의학석사 학위논문

Efficacy and safety of nab-paclitaxel in combination with gemcitabine for metastatic pancreatic cancer

전이성 췌장암에서 nab-paclitaxel과 gemcitabine 병합요법의 효능과 안전성

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Abstract

Efficacy and safety of nab-paclitaxel in combination with gemcitabine for metastatic pancreatic cancer

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Background: Metastatic pancreatic cancer (MPC) is one of the most fatal malignancies with extremely high mortality. Nab-paclitaxel plus gemcitabine have been commonly used in patients with MPC on the basis of positive results from recent randomized controlled trial. The purpose of this study was to evaluate efficacy and safety of this combination chemotherapy

in real clinical practice.

Methods: Patients diagnosed with MPC based on pathologic findings and treated with nab-paclitaxel plus gemcitabine between June 2015 and July 2017 were included. Medical records about patient demographics, laboratory and image findings, and cycles and doses of chemotherapy were retrospectively reviewed in total of 101 patients. Overall survival (OS) and progression free survival (PFS) were estimated by Kaplan-Meier method and Cox proportional hazard regression linear model was applied to assess the prognostic factors.

Results: Median age was 62.1±9.5, and 64 patients (63.4%) were male. Metastasis was identified most commonly in liver followed by peritoneum and lung; 61 patients (60.4%), 30 patients (29.7%) and 19 patients (18.8%), respectively. Patients received total cycles of 6.2±3.6 during 5.7±3.7 months. Median OS and PFS were 14.7 and 7.3 months, respectively. Tumor control was achieved in 73 patients (72.3%); overall partial response in 27 patients (26.7%) and stable disease in 46 patients (45.5%). Multivariable Cox analysis showed poor survival in patients with liver metastasis (HR = 2.15, 95% CI 1.07 – 4.31; p= 0.027). Several adverse events over grade 3 were observed as follows; neutropenia in 41 patients (40.6%), anemia in 23 patients (22.8%) and peripheral neuropathy in 15 patients (14.9%). Febrile neutropenia occurred in 6 patients (5.9%) during follow-up.

Conclusions: Combination chemotherapy of gemcitabine and nab-paclitaxel for patients with MPC showed significant survival advantage and is a reasonable choice in palliative setting. However, careful attention for development of hematologic adverse events and severe peripheral neuropathy is required.

Keywords: Metastatic pancreatic cancer, Chemotherapy, Outcome, Gemcitabine, Nab-paclitaxel

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INTRODUCTION

Pancreatic cancer, one of the most deadly malignancies with high mortality, is now the fourth leading cause of cancer-related death and expected to rank the second by 2030 [1, 2]. Most patients are progressive stages at the time of diagnosis since there are no evidence of adequate screening tests and lack of specific symptoms in early stage [3]. While curative surgery is attempted in some patients with locally advanced cancer invading adjacent vascular or lymphatic systems [4], only palliative or supportive care are possible in patients with metastatic pancreatic cancer (MPC), which results in extremely poor prognosis; 5-year survival rate of 2.6% [5].

Single agent gemcitabine has been widely used in patients with MPC for palliative intent after randomized controlled study in 1997 until recent study has demonstrated that combination of gemcitabine and erlotinib resulted in modest increase in overall survival; however, the duration of survival increase was very limited [6, 7] . More recently, 2 combination therapies of folinic acid, 5-fluorouracil (5-FU), irinotecan, and oxaliplatin (FOLFIRINOX) and nanoparticle albumin-bound paclitaxel (nab-P) plus Gem (nab-P/Gem) showed significant increase in overall survival and progression-free survival [8, 9]. The FOLFIRINOX regimen was approved based on a phase III trial that described significant increase in OS, but was limited by the selection of patients due to its toxicities [10]. The nab-P/Gem regimen has been approved in many countries after the phase III

MPACT trial reported that the addition of nab-paclitaxel to gemcitabine significantly increased overall survival whereas adverse events were tolerable [9]. Subsequent retrospective series have stated that the nab-P/Gem was effective and well-tolerated, cost-effective and an active regimen in pretreated patients [11-14].

Meanwhile, one study that reported ~30% of severe neuropathy after receiving the nab-P/Gem raises questions about discrepancy regarding its safety profile between the clinical trial and real-world practice [11]. In addition, most of the retrospective studies about safety and efficacy of nab-P/Gem are limited by the small number of patients and little is known about factors affecting the course of MPC in patients receiving the combination therapy [11, 13-15]. Therefore, we aimed to investigate the efficacy and safety of nab-P/Gem and factors related to prognosis in patients with MPC.

METHODS

Study subjects

Medical records of 101 patients treated with nab-P/Gem for metastatic pancreatic cancer at Seoul National University Hospital from June 2015 to July 2017 were reviewed. All patients were diagnosed with pancreatic carcinoma by pathologic examination and were classified into metastatic disease based on the results of imaging tests of distant organ or lymph node involvement by 18F-fluoro-2-deoxy-D-glucose positron emission tomography with computed tomography and contrast-enhanced computed tomography (CT) scan. Distant lymph nodes were defined as the presence of enlarged lymph node beyond regional area with or without pathologic confirmation. Patients with previous cytotoxic doses of gemcitabine or any other palliative chemotherapies were also included. In total of 131 MPC patients who received a combination of nab-paclitaxel plus cisplatin, 26 patients who failed to perform the combination therapy more than 2 cycles and 4 patients who had other active cancer within 5 years were excluded. This study was conducted after Institutional Review Board approval.

Data collection

All patients received at least 2 cycles of combination chemotherapy; each cycle comprised nab-P at 125 mg/m2 followed by gemcitabine at 1,000 mg/m2 on days 1, 8 and 15 every 4 weeks. The dose and interval of treatment were adjusted

according to patient's performance status, occurrence of adverse events including peripheral neuropathy and hematologic adverse events such as neutropenia and thrombocytopenia. If progression or death was confirmed, the treatment was discontinued. All patients were evaluated for initial tumor response after first 3 cycles of therapy except for 11 (10.1%) patients: 10 patients who were suspicious of tumor progression underwent CT scan after 2nd cycle and 1 patent was lost to follow-up.

Data regarding patient demographics, Eastern Cooperative Group (ECOG) Performance Status (PS), Charlson comorbidity index, primary tumor site, metastatic location, baseline and follow-up laboratory findings, further subsequent lines of therapy, reasons for therapy discontinuation, history of previous curative surgery, radiotherapy, biliary drainage procedures and adjuvant or palliative chemotherapy were collected.

Statistical analysis

The primary outcome measures were overall survival (OS) and progression-free survival (PFS). OS was determined from the date of the first chemotherapy to death from any cause whereas patients who were still alive were censored at the date of last known follow-up. PFS was calculated from the date of first chemotherapy to the earliest date of radiographic progression or death. Mortality data of 40 (40%) patients were collected by the National Ministry of the Interior and Safety. Response Evaluation Criteria in Solid Tumors guideline was used for assessment of

tumor response and best overall response was evaluated [23] Carbohydrate antigen 19-9 (CA 19-9) was measured at baseline and intervals of every 2~3 cycles thereafter to evaluate the relationship between tumor marker and prognosis.

For baseline characteristics, numerical data were expressed as means and standard deviation or medians and interquartile range depending on distribution of the data. Survival analysis was based on the method of Kaplan–Meier with median with 95% confidence intervals (CIs). A multivariate analysis of survival was performed by Cox proportional-hazard model to reveal the prognostic factors related to overall survival.

RESULTS

Baseline patient characteristics are shown in Table 1. Patients received total cycles of 6.2±3.6 during 5.7±3.7 months. Primary tumor located most commonly in pancreatic head and metastasis was identified in the liver in 61 (60.4%) patients. There were 5 (5.0%) patients with metastasis to distant organ other than liver, peritoneum and lung; 3 (3.0%) patients to bone and 2 (2.0%) patients to adrenal gland. In univariate analysis, primary location in pancreatic head was not significantly related with prognosis (HR 1.58, 95% CI 0.84-2.99; P=0.155) while metastasis to liver showed significant relationship with OS (HR 2.5, 95% CI 10.7-4.31; P=0.032).

There were 9 (8.9%) patients with baseline hyperbilirubinemia (>1.5 × ULN) due to malignant biliary obstruction and 5 (5.0%) patients with increase in baseline aminotransferases of > 2 × ULN caused by liver metastasis. Baseline abnormal levels of laboratory tests in all 9 patients with hyperbilirubinemia and 5 patients with hypertransaminasemia recovered to normal level during the course of the combination chemotherapy and median duration to the recovery was 14.0 (interquartile range, 13.0~37.0) days and 13.7 (interquartile range, 7.0-30.1) days, respectively.

Baseline CA19-9 level was available in 99 patients and was ≥59 ULN in 35 (34.7%) patients. Baseline increase in CA 19-9 level didn't have significant associations with OS (HR 1.39, 95% CI 0.74-2.63; P=0.308). Decrease in CA 19-9

by 30%, 50% and 70% were observed in 45 (44.6%), 57 (56.4%) and 68 (67.3%) patients, respectively. There were no statistical significances in univariate analysis between OS and decrease in CA 19-9 level by 30%, 50% or 70% (HR 0.61, 95% CI 0.32-1.18, P=0.141, HR 0.76, 95% CI 0.41-1.42, P=0.391, and HR 0.75, 95% CI 0.40-1.41, P=0.376, respectively).

While nab-P/Gem was the first-line chemotherapy in most patients, 13 (12.9%) patients had history of previous palliative chemotherapy; second-line in 8 patients, third-line in 3 patients, and fourth- and fifth-line in one patient each, respectively. During the previous courses of chemotherapy, 10 patients received FOLFIRINOX and 3 patients were treated with gemcitabine-based chemotherapy. Univariate analysis of previous palliative chemotherapy didn't indicate significant correlation with OS (HR 0.51, 95% CI 0.18-1.43, P=0.199).

Response rate is summarized in table 2. Tumor control was achieved in 73 (72.3%) patients and best overall response was not evaluable in 18 (17.8%) patients; less than 2 consecutive imaging tests in 17 patients and lost to follow-up right after 2nd cycle chemotherapy in 1 patient. There was no patient who achieved complete response. Of the patients with progressive disease, further regimens were employed in 51 (50.5%) patients; FOLFIRINOX in 48 (35.3%) patients, gemcitabine single therapy in 14 (27.5%) patients, combination of folinic acid, 5-FU and oxaliplatin in 10 (9.9%) patients, oral fluoropyrimidine in 5 (5.0%) patients, combination of folinic acid, 5-FU, and irinotecan in 2 (2.0%) patients, and clinical trial in 1 (1.0%) patient. More than 2 subsequent lines of chemotherapy regimens were applied in

10 (9.9%) patients.

OS and PFS are illustrated in Fig. 1. Variables which indicated P value of <0.20 in univariate analysis are as follows; primary location in head, decrease of CA 19-9 by 30%, history of previous palliative chemotherapy and metastasis to liver. Multivariable Cox analysis showed poor survival in patients with liver metastasis (HR=2.20, 95% CI 1.09 – 4.41, P=0.027).

Adverse events over grade II are summarized in table 3. Several adverse events over grade 3 were observed as follows; neutropenia in 41 (40.6%) patients, anemia in 23 (22.8%) patients and peripheral neuropathy in 15 (14.9%) patients. Febrile neutropenia occurred in 6 (5.9%) patients and peripheral neuropathy of grade 1 affected 28 (27.7%) patients during follow-up.

The most common cause of discontinuation of therapy was tumor progression (43.6%) followed by peripheral neuropathy of grade 3 (14.9%) and the reason for dose reduction was most frequently neutropenia of grade 3 or 4 (15.8%) and peripheral neuropathy of grade 2 (11.9%). The median number of cycle that initiated dose reduction due to peripheral neuropathy was 4 and no patients were able to receive the standard dose again. The number of patients who underwent dose reduction on each cycle is diagrammed in Fig. 2. Overall, dose reduction was needed in 47 (46.5%) patients for nab-paclitaxel and 35 (34.7%) patients for gemcitabine. After 3 cycles of therapy, 52 (51.5%) patients stopped treatment or had to undergo DR.

DISCUSSION

It was the objective of this study to investigate the efficacy and safety of nab-P/Gem combination chemotherapy in patients with MPC. The results of this single-center retrospective study showed longer OS and PFS than the previous randomized controlled trial and the extension study of MPACT trial based on mortality data from 90% of the enrolled patients [9, 16] . The reason for longer OS and PFS than the other studies may stem from the restricted range of patient selection; in this study, patients who received more than 2 cycles of the therapy were included. By the same token, total cycles and treatment duration in this study were longer than in MPACT trial that showed treatment duration of 3.9 (1.0-21.9) months and the other retrospective study which indicated median cycle of 4 [9, 15].

Moreover, as this study was based on mortality data of only 40 patients, OS and PFS duration could be longer with long term follow-up. The primary outcome of this study showed a significant survival advantage compared to the previous results of gemcitabine only (5.65 months) and gemcitabine plus erlotinib (6.24 months) [6, 7]. The improvement of clinical outcome is the mainstay of evidence that supports nab-P/Gem not only as a first line therapy but also as a backbone of several clinical trials [3, 17, 18]. To evaluate the efficacy and safety more adequately, we included only patients who underwent two or more cycles and this study has strength in that number of enrolled patients was higher than that of previous retrospective studies even though patients who received one cycle of treatment were excluded [11, 14, 15].

Tumor control rate of 72.3% in this study is consistent with other retrospective studies ranging 43.5%~81.0% [13-15], which were variable depending whether they included pretreated patients, patients with liver function test (LFT) abnormalities and patients with advanced pancreatic cancer or only metastatic pancreatic cancer. Despite the fact that more than half of the patients had to stop the regimen or reduce dose of the agents in this study, clinical benefit rate was significantly high. These findings coincides well with 2 other studies that indicated effectiveness of biweekly regimen and reduced dose of the agents [19, 20] . Because the previous studies were not evaluated by comparative design, caution should be exercised in choosing an appropriate dose and intervals and further discussion is warranted.

Several studies have reported different outcomes whether CA19-9 is associated with prognosis in patients with MPC. In one retrospective study, as in the long-term survival analysis of MPACT trial [16], high baseline CA19-9 (≥59 × ULN) did not show a significant correlation with OS in multivariate analysis [15]. On the other hand, another follow-up study of MPACT trial has suggested that a decrease in CA19-9 levels measured at 8 weeks of treatment is significantly related to OS [21]. In this study, the baseline and follow-up CA19-9 levels were not statistically significant in multivariate analysis, and one of the reason why decrease in CA19-9 level did not show significant correlation with OS was due to its retrospective design where optimal timing of measurement of CA19-9 was different for each patient. This study was intended to find out relationship between lowest level of CA 19-9 during follow-up duration rather than the level estimated in specific time

point.

There was a difference in frequencies of peripheral neuropathy compared with other studies. In MPACT trial, neuropathy grade 3 was reported in 17% of patients; 10% in need of dose reduction, and 8% in need of discontinuation of chemotherapy [9]. In our study, peripheral neuropathy that resulted in dose reduction and discontinuation of the treatment were 11.9% and 14.9%, respectively. Severe neuropathy was the second most common reason for the discontinuation of therapy and the percentage of the patients who had to stop the treatment was almost twice higher than that of the previous clinical trial. Moreover, no patients who needed dose reduction due to peripheral neuropathy were able to resume standard dose of the regimen again. In several retrospective studies, the incidences of peripheral neuropathy grade 3 ranged 10.3 – 30.4% [11, 13, 15]. Although the grading systems of peripheral neuropathy in other studies are based on the CTCAE guideline in common, the grading may be subjective and different for each medical institution and for each clinician. In this study, the proportion of patients with peripheral neuropathy grade 3 was less than MPACT trial, but the comparison of the percentage of patients who had to reduce the dose or stop the regimen described significantly higher incidence in development of moderate and severe peripheral neuropathy.

Since nab-P/Gem can cause hepatic impairment pharmacokinetically, care must be taken in patients with LFT abnormalities and hyperbilirubinemia and those patients should be monitored frequently [22]. Results of this study demonstrated

that abnormal baseline laboratory findings of patients with baseline hyperbilirubinemia and hypertransaminasemia recovered to normal level after initiation of chemotherapy. These findings suggest that elevation of bilirubin and LFT abnormalities caused by malignant biliary obstruction and liver metastasis in patients with MPC is not an absolute contraindication of the chemotherapy, but rather an integral part of the inclusion criteria.

It is the limit of this study that the OS and PFS were evaluated based on somewhat short mortality data. However, it does not seem to be constrain the aim of this study in evaluating the effectiveness of nab-P/Gem, since OS and PFS were in close agreement in other studies. It is also a limitation that this study is retrospective and patient groups are heterogeneous. Patients had history of different types of pervious therapy and there were slight time differences in the follow-up period during which imaging and laboratory tests were not performed at the same time. These factors may have served as confounding factors. In further studies, such heterogenetic factors should be considered for more accurate assessment.

Conclusively, combination chemotherapy of nab-P/Gem for patients with MPC showed significant survival advantage and is a reasonable choice for palliative intent. However, careful attention for development of severe peripheral neuropathy and hematologic adverse events is required.

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Table 1. Baseline characteristics

	Patients with MPC (N = 101)
Age	62.1 ± 9.5
Sex	
- Female	37 (36.6%)
- Male	64 (63.4%)
Primary tumor location	
- Head	43 (42.6%)
- Body	34 (33.7%)
- Tail	35 (34.7%)
Metastasis	
- Liver	61 (60.4%)
- Lung	19 (18.8%)
- Peritoneum	30 (29.7%)
- Distant LNs	14 (13.9%)
ECOG	
- 0-1	98 (97.0%)
- 2	3 (3.0%)
Charlson score	8.5 ± 1.3
Previous therapy	
- Bile duct stent	17 (16.8%)
- Curative surgery	21 (20.8%)
- Radiotherapy	15 (14.9%)
- Adjuvant chemotherapy	10 (9.9%)
- Palliative chemotherapy	13 (12.9%)
Baseline laboratory findings	
- Hemoglobin (g/dL)	12.5 ± 1.5
- Platelet (/mm^3)	228.5 ± 73.6
- ANC (/mm^3)	4531.9 ± 2584.0
- AST (IU/L)	31.6 ± 25.9
- ALT (IU/L)	37.4 ± 50.4
- Total bilirubin (mg/dL)	0.8 ± 0.8
- Creatinine (mg/dL)	0.8 ± 0.2
- eGFR (mL/min/1.73m^2)	95.8 ± 19.9
- CA 19-9 (U/mL)[a]	522.0 (54.2-5322.5)
Total cycle	6.2 ± 3.6

[a]Data are medians (interquartile range).

Abbreviations: ANC, absolute neutrophil count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerluar filatration rate; CA 19-9, carbohydrate antigen 19-9

Table 2. Response rate

Response	
PR	27 (26.7%)
SD	46 (45.5%)
PD	14 (13.7%)
NE	14 (13.7%)

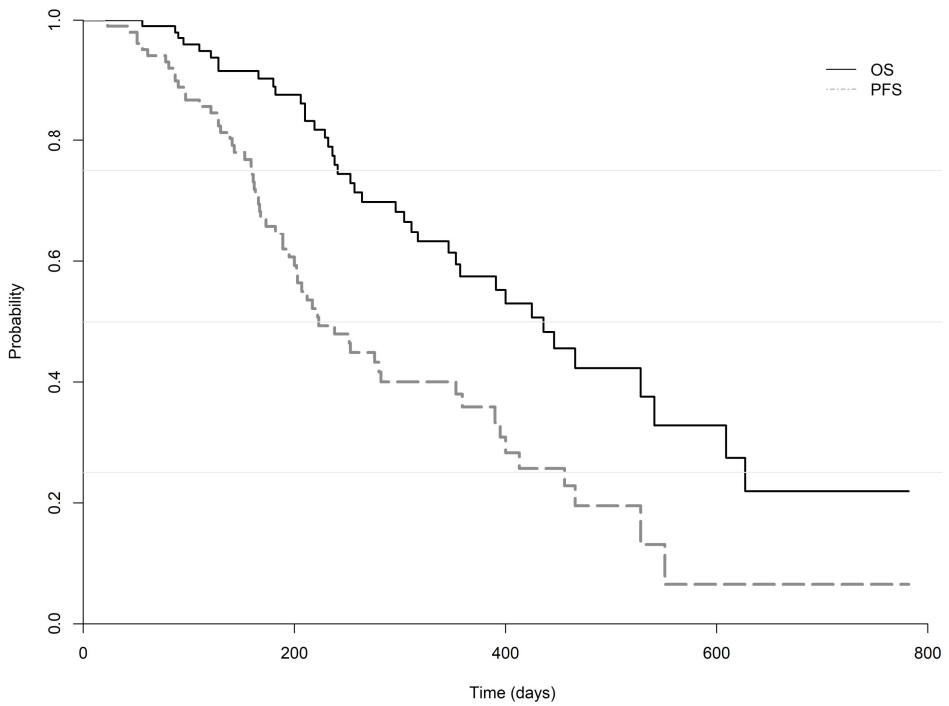
Abbreviations: PR, partial response; SD, stable disease; PD, progressive disease;

NE, not evaluable

Table 3. Adverse events

Complications	Grade 2	Grade 3	Grade 4
Febrile neutropenia	-	6 (5.9%)	-
Anemia	43 (42.6%)	23 (22.8%)	-
Thrombocytopenia	8 (7.9%)	4 (4.0%)	3 (3.0%)
Neutropenia	25 (24.8%)	23 (22.8%)	18 (17.8%)
Neuropathy	12 (11.9%)	15 (14.9%)	-
Peripheral edema	18 (17.8%)	4 (4.0%)	-
Diarrhea	4 (4.0%)	4 (4.0%)	-
Nausea, vomiting	18 (17.8%)	3 (3.0%)	-

Figure 1.



OS and PFS graph in patients treated with nab-P/Gem by Kaplan-Meier survival method. Median OS and PFS were 14.7 (95% CI 11.6 to 20.0) and 7.3 (95% CI 6.6 to 11.8) months, respectively. OS, overall survival, PFS, progression-free survival. OS, overall survival, PFS, progression-free survival

Figure 2. A.

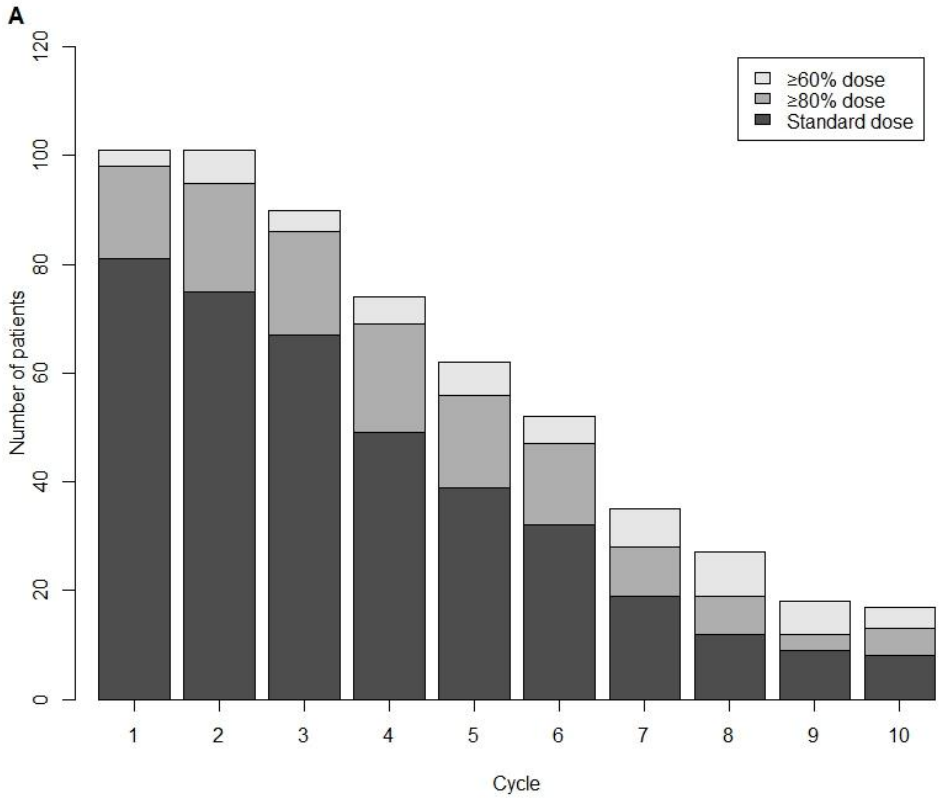
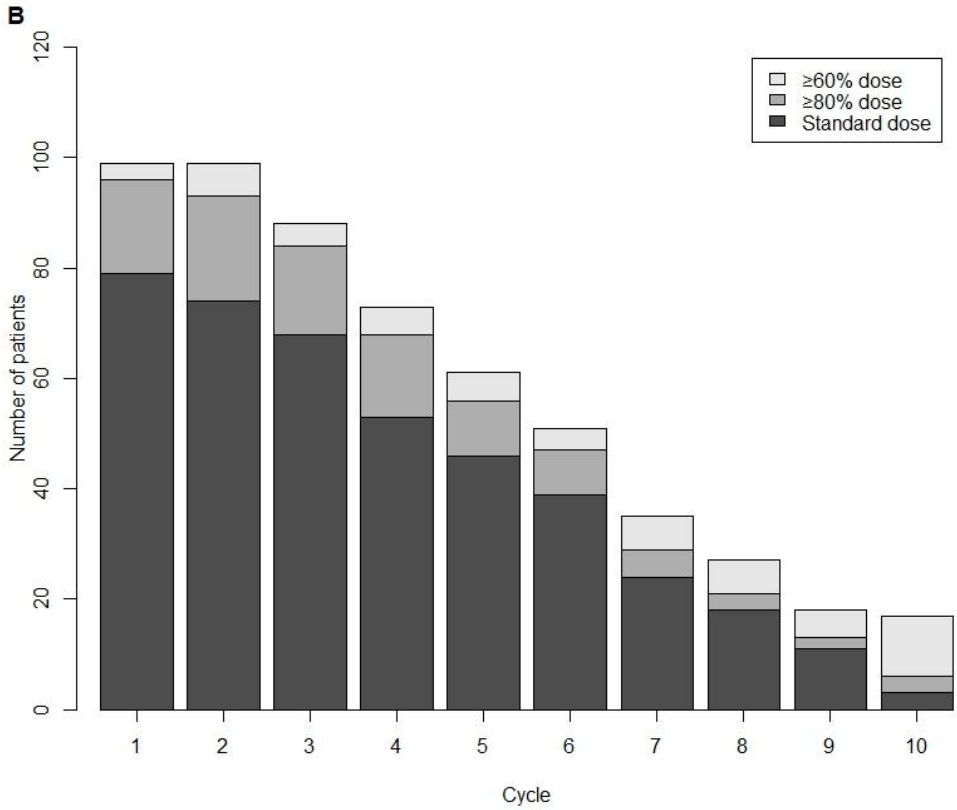

A
≥60% dose
≥80% dose
Standard dose
Number of patients
0
20
40
60
80
100
120
1
2
3
4
5
6
7
8
9
10
Cycle

Figure 2. B.



Cycles and doses during the course of combination chemotherapy. (A) nab-paclitaxel (B) gemcitabine. '≥80% dose' was defined as range of 80% to less than standard dose and '≥60% dose' was defined as 60% to less than 80% of standard dose.

요약 (국문 초록)

배경: 전이성 췌장암은 사망률이 극히 높은 치명적인 악성 종양 중 하나이다. 최근 시행된 무작위 임상 시험에서 젬시타빈과 냅-파클리탁셀 병합효법의 효능이 입증된 이후로 고식적 목적의 치료로 널리 쓰이는 추세이다. 이에 본 연구에서는 실제 임상에서 젬시타빈과 냅-파클리탁셀의 병합요법과 관련한 효능 및 안정성을 평가하고자 하였다.

방법: 2015년 6월부터 2017년 7월까지 병리학적 소견으로 전이성 췌장암을 진단받아 젬시타빈과 냅-파클리탁셀 병합 요법으로 치료한 환자를 대상으로 하였다. 총 101명 환자의 의무기록을 후향적으로 리뷰하였으며, 성별, 나이, 기저 질환, 실험실 및 영상 검사 소견, 항암 주기 및 용량에 대한 정보를 분석하였다. 카플란-메이어 방법으로 전체 생존율과 무진행 생존율을 예측하였고, 예후 인자를 평가하기 위해 콕스 비례 위험모형을 적용하였다.

결과: 평균 연령은 62.1±9.5세였으며, 남자는 64명(63.4%)이었다. 전이는

간에서 61명(60.4%)으로 가장 흔하게 발견되었고 복막에서 30명(29.7%), 폐에서 19명(18.8%)이 발생하였다. 환자는 5.7±3.7개월동안 6.2±3.6의 주기를 시행받았다. 전체 생존률과 무진행 생존률의 중앙값은 각각 14.7 개월과 7.3개월이었다. 종양 조절은 73 명(72.3 %)에서 이루어졌으며 전반적인 부분 반응은 27명(26.7 %)이었고 안정된 질환은 46명(45.5 %)이었다. 다변수 콕스 분석 결과에서는 간 전이 환자가 낮은 생존율을 보였다 (HR=2.15, 95% CI 1.07-4.31, p=0.027). 중증도 3 이상의 이상 반응으로는, 호중구 감소증 41예(40.6 %), 빈혈 23예(22.8 %), 말초 신경 병증 15예(14.9 %)가 있었으며, 열성 호중구 감소증이 6명(5.9 %)에서 추적 관찰 기간 동안 발생하였다.

결론: 전이성 환자에서 젬시타빈과 냅-파클리탁셀 병합 요법은 생존율면에서 유리하였으며, 완화 목적의 치료로서 합리적인 치료법이었다. 그러나 혈액학적 부작용과 중증의 말초 신경 병증 발생 가능성이 있어 치료에 주의를 기울여야 한다.

주요어: 전이성 췌장암, 병합화학요법, 효능, gemcitabine, nab-paclitaxel

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