. 2013;369(18):1691-703.

6. Yoo C, Hwang I, Song TJ, Lee SS, Jeong JH, Park DH, et al. FOLFIRINOX in borderline resectable and locally advanced unresectable pancreatic adenocarcinoma. Therapeutic advances in medical oncology. 2020;12:1758835920953294.

7. Chae H, Jeong H, Cheon J, Chon HJ, Ryu H, Kim I-H, et al. Efficacy and safety of second-line nab-paclitaxel plus gemcitabine after progression on FOLFIRINOX for unresectable or metastatic pancreatic ductal adenocarcinoma: multicenter retrospective analysis. Therapeutic Advances in Medical Oncology. 2020;12:1758835920923424.

8. Kang J, Hwang I, Yoo C, Kim K-p, Jeong JH, Chang H-M, et al. Nab-paclitaxel plus gemcitabine versus FOLFIRINOX as the first-line chemotherapy for patients with metastatic pancreatic cancer: retrospective analysis. Investigational New Drugs. 2018;36(4):732-41.

9. Kalra AV, Kim J, Klinz SG, Paz N, Cain J, Drummond DC, et al. Preclinical activity of nanoliposomal irinotecan is governed by tumor deposition and intratumor prodrug conversion. Cancer Res. 2014;74(23):7003-13.

10. Ko A, Tempero M, Shan Y, Su W, Lin Y, Dito E, et al. A multinational phase 2 study of nanoliposomal irinotecan sucrosofate (PEP02, MM-398) for patients with gemcitabine-refractory metastatic pancreatic cancer. British journal of cancer. 2013;109(4):920-5.

11. Wang-Gillam A, Li C-P, Bodoky G, Dean A, Shan Y-S, Jameson G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. The Lancet. 2016;387(10018):545-57.

12. Glassman DC, Palmaira RL, Covington CM, Desai AM, Ku GY, Li J, et al. Nanoliposomal irinotecan with fluorouracil for the treatment of advanced pancreatic cancer, a single institution experience. BMC Cancer. 2018;18(1):693.

13. Yoo C, Im HS, Kim KP, Oh DY, Lee KH, Chon HJ, et al. Real-world efficacy and safety of liposomal irinotecan plus fluorouracil/leucovorin in patients with metastatic pancreatic adenocarcinoma: a study by the Korean Cancer Study Group. Ther Adv Med Oncol. 2019;11:1758835919871126.

14. Drummond DC, Noble CO, Guo Z, Hong K, Park JW, Kirpotin DB. Development of a highly active nanoliposomal irinotecan using a novel intraliposomal stabilization strategy. Cancer research. 2006;66(6):3271-7.

15. Chang T, Shiah H, Yang C, Yeh K, Cheng A, Shen B, et al. Phase I study of nanoliposomal irinotecan (PEP02) in advanced solid tumor patients. Cancer chemotherapy and pharmacology. 2015;75(3):579-86.

16. Adiwijaya BS, Kim J, Lang I, Csoszi T, Cubillo A, Chen JS, et al. Population Pharmacokinetics of Liposomal Irinotecan in Patients With Cancer. Clin Pharmacol Ther. 2017;102(6):997-1005.

국문요약

배경: 전이성 췌장암 환자에서 Gemcitabine 항암요법 시행 후 Liposomal irinotecan (nal-IRI)과 fluorouracil/leucovorin (5-FU/LV) 병합요법의 임상적 효과는 밝혀졌고, 본 연구는 이전 irinotecan 항암요법을 시행한 경우에서 상기 병합요법의 효과에 대해 연구하고자 하였다.

방법: 2017 년 1 월부터 2020 년 3 월까지, 울산의대 서울아산병원과 울산대학교 병원에서 이전 irinotecan 항암요법 시행 후 진행하여 nal-IRI 와 5-FU/LV 병합요법 치료를 받은 전이성 췌장암 환자에서 후향적 연구를 진행하였다. Nal-IRI 와 5-FU/LV 병합요법과 기존 irinotecan 항암요법의 질병 진행까지의 시간 (TTP)에 대한 비 (TTPr)를 계산하여, 이와 이전 irinotecan 의 치료 기간 및 누적 용량과의 관계를 분석하였다.

결과: 연구 대상자 35 명의 평균 연령은 58 세였고, 16 명 (46%)이 남성이었다. 이전 irinotecan 치료 기간은 중앙값으로 4.6 개월, 누적 용량은 중앙값으로 1230 mg 이었다. Nal-IRI 와 5-FU/LV 병합요법의 반응률은 2.9%이고 불변 (SD)인 경우는 11 명 (31.4%) 이었다. 중앙값 9.2 개월의 추적 기간 동안, 무진행 생존기간은 2.0 개월, 전체 생존기간은 4.4 개월이었다. 6 개월 무진행 생존율과 전체 생존율은 각각 16.3%와 37.5% 였다. TTPr 의 중앙값은 0.41 이었고 이전 irinotecan 의 누적 용량과 유의한 음의 상관 관계를 가졌고 (R=-0.37, p=0.041), 치료 기간과는 경향성만 확인되었다 (R=-0.35, p=0.062). 가장 흔한 3-4 단계 독성은 호중구 감소 (20%)와 피로감 (8.6%) 이었다.

결론: Nal-IRI와 5-FU/LV 병합요법은 이전 irinotecan 항암요법을 받은 전이성 췌장암 환자에서 보통 정도의 효과와 수용 가능한 정도의 독성을 보였다. 이전 irinotecan 누적 용량과 치료기간은 이 병합요법의 효과와 음의 관계 경향성을 갖는다.

중심단어: 전이성 췌장암, 리포좀 이리노테칸, 플루오로우라실/류코보린, 이리노테칸