ANTICANCER RESEARCH *38*: 6537-6542 (2018)
doi:10.21873/anticanres.13019

Feasibility of Combination Therapy with Nab-paclitaxel Plus Gemcitabine in Patients with Recurrent Pancreatic Cancer

HIROMICHI KAWAIDA[1], HIROSHI KONO[1], HIDETAKE AMEMIYA[1], RYOU SAITOU[1], ATSUSHI YAMAMOTO[1], NAOHIRO HOSOMURA[1], MITSUAKI WATANABE[1], AYAKO KIMURA[1], SHINJI FURUYA[1], HIROKI SHIMIZU[1], HIDENORI AKAIKE[1], YOSHIHIKO KAWAGUCHI[1], MAKOTO SUDO[1], JUN ITAKURA[1], HIROSHI HAYAKAWA[2], HIROKO SHINDO[2], EI TAKAHASHI[2], SHINICHI TAKANO[2], MITSUHARU FUKASAWA[2], SHINTARO ICHIKAWA[3], HIDEKI FUJII[1] and DAISUKE ICHIKAWA[1]

[1]First Department of Surgery, [2]First Department of Internal Medicine, and [3]Department of Radiology, Faculty of Medicine, University of Yamanashi, Yamanashi, Japan

Abstract. *Background/Aim: Nab-paclitaxel plus gemcitabine (nab-P+Gem) is one of most reliable and effective regimens for borderline or unresectable pancreatic cancer (PC). However, the feasibility and clinical benefits of this regimen have never been evaluated for patients with recurrent PC after pancreatectomy. The aim of this study was to investigate the feasibility of combination therapy with nab-paclitaxel plus gemcitabine (nab-P+Gem) for patients with recurrent PC. Patients and Methods: Twenty-two patients with recurrent PC received an intravenous infusion of nab-P (125 mg/m^2) and Gem (1,000 mg/m^2) on days 1, 8, and 15 of a 4-week cycle. The primary end-point of this study was completion of the 4 cycles. The secondary end-points were the safety, efficacy, and disease control rate. Results: The treatment completion rate of the 4 cycles was 90.9%. The objective response rate was 13.6% and the disease control rate was 63.6%. The median progression-free survival was 7.2 months. The most common grade 3 or higher hematological toxicity was neutropenia (72.7%). There was no treatment-related death. Furthermore, the chemotherapeutic effects varied with the time of recurrence. Conclusion: Combination nab-P+Gem therapy was well-tolerated and effective in patients with recurrent PC.*

Pancreatic cancer (PC) is the seventh most common cause of cancer-related mortality worldwide (1) and surgical resection is the only potential cure. However, even when curative surgery is performed, the prognosis after pancreatic surgery is poor (2). Currently, adjuvant chemotherapy is considered to be the standard strategy for patients with macroscopically-resected PC, based on several randomized controlled studies (2-4). However, most patients with relatively advanced disease experience recurrence after macroscopically curative surgical resection with post-operative adjuvant chemotherapy (5-8), and the 5-year survival rate is 12-19% (9-11). Therefore, an optimal treatment for recurrent disease is required.

Recently, the efficacy of several chemotherapeutic regimens has been demonstrated for borderline or unresectable PC (12, 13). Among them, nanoparticle albumin-bound (nab)-paclitaxel plus gemcitabine (nab-P+Gem) is one of most reliable and effective regimens (12, 13). However, the feasibility and clinical benefits of this intensive regimen have never been fully evaluated for patients with recurrent PC in weak physical condition after pancreatectomy. The purpose of this study was to assess the safety and efficacy of combination nab-P +Gem therapy in patients with recurrent PC.

Patients and Methods

Patients. Twenty-two patients with recurrent PC after radical surgery were treated at our hospital from January 2016 to November 2017. The main treatment regimen of adjuvant chemotherapy was orally administered S-1 (TS-1, Taiho Pharmaceutical, Tokyo, Japan), 40 mg, 50 mg or 60 mg according to body-surface area twice a day for 28 days followed by a 14-day rest (1 cycle) for up to 4 cycles (4), while 2 patients received intravenous gemcitabine, 1000 mg/m^2, on days 1, 8, and 15 every 4 weeks (one cycle) for up to 6 cycles because of allergic reactions for TS-1. One patient did not receive adjuvant chemotherapy because he developed recurrence before starting adjuvant chemotherapy.

Twenty-one patients who underwent adjuvant chemotherapy were classified into the following three groups according to the time of recurrence: the early group (recurrence during adjuvant chemotherapy), the intermediate group (recurrence within 6

Correspondence to: Hiromichi Kawaida, MD, Ph.D., First Department of Surgery, Faculty of Medicine, University of Yamanashi, 1110 Shimokato, Chuou-shi, Yamanashi, 409-3898 Japan. Tel/Fax: +81 552737390, e-mail: kawaidah@yamanashi.ac.jp

Key Words: Nab-paclitaxel, gemcitabine, pancreatic cancer, pancreatectomy.

months after adjuvant chemotherapy), or the late group (recurrence after 6 months from completion after chemotherapy). The patients were also divided into two groups according to history of gemcitabine usage.

The safety and efficacy of the nab-P+Gem regimen were retrospectively analyzed for all patients and each patient group separately.

Tumor markers [carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA) and Duke pancreatic monoclonal antigen type 2 (DuPAN-2)] were measured every 4 weeks and computed tomography (CT) was performed every three months after surgery. Recurrence of PC was defined as appearance of tumors on CT and/or successive increases of tumor markers 2 times above the normal level.

The criteria for patient treatment were performance status (PS) Eastern Cooperative Oncology Group (ECOG) <3 and adequate hematological, hepatic, renal, cardiac, and respiratory function.

Treatment. Twenty-two patients were administered a 30-min intravenous infusion of nab-P (125 mg/m^2) followed by a 30-min intravenous infusion of Gem (1,000 mg/m^2) on days 1, 8, and 15 every 4 weeks. Antiemetic prophylaxis with 5-HT3 antagonists plus dexamethasone was used for all patients.

If patients developed grade 4 hematological toxicities or grade 3 peripheral sensory neuropathy (PSN), the dosage of nab-paclitaxel and gemcitabine was reduced. The reduced dose was 100 mg/m^2 for nab-paclitaxel and 800 mg/m^2 for gemcitabine. Treatment continued until disease progression or an unacceptable level of adverse events.

Study evaluations. Objective responses of target lesions were evaluated with the Response Evaluation Criteria in Solid Tumors (RECIST ver.1.1) criteria. Radiological response was assessed by investigators and a radiologist from the institution. Tumor marker response was defined as a decrease of greater than 50% from baseline for response and an increase of greater than 20% from baseline for progression (14-17). Toxicity was graded according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) v4.0. The median progression-free survival (PFS) was defined as the time elapsed from treatment start to the first progression of the cancer.

The primary end-point of this study was completion of the 4 cycles of combination nab-P+Gem therapy by patients with recurrent PC. The secondary end-points of this study were the safety, efficacy, and disease control rate (DCR). DCR was defined as the proportion of patients with complete response (CR), partial response (PR), and stable disease (SD) for 4 weeks or longer. All patients gave informed consent for treatment.

Statistical analysis. PFS from the start of nab-P+G was estimated using the Kaplan-Meier method. Statistical significance was set at $p<0.05$.

Ethics approval and consent to participate. This study was reviewed and approved by the ethics committee of the University of Yamanashi. Clinical trial registration number: UMIN ID: 000031203.

Informed consent statement. Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Table I. *Clinical characteristics of patients*.

Characteristics	N
Age,years	
Median	68
Range	58-79
Gender	
Male	16
Female	6
ECOG Performance status	
0	14
1	8
Surgical procedure	
Pancreaticoduodenectomy	11
Distal pancreatectomy	9
Total pancreatectomy	2
UICC stage	
IIA	4
IIB	15
IV	3

ECOG, Eastern Cooperative Oncology Group; UICC, Union for International Cancer Control.

Table II. *Site of recurrences*.

	N	%
Local	6	27.3
Lymph nodes	2	9.1
Liver	8	36.4
Lung	5	22.7
Peritonium	1	4.5
Bone	1	4.5
Other	1	4.5

Results

Patient characteristics and treatment details. Clinical characteristics of patients are summarized in Table I. The median age was 68.0 years. Pancreaticoduodenectomy was performed in 11 patients, distal pancreatectomy in 9 patients, and total pancreatectomy in 2 patients. Three patients had stage IV disease; all of them had localized metastasis to para-aortic lymph nodes and macroscopically curative surgery was possible. The sites of recurrence are shown in Table II. Eight patients had recurrence in the liver, 5 patients had recurrence in the lung, and 6 patients presented with local recurrence. Among all patients, 124 treatment cycles were administered (median=5.6 cycles, range=2-11). The main causes of treatment discontinuation were disease progression and toxicity. There were 8 patients who received the reduced dosage of nab-P+Gem (36.4%).

Table III. *Summary of grade 2 (G2), G3 or G4 adverse events.*

Toxicity	G2		G3		G4	
	N	%	N	%	n	%
Leukopenia	1	4.5	8	36.4	1	4.5
Neutropenia	1	4.5	9	40.9	7	31.8
Lymphopenia	1	4.5	1	4.5	1	4.5
Thrombocytopenia	3	13.6	1	4.5	0	0
Alopecia	17	77.3	0	0	0	0
Peripheral sensory neuropathy	9	40.9	1	4.5	0	0
Anorexia	5	22.7	1	4.5	0	0
Fatigue	2	9.1	1	4.5	0	0

Table IV. *Efficiency estimates of nab-paclitaxel plus gemcitabine.*

	N	%
Response to therapy		
Complete response	0	0
Partial response	3	13.6
Stable disease	11	50
Progressive disease	8	36.4
Objective response (CR+PR)	3	13.6
Disease control (CR+PR+SD)	14	63.6
Treatment completion rate		90.9

Table V. *Relationship between recurrence time, history of gemcitabine use, and DCR.*

	N	DCR (%)
Recurrence time		
Early	12	50
Intermediate	5	80
Late	4	100
A history of gemcitabine use	9	55.6
Gemcitabine-naïve	13	69.2

DCR, Disease control rate.

Safety. The treatment-related CTC adverse events are presented in Table III. Hemotological and non-hematological grade 3 or higher toxicity occurred in 19 patients (86.4%). The most common grade 3 or higher hematological toxicities were neutropenia (16 patients, 72.7%) and leukopenia (9 patients, 40.9%). However, no patients were treated with granulocyte-colony stimulating factor (G-CSF). Regarding non-hematological toxicities, grade 3 fatigue, anorexia, and PSN were observed in one patient each. The most frequent toxicity was grade 2 alopecia (17 patients, 77.3%), followed by PSN in 10 patients (45.5%, including grade 3 in 1 patient as described above).

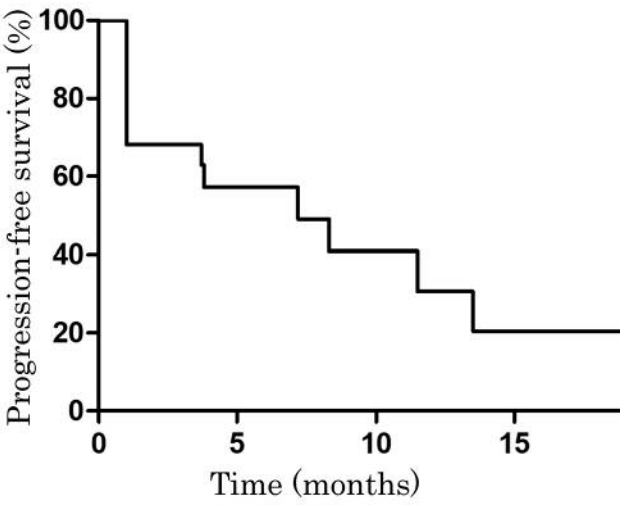

Figure 1. *Progression-free survival (PFS). The median-PFS was 7.2 months based on the Kaplan–Meier curve.*

Dose reduction was required for 8 patients (36.4%), and doses were skipped for 19 patients (86.4%), mainly because of neutropenia. However, there was no treatment-related death. Two patients discontinued treatment at the end of 2 cycles due to progressive disease and fatigue, respectively. Twenty patients received more than 4 cycles of treatment, and the treatment completion rate was 90.9% (Table IV).

Efficacy. Among 22 patients, 3 demonstrated PR (13.6%), and 11 demonstrated SD (50.0%), while none had CR. Three patients presented an objective response (CR+PR 3/22, 13.6%) and the DCR (CR+PR+SD) was 63.6% (PR+SD 14/22) (Table IV). The median PFS was 7.2 months (Figure 1).

Regarding recurrence time, there were 12, 5, and 4 patients in the early, intermediate and late groups, respectively. The DCRs were 50%, 80%, and 100%, respectively, which slightly increased with the postoperative time. On the other hand, the DCR of patients with a history of gemcitabine use as adjuvant chemotherapy was 55.6%, which was slightly lower than the 69.2% of gemcitabine-naïve patients. However, there was no significant difference between the 2 groups (p=0.535) (Table V).

Discussion

Since the effects of gemcitabine were first reported (12), many chemotherapy regimens have been evaluated for treatment of patients with PC. The Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT) demonstrated

significant tumor shrinkage and survival benefits for nab-P+Gem for both primary pancreatic and metastatic lesions (13). However, many clinical trials are performed on unresectable or borderline PC, and the efficacy of nab-P+Gem in patients with recurrent PC has not been investigated.

Following surgical resection of the pancreas, especially pancreaticoduodenectomy, most patients have significant weight loss and malnutrition due to anorexia and malabsorption (18, 19). In addition, many patients undergoing pancreatectomy have diabetes and diet therapy is necessary. However, the efficacy of aggressive chemotherapeutic treatment correlates with the performance and nutritional status of patients (20-22). Therefore, the feasibility and clinical impact of combination nab-P+Gem therapy were examined in patients with recurrent PC after pancreatectomy.

For this study, 4 cycles of combination nab-P+Gem therapy were administered in patients with recurrent PC according to previous studies (13, 23). The treatment completion rate was 90.9%, even after aggressive pancreatic surgery. Furthermore, the safety and efficacy of nab-P+Gem in patients with recurrent PC after pancreatectomy were confirmed. The most common adverse events were neutropenia, leukopenia, alopecia, and PSN. Our results were similar with past study results using nab-P+Gem, including MPACT (13, 24-31).

In this study, the DCR was 63.6% and the PFS was 7.2 months, which are higher than those in previous studies on nab-P+Gem (13, 24-31). One possible explanation for this is that all patients were observed post-operatively and recurrence was diagnosed earlier. The suitability of the dosing regimen was also similar with that of MPACT, and 68.2% of patients did not require dose reduction.

Treatment results for PC are improving due to advances in surgical procedures, neoadjuvant chemotherapy (32-36) and adjuvant chemotherapy (2-4). However, PC recurs in many patients, and the prognosis after pancreatic surgery is still poor (2-4, 11). It may be difficult to select the most effective treatment in recurrent cases because the optimal treatment remains controversial.

Among recent clinical trials performed with patients with unresectable PC, irinotecan, oxaliplatin and leucovorin-modulated fluorouracil (FOLFIRINOX) was found to be one of the most effective treatments (37, 38), but it is not applicable for patients older than 75 years old (38). Nevertheless, herein, 4 patients older than 75 years old were included. Furthermore, some reports suggest that the nab-P+Gem regimen yields a better clinical outcome and fewer toxicities than FOLFIRINOX for patients with pancreatic cancer (39, 40). Therefore, nab-P+Gem may be a safe and effective regimen even for patients after aggressive pancreatic surgery.

Of note, the chemotherapeutic effects in this study varied with the time of recurrence; later recurrence led to a better response. Thus, intense chemotherapeutic treatment for the late recurrent group, such as FOLFIRINOX, is not needed because nab-P+Gem may be sufficient. Moreover, there was no change in the chemotherapeutic effect regardless of past gemcitabine use.

The limitation of the present study is associated with the small number of patients, thus a larger multicenter study is recommended. Furthermore, it is necessary to select patients who can expect the therapeutic effect of nab-P+Gem.

These results suggest nab-P+Gem to be a safe and efficacious chemotherapeutic option for patients with recurrent PC. Further studies using a larger number of patients and prospective study design are recommended in the future.

Conclusion

Nab-P+Gem may be a safe and effective treatment option for patients with recurrent PC or borderline and unresectable PC. This treatment may improve the prognosis of patients with recurrent PC.

References

1 Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J and Jemal A: Global cancer statistics, 2012. CA Cancer J Clin *65(2)*: 87-108, 2015.

2 Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, Schramm H, Fahlke J, Zuelke C, Burkart C, Gutberlet K, Kettner E, Schmalenberg H, Weigang-Koehler K, Bechstein WO, Niedergethmann M, Schmidt-Wolf I, Roll L, Doerken B and Riess H: Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA *297(3)*: 267-277, 2007.

3 Neoptolemos JP, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, Padbury R, Moore MJ, Gallinger S, Mariette C, Wente MN, Izbicki JR, Friess H, Lerch MM, Dervenis C, Oláh A, Butturini G, Doi R, Lind PA, Smith D, Valle JW, Palmer DH, Buckels JA, Thompson J, McKay CJ, Rawcliffe CL and Büchler MW: European Study Group for Pancreatic Cancer. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA *304(10)*: 1073-1081, 2010.

4 Uesaka K, Boku N, Fukutomi A, Okamura Y, Konishi M, Matsumoto I, Kaneoka Y, Shimizu Y, Nakamori S, Sakamoto H, Morinaga S, Kainuma O, Imai K, Sata N, Hishinuma S, Ojima H, Yamaguchi R, Hirano S, Sudo T and Ohashi Y: JASPAC 01 Study Group. Adjuvant chemotherapy of S-1 *versus* gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). Lancet *388(10041)*: 248-257, 2016.

5 Shima Y, Okabayashi T, Kozuki A, Sumiyoshi T, Tokumaru T, Saisaka Y, Date K and Iwata J: Completion pancreatectomy for recurrent pancreatic cancer in the remnant pancreas: report of six cases and a review of the literature. Langenbecks Arch Surg *400(8)*: 973-978, 2015.

6 Suzuki S, Furukawa T, Oshima N, Izumo W, Shimizu K and Yamamoto M: Original Scientific Reports: Clinicopathological findings of remnant pancreatic cancers in survivors following curative resections of pancreatic cancers. World J Surg *40(4)*: 974-981, 2016.

7 Miyazaki M, Yoshitomi H, Shimizu H, Ohtsuka M, Yoshidome H, Furukawa K, Takayasiki T, Kuboki S, Okamura D, Suzuki D and Nakajima M: Repeat pancreatectomy for pancreatic ductal cancer recurrence in the remnant pancreas after initial pancreatectomy: is it worthwhile? Surgery *155(1)*: 58-66, 2014.

8 Hashimoto D, Chikamoto A, Ohmuraya M, Sakata K, Miyake K, Kuroki H, Watanabe M, Beppu T, Hirota M and Baba H: Pancreatic cancer in the remnant pancreas following primary pancreatic resection. Surg Today *44(7)*: 1313-1320, 2014.

9 Ferrone CR, Pieretti-Vanmarcke R, Bloom JP, Zheng H, Szymonifka J, Wargo JA, Thayer SP, Lauwers GY, Deshpande V, Mino-Kenudson M, Fernández-del Castillo C, Lillemoe KD and Warshaw AL: Pancreatic ductal adenocarcinoma:long-term survival does not equal cure. Surgery *152*: S43-49, 2012.

10 Ferrone CR, Brennan MF, Gonen M, Coit DG, Fong Y, Chung S, Tang L, Klimstra D and Allen PJ: Pancreatic adenocarcinoma: the actual 5-year survivors. J Gastrointest Surg *12(4)*: 701-706, 2008.

11 Winter JM, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J, Hodgin MB, Sauter PK, Hruban RH, Riall TS, Schulick RD, Choti MA, Lillemoe KD and Yeo CJ: 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. J Gastrointest Surg *10(9)*: 1199-1210, 2006.

12 Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD and Von Hoff DD: Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol *15(6)*: 2403-2413, 1997.

13 Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, IglesiasJ and Renschler MF: Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med *369(18)*: 1691-1703, 2013.

14 Boeck S, Stieber P, Holdenrieder S, Wilkowski R and Heinemann V: Prognostic and therapeutic significance of carbohydrate antigen 19-9 as tumor marker in patients with pancreatic cancer. Oncology *70(4)*: 255-264, 2006.

15 Katz MH, Varadhachary GR, Fleming JB, Wolff RA, Lee JE, Pisters PW, Vauthey JN, Abdalla EK, Sun CC, Wang H, Crane CH, Lee JH, Tamm EP, Abbruzzese JL and Evans DB: Serum CA 19-9 as a marker of resectability and survival in patients with potentially resectable pancreatic cancer treated with neoadjuvant chemoradiation. Ann Surg Oncol *17(7)*: 1794-1801, 2010.

16 Ballehaninna UK and Chamberlain RS: The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: An evidence based appraisal. J Gastrointest Oncol *3*: 105-119, 2012.

17 Bauer TM, El-Rayes BF, Li X, Hammad N, Philip PA, Shields AF, Zalupski MM and Bekaii-Saab T: Carbohydrate antigen 19-9 is a prognostic and predictive biomarker in patients with advanced pancreatic cancer who receive gemcitabine-containing chemotherapy: a pooled analysis of 6 prospective trials. Cancer *119*: 285-292, 2013.

18 Richter E, Denecke A, Klapdor S and Klapdor R: Parenteral nutrition support for patients with pancreatic cancer – improvement of the nutritional status and the therapeutic outcome. Anticancer Res *32(5)*: 2111-2118, 2012.

19 Zhu XH, Wu YF, Qiu YD, Jiang CP and Ding YT: Effect of early enteral combined with parenteral nutrition in patients undergoing pancreaticoduodenectomy: World J Gastroenterol *19(35)*: 5889-5896, 2013.

20 Ockenga J and Valentini L: Review article: anorexia and cachexia in gastrointestinal cancer. Aliment Pharmacol Ther *22(7)*: 583-594, 2005.

21 Bossola M, Pacelli F, Tortorelli A and Doglietto GB: Cancer cachexia: it's time for more clinical trials. Ann Surg *14*: 276-285, 2007.

22 Howard L and Ashley C: Nutrition in the perioperative patient. Annu Rev Nutr *23*: 263-282, 2003.

23 Von Hoff DD, Ramanathan RK, Borad MJ, Laheru DA, Smith LS, Wood TE, Korn RL, Desai N, Trieu V, Iglesias JL, Zhang H, Soon-Shiong P, Shi T, Rajeshkumar NV, Maitra A and Hidalgo M: Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. J Clin Oncol *29(34)*: 4548-4554, 2011.

24 Vogel A, Römmler-Zehrer J, Li JS, McGovern D, Romano A and Stahl M: Efficacy and safety profile of nab-paclitaxel plus gemcitabine in patients with metastatic pancreatic cancer treated to disease progression: a subanalysis from a phase 3 trial (MPACT). BMC Cancer *16(1)*: 817, 2016.

25 Goldstein D, El-Maraghi RH, Hammel P, Heinemann V, Kunzmann V, Sastre J, Scheithauer W, Siena S, Tabernero J, Teixeira L, Tortora G, Van Laethem JL, Young R, Penenberg DN, Lu B, Romano A and Von Hoff DD: nab-Paclitaxel plus gemcitabine for metastatic pancreatic cancer: long-term survival from a phase III trial. J Natl Cancer Inst *107(2)*: dju413, 2015.

26 Tehfe M, Dowden S, Kennecke H, El-Maraghi R, Lesperance B, Couture F, Letourneau R, Liu H and Romano A: nab-Paclitaxel plus gemcitabine *versus* gemcitabinein patients with metastatic pancreatic adenocarcinoma: Canadian subgroup analysis of the phase 3 MPACT trial. Adv Ther *33(5)*: 747-759, 2016.

27 Ueno H, Ikeda M, Ueno M, Mizuno N, Ioka T, Omuro Y, Nakajima TE and Furuse J: Phase I/II study of nab-paclitaxel plus gemcitabine for chemotherapy-naïve Japanese patients with metastatic pancreatic cancer. Cancer Chemother Pharmacol *77(3)*: 595-603, 2016.

28 Kunzmann V, Ramanathan RK, Goldstein D, Liu H, Ferrara S, Lu B, Renschler MF and Von Hoff DD: Tumor reduction in primary and metastatic pancreatic cancer lesions with nab-paclitaxel and gemcitabine: An exploratory analysis from a phase 3 study. Pancreas *46(2)*: 203-208, 2017.

29 De Vita F, Ventriglia J, Febbraro A, Laterza MM, Fabozzi A, Savastano B, Petrillo A, Diana A, Giordano G, Troiani T, Conzo G, Galizia G, Ciardiello F and Orditura M: NAB-paclitaxel and gemcitabine in metastatic pancreatic ductal adenocarcinoma (PDAC): from clinical trials to clinical practice. BMC Cancer *16(1)*: 709, 2016.

30 Ottaiano A, Capozzi M, DE Divitiis C, VON Arx C, DI Girolamo E, Nasti G, Cavalcanti E, Tatangelo F, Romano G, Avallone A and Tafuto S: Nab-paclitaxel and in advanced pancreatic cancer: The one-year experience of the national cancer institute of Naples. Anticancer Res *37(4)*: 1975-1978, 2017.

31 Peterson SL, Husnain M, Pollack T, Pimentel A, Loaiza-Bonilla A, Westendorf-Overley C, Ratermann K, Anthony L, Desimone P, Goel G, Kudrimoti M, Dineen S, Tzeng CD and Hosein PJ: Neoadjuvant nab-paclitaxel and gemcitabine in borderline resectable or locally advanced unresectable pancreatic adenocarcinoma in patients who are ineligible for FOLFIRINOX. Anticancer Res *38(7)*: 4035-4039, 2018.

32 Rose JB, Rocha FG, Alseidi A, Biehl T, Moonka R, Ryan JA, Lin B, Picozzi V and Helton S: Extended neoadjuvant chemotherapy for borderline resectable pancreatic cancer demonstrates promising postoperative outcomes and survival. Ann Surg Oncol *21(5)*: 1530-1537, 2014.

33 Petrelli F, Coinu A, Borgonovo K, Cabiddu M, Ghilardi M, Lonati V, Aitini E and Barni S: Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente (GISCAD). FOLFIRINOX-based neoadjuvant therapy in borderline resectable or unresectable pancreatic cancer: a meta-analytical review of published studies. Pancreas *44(4)*: 515-521, 2015.

34 Ielpo B, Duran H, Diaz E, Fabra I, Caruso R, Ferri V, Malavé L, Hidalgo M, Alvarez R, Plaza C, Quijano Y and Vicente E: Preoperative treatment with gemcitabine plus nab-paclitaxel is a safe and effective chemotherapy for pancreatic adenocarcinoma. Eur J Surg Oncol *42(9)*: 1394-1400, 2016.

35 Dadi N, Stanley M, Shahda S, O'Neil BH and Sehdev A: Impact of nab-paclitaxel-based second-line chemotherapy in metastatic pancreatic cancer. Anticancer Res *37(10)*: 5533-5539, 2017.

36 Kokkali S, Tripodaki ES, Drizou M, Stefanou D, Magou E, Zylis D, Kapiris M, Nasi D, Georganta C and Ardavanis A: Biweekly gemcitabine/nab-paclitaxel as first-line treatment for advanced pancreatic cancer. In Vivo *32(3)*: 653-657, 2018.

37 Vaccaro V, Sperduti I and Milella M: FOLFIRINOX *versus* gemcitabine for metastatic pancreatic cancer. N Engl J Med *365(8)*: 768-769, 2011.

38 Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M, Groupe Tumeurs Digestives of Unicancer and PRODIGE Intergroup: FOLFIRINOX *versus* gemcitabine for metastatic pancreatic cancer. N Engl J Med *364(19)*: 1817-1825,2011.

39 Muranaka T, Kuwatani M, Komatsu Y, Sawada K, Nakatsumi H, Kawamoto Y, Yuki S, Kubota Y, Kubo K, Kawahata S, Kawakubo K, Kawakami H and Sakamoto N: Comparison of efficacy and toxicity of FOLFIRINOX and gemcitabine with nab-paclitaxel in unresectable pancreatic cancer. J Gastrointest Oncol *8(3)*: 566-571, 2017.

40 Braiteh F, Patel MB, Parisi M, Ni Q, Park S and Faria C: Comparative effectiveness and resource utilization of nab-paclitaxel plus gemcitabine vs FOLFIRINOX or gemcitabine for the first-line treatment of metastatic pancreatic adenocarcinoma in a US community setting. Cancer Manag Res *9*: 141-148, 2017.

Received September 5, 2018
Revised September 22, 2018
Accepted September 28, 2018