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Tolerability of Nab-Paclitaxel Plus Gemcitabine as Adjuvant Setting in Japanese Patients With Resected Pancreatic Cancer

Phase I Study

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Objective: The combination of gemcitabine plus nab-paclitaxel (GnP) has not been studied in Japanese patients with resectable pancreatic cancer (PC). This study aimed to assess the tolerability of adjuvant GnP in Japanese patients with resected PC.

Methods: This was a Phase I, open-label, multicenter, single-arm study of patients with resected PC in Japan. Patients received 125 mg/m^2 of nab-paclitaxel and 1000 mg/m^2 of gemcitabine on days 1, 8, and 15 of a 28-day cycle for a total of 6 cycles. The primary end point was tolerability, defined as the absence of specific grade 3 or higher treatment-related adverse events by the end of cycle 2. Secondary end points included safety, disease-free survival, and overall survival.

Results: Forty-one patients were enrolled between June 2016 and February 2017 (median age, 68 years; 51% male; stage II, 95%). Gemcitabine plus nab-paclitaxel met the tolerability criteria in 39 of the 40 patients included in the tolerability analysis set (97.5%). The most common treatment-related adverse events were leukopenia, neutropenia, alopecia, and peripheral sensory neuropathy. After a follow-up of 30.1 months, median disease-free survival was 17.0 months and median overall survival was not reached.

Conclusions: These results show that adjuvant GnP is tolerable in Japanese patients with resected PC.

Clinical Trial Registration No.: JapicCTI-163179

Key Words: GnP, ABI-007, albumin-bound paclitaxel, resectable, pancreatic ductal adenocarcinoma, PDAC

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In 2018, pancreatic cancer (PC) was estimated to be the 11th most common cancer in the world, accounting for almost 459,000 new cases and more than 432,000 deaths.[1,2] Pancreatic cancer ranks as the seventh most common cause of cancer-related death, responsible for 4.5% of cancer deaths globally in 2018[3]; in Japan, the number of deaths due to PC was 34,224 in 2017.[4] Surgical resection offers the only hope for cure of PC, but more than 90% of patients who undergo macroscopically curative resection still present with local recurrence and/or distant metastases.[5] Survival in patients with PC is poor, with a 5-year survival rate of 9%.[6]

Based on clinical trial evidence, gemcitabine- or fluoropyrimidine-based adjuvant chemotherapy for 6 months after resection is the current standard therapy for patients with resectable PC.[7–11] In Japan, S-1 is used as standard adjuvant therapy

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after surgical resection, based on the results of the JASPAC 01 trial, which demonstrated that adjuvant chemotherapy with S-1 results in a significant improvement in overall survival (OS) and disease-free survival (DFS) compared with gemcitabine.[12] In western countries, various types of adjuvant therapy have also been investigated, including 5-fluorouracil/leucovorin plus irinotecan plus oxaliplatin (modified FOLFIRINOX) in the PRODIGE 24/CCTG PA.6 trial,[13] gemcitabine plus capecitabine in the ESPAC-4 trial,[14] and gemcitabine plus nab-paclitaxel (GnP) in the APACT study (Adjuvant Pancreatic Adenocarcinoma Clinical Trial).[15,16] Patients receiving modified FOLFIRINOX had a significant improvement in OS and DFS compared with patients receiving gemcitabine[13] and patients receiving gemcitabine plus capecitabine had significantly prolonged OS compared with those receiving gemcitabine alone,[14] while patients receiving GnP did not show a significant improvement in independent reviewer-assessed DFS (primary end point) but showed improvements in investigator-assessed DFS and interim OS.[15] In the United States, GnP is not approved for the adjuvant treatment of patients with resected PC, although it is approved for use in the first-line treatment of patients with metastatic PC.[17] In Japan, a Phase II study confirmed the high efficacy of GnP for the first-line treatment of patients with metastatic PC (objective response rate, 58.8%),[18] and GnP is one of the regimens strongly recommended as first-line therapy for metastatic PC in Japanese guidelines.[19]

To date, there have been no studies of GnP in Japanese patients with resected PC. The main objective of the present study was to assess the tolerability of adjuvant GnP in Japanese patients with resected PC.

MATERIALS AND METHODS

Study Design

This was a Phase I, open-label, multicenter, single-arm study conducted in Japan in accordance with the Declaration of Helsinki and Japanese Good Clinical Practice guidelines. The study was approved by the institutional review board of each participating site, and all participants provided written informed consent. The trial registration number for this study is JapicCTI-163179.

Main Inclusion and Exclusion Criteria

The main inclusion criteria were: 20 years to younger than 80 years at the time of consent; histologically confirmed infiltrating pancreatic ductal adenocarcinoma; macroscopic complete resection (R status: R0 or R1); TNM classification (Union for International Cancer Control, Seventh Edition[20]) of T1–3, N0–1, M0; pancreatic surgery within 12 weeks of study treatment; Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1; and sufficient organ function to complete treatment. Key exclusion criteria were receipt of prior treatment for primary PC other than surgery (chemotherapy, radiotherapy, etc) and grade 2 or higher peripheral sensory neuropathy. See Supplemental Tables 1 and 2 (http://links.lww.com/MPA/A844) for complete inclusion/exclusion criteria.

Treatment Regimens

Patients received a 30-minute infusion of nab-paclitaxel, followed by a 30-minute infusion of gemcitabine on days 1, 8, and 15 of a 28-day cycle for a total of 6 cycles. The starting doses were 125 mg/m^2 for nab-paclitaxel and 1000 mg/m^2 for gemcitabine; the doses and treatment schedule were based on the APACT study and other studies of GnP combination in the treatment of metastatic PC.[15,18,21]

Patients could only begin the cycle if their neutrophils were 1500/mm^3 or greater and their platelets were 100,000/mm^3 or greater. In the event of toxicities during the cycle, dose reductions and dose delays were permitted. Treatment continued until disease progression, unacceptable adverse event (AE), or withdrawal of consent, whichever occurred first.

End Points and Definitions

The primary end point was tolerability. Tolerability was defined as the absence of the following AEs related to treatment by the end of cycle 2: grade 4 neutropenia persisting for 7 days

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or more, febrile neutropenia that affected treatment continuation, grade 4 platelet count decrease persisting for 7 days or more, grade 3 or higher nausea/vomiting, diarrhea, or fatigue persisting for 7 days or more despite appropriate treatment, and nonhematologic toxicity of grade 3 or higher that affected treatment continuation (excluding nausea/vomiting, diarrhea, and fatigue). Overall, the treatment was considered tolerable if more than 66% of patients met the definition of tolerability.

Secondary end points were the incidence and severity of AEs and treatment-related AEs, treatment exposure and dose intensity, DFS, and OS. Adverse events were classified according to the Japan Clinical Oncology Group version of the Common Terminology Criteria for AEs version 4.03. Serious AEs were defined as AEs that resulted in death, were life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity or congenital anomaly/birth defect, and/or resulted in other serious medical events.

Clinical and Laboratory Assessments

Data collected at baseline included patient demographics and history, vital signs, ECOG PS, hematology and biochemistry, urinalysis, clinical symptoms, electrocardiogram, computed tomography (CT) scan, and tumor markers. Vital signs, ECOG PS, hematology and biochemistry testing, and clinical symptoms were assessed once a week during the first 2 cycles, then on or the day before administration day for cycles 3 to 6 and on the day of treatment discontinuation. Clinical symptoms, hematology, and biochemistry were also assessed on days 14 and 28 after treatment discontinuation. Computed tomography scans and tumor marker testing were conducted at 12 and 24 weeks after onset of therapy and then every 12 to 24 weeks until recurrence or the detection of a second cancer.

Statistical Analysis

The planned sample size for this study was 40 patients. The sample size was not determined statistically.

The tolerability evaluable population was defined as those patients who received at least 1 dose of nab-paclitaxel or gemcitabine and had no significant protocol deviations, who were able to evaluate any treatment-related AEs that occurred during the first 2 treatment cycles according to the definition of tolerability, and could complete up to 2 cycles of treatment. The efficacy evaluable population was defined as those patients who received the study drug and had at least 1 efficacy end point measurement (primary or secondary end point) after study drug administration.

The Kaplan-Meier method was used to generate curves for DFS and OS. All measured data were used for analyses using SAS Version 9.4 (SAS Analytics, Cary, NC).

RESULTS

Patients

Between June 2016 and February 2017, a total of 41 patients were enrolled in the study. All enrolled patients received GnP. The median age of the population was 68 years (range, 48–79 years) and 51.2% of the population were male (Table 1). The majority (92.7%) had an ECOG PS of 0, with the remaining patients having an ECOG PS of 1. R0 resection had been achieved in 82.9% of patients, with R1 resection achieved in 17.1% (Table 1). Most patients had stage II PC (IIA, 24.4%; IIB, 70.7%). Positive peritoneal cytology was found in three patients (7.3%). The median number of days between surgery and initiation of adjuvant chemotherapy was 59 (range, 22–88 days; Table 1).

TABLE 1. Baseline Patient Demographics and Disease Characteristics

Characteristics (N = 41)	n (%)
Sex	
Male	21 (51.2)
Female	20 (48.8)
Age, median (range), y	68 (48–79)
ECOG PS	
0	38 (92.7)
1	3 (7.3)
T status	
T1	2 (4.9)
T2	1 (2.4)
T3	38 (92.7)
N status	
N0	12 (29.3)
N1	29 (70.7)
Stage	
IA	2 (4.9)
IB	0 (0.0)
IIA	10 (24.4)
IIB	29 (70.7)
Histological type	
Well-differentiated	13 (31.7)
Moderately differentiated	26 (63.4)
Poorly differentiated	2 (4.9)
Operative procedure	
Pancreaticoduodenectomy	27 (65.9)
Pylorus-preserving pancreaticoduodenectomy	4 (9.8)
Distal pancreatectomy	10 (24.4)
Median days from surgery to adjuvant chemotherapy (range)	59 (22–88)
Residual tumor status	
R0	34 (82.9)
R1	7 (17.1)
Peritoneal cytology	
Positive	3 (7.3)
Negative	37 (90.2)
Unknown	1 (2.4)

N indicates node; T, tumor.

Thirty-six patients (87.8%) completed all 6 cycles of therapy. Three patients discontinued because of AEs (tuberculosis, rash, pancreatic fistula) and 2 patients requested treatment discontinuation. No patients discontinued because of disease recurrence, and there were no deaths during the study.

Treatment Exposure

The median number of cycles administered was 6 (range, 1–6). The median total dose for nab-paclitaxel and gemcitabine was 2496 mg (range, 333–3654 mg) and 20,033 mg (range, 2665–29,719 mg), respectively, and the relative dose intensity was 75.3% and 75.5%, respectively. The dose of nab-paclitaxel was reduced in 53.7% of patients and 75.6% skipped doses. The gemcitabine dose was reduced in 43.9% of patients and 68.3% skipped doses. Administration of both treatments was delayed in 70.7% of patients.

TABLE 2. Treatment-Related AEs Occurring During the Study

	Any Grade	Grade ≥3
	n (%)	n (%)
Hematological toxicities		
Neutropenia	38 (92.7)	30 (73.2)
Leukopenia	39 (95.1)	16 (39.0)
Anemia	23 (56.1)	6 (14.6)
Thrombocytopenia	19 (46.3)	0 (0.0)
Febrile neutropenia	1 (2.4)	1 (2.4)
Nonhematological toxicities		
Peripheral sensory neuropathy	33 (80.5)	3 (7.3)
Rash	13 (31.7)	1 (2.4)
Constipation	8 (19.5)	1 (2.4)
Diarrhea	7 (17.1)	0 (0.0)
Alopecia	36 (87.8)	—
Dysgeusia	14 (34.1)	0 (0.0)
Appetite loss	13 (31.7)	0 (0.0)
Nausea	10 (24.4)	0 (0.0)
Fatigue	9 (22.0)	0 (0.0)
Edema	9 (22.0)	0 (0.0)
Pancreatic fistula	2 (4.9)	0 (0.0)

Tolerability

The tolerability analysis set included 40 patients, with 1 patient who requested treatment discontinuation at cycle 1 excluded. Based on the evaluation of treatment-related AEs defined for tolerability that occurred up to cycle 2, GnP was considered well tolerated in 39 (97.5%) of the 40 patients; grade 3 skin eruption occurred in 1 patient, which was evaluated as not tolerable.

Safety

Table 2 summarizes the frequency of treatment-related AEs in the safety analysis set (n = 41). The most common treatment-related AEs were leukopenia, neutropenia, alopecia, and peripheral sensory neuropathy. Major treatment-related AEs of grade 3 or higher were neutropenia (30 patients, 73.2%), leukopenia (16 patients, 39.0%), anemia (6 patients, 14.6%), and peripheral sensory neuropathy (3 patients, 7.3%; Table 2). Febrile neutropenia occurred in 1 patient (2.4%). Granulocyte colony stimulating factor was administered to 5 patients (12.2%). Serious AEs occurred in 9 patients (22.0%). Treatment-related serious AEs occurred in 7 patients (17.1%), including pancreatic leak (2 patients), febrile neutropenia (1 patient), anemia (1 patient), fever (1 patient), neutropenia (1 patient), and constipation (1 patient). There were no treatment-related deaths.

Efficacy

Efficacy was evaluated in all 41 patients. The median follow-up period (cutoff: July 2019) was 30.1 months. Median DFS was 17.0 months (95% confidence interval, 14.3–23.5) and median OS was not reached; 1-year OS rate was 95.1% and 2-year OS rate was 78.0% (Fig. 1).

At the time of study cutoff, recurrence was evident in 28 of 41 patients, 25 of 28 received posttreatment after recurrence. Posttreatment regimens received included GnP (10 patients), modified FOLFIRINOX (5 patients), S-1 (6 patients), gemcitabine (1 patient), S-1 plus radiotherapy (1 patient), FOLFOX (1 patient), and gemcitabine plus S-1 (1 patient).

DISCUSSION

This study is the first evaluation of adjuvant GnP in Japanese patients with resected PC. The results of this study show that adjuvant GnP is tolerable in Japanese patients.

The treatment completion rate in this trial was 87.8%, which was much higher than the 66% completion rate in patients treated with adjuvant GnP in the international Phase III APACT study.[15] This difference in completion rate is likely due to the fact that the present trial was conducted at a limited number of study sites (12 centers vs 188 centers in APACT) and that a higher proportion of patients with an ECOG PS of 0 were enrolled in the present study compared with that in APACT study (92.7% vs 58.3%).[15,16]

The safety profile of GnP in the present study was similar to that seen in the Phase II study of Japanese patients with metastatic PC,[18] based on the overall reported incidence of treatment-related AEs, as well as the incidence of key grade 3 or higher events.[15,18] Neutropenia grade 3 or higher developed in 73.2% of patients in the current study compared with 70.6% in the Japanese Phase II study, whereas febrile neutropenia occurred in 2.4% versus 5.9%, and peripheral sensory neuropathy grade 3 or higher in 7.3% versus 11.8%. No new safety signals were observed in this study.

Peripheral sensory neuropathy is a known issue with nab-paclitaxel.[22] No patients discontinued the present study because of peripheral sensory neuropathy. Although no data regarding peripheral sensory neuropathy were recorded after the completion of adjuvant therapy in this trial, GnP was the most commonly used postrelapse treatment (in 10 of 25 patients). Thus, it is likely that any peripheral sensory neuropathy that occurred was not sufficiently severe to influence subsequent treatment decisions.

Median DFS was 17.0 months in this study, which is comparable to the investigator-assessed DFS seen with GnP in the APACT study (16.6 months),[15] but shorter than the relapse-free survival

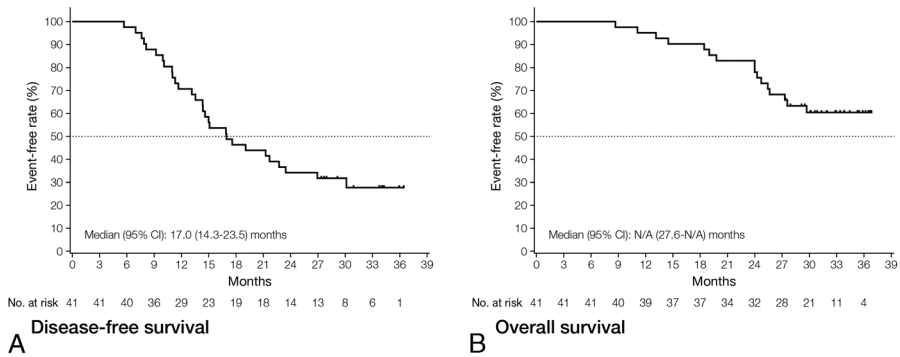

FIGURE 1. Disease-free survival (A) and OS (B) of patients. N/A, not available.

seen with S-1 in the JASPAC 01 study (22.9 months).[12] Of note, the JASPAC 01 study had different inclusion criteria and did not include any patients with positive peritoneal cytology; in contrast, our study included 3 patients with positive cytology, making comparison between the studies difficult. Median OS was not reached during the follow-up period in the current study (30.1 months), but the 1- and 2-year OS rates were 95.1% and 78.0%, respectively. It is likely that the treatment regimens used after recurrence contributed to the high rates of 1- and 2-year OS seen in this study, because new treatment regimens such as GnP and FOLFIRINOX may have contributed to OS prolongation.

The large-scale Phase III APACT study did not demonstrate the superiority of adjuvant GnP over gemcitabine.[15] Although investigator-assessed DFS and interim OS were improved with GnP compared with gemcitabine (hazard ratio, 0.82 for both), these improvements are likely to be underpowered compared with the therapeutic effects reported in clinical trials of modified FOLFIRINOX and S-1 versus gemcitabine (hazard ratio, 0.64 and 0.57, respectively).[12,13]

Adjuvant therapy with fluorouracil-based regimens has been established as standard of care for other gastrointestinal cancers,[23,24] with these regimens considered highly effective for the prevention of micrometastases. Nab-paclitaxel has been shown to increase the antitumor effect of GnP via disruption of desmoplastic tumor-associated stroma in advanced PC, resulting in a marked tumor response[25]; in the adjuvant setting, GnP may not result in as marked a response as that obtained for metastatic PC. Gemcitabine plus nab-paclitaxel has been used as neoadjuvant therapy before surgical resection in locally advanced PC and borderline resectable PC,[26,27] and promising results were reported, although these studies were single arm or retrospective.[26,27] Recently, OS was found to be significantly prolonged in patients with resectable PC who received prior therapy with gemcitabine plus S-1 before surgical resection versus those receiving surgery first (the Prep-02/JSAP-05 study).[28] Although the efficacy of GnP as postoperative adjuvant chemotherapy is limited, it is expected that GnP will be used as preoperative treatment, mainly for borderline PC.

Our study has some limitations. It may be difficult to extrapolate the results of our study to those of other similar studies because it was a single-arm study with a small number of patients evaluated for tolerance and safety. In addition, the population size was not based on statistical calculations.

In conclusion, adjuvant GnP was well tolerated in Japanese patients with resected PC. The results for safety and efficacy were comparable with those reported in the APACT study.

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