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Clinical Trial Note

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Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 versus upfront surgery for resectable pancreatic cancer (Prep-02/JSAP05)

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Abstract

A randomized, controlled trial has begun to compare neoadjuvant chemotherapy using gemcitabine and S-1 with upfront surgery for patients planned resection of pancreatic cancer. Patients were enrolled after the diagnosis of resectable or borderline resectable by portal vein involvement pancreatic cancer with histological confirmation. They were randomly assigned to either neoadjuvant chemotherapy or upfront surgery. Adjuvant chemotherapy using S-1 was administered for 6 months to patients with curative resection who fully recovered within 10 weeks after surgery in both arms. The primary endpoint is overall survival; secondary endpoints include adverse events, resection rate, recurrence-free survival, residual tumor status, nodal metastases and tumor marker kinetics. The target sample size was required to be at least 163 (alpha-error 0.05; power 0.8) in both arms. A total of 360 patients were required after considering ineligible cases. This trial began in January 2013 and was registered with the UMIN Clinical Trials Registry (UMIN000009634).

Key words: pancreatic cancer, neoadjuvant chemotherapy, gemcitabine, S-1, phase III

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a lethal disease worldwide and is the fourth leading cause of cancer-related death in Japan (1), the USA (2) and Europe (3). Surgical resection offers the best chance for long-term survival, but the median survival of patients undergoing curative pancreatectomy alone is 18–20 months, with a 5-year survival rate of 10% (4,5). Adjuvant chemotherapy improves the median and 5-year overall survival (OS) of patients with curatively resected PDAC. Gemcitabine adjuvant therapy prolongs OS with a 5-year survival rate of 23–24% for PDAC patients undergoing curative resection (4,5). In Japanese patients, post-operative adjuvant chemotherapy with S-1 significantly extended OS of patients with resected PDAC compared with gemcitabine. Adjuvant chemotherapy with S-1 is now standard care for curatively resected PDAC in Japan, with the 5-year survival rate in the S-1 group of 44.1% (6).

To date, upfront surgery is the most universally accepted approach for potentially resectable PDAC. The survival outcome of upfront surgery followed by adjuvant therapy has several limitations in terms of clinical interpretation. First, 20–30% of potentially resectable tumors could not be resected due to undetected small metastases or underestimated local tumor invasion at the time of surgery (7,8). Second, up to 20% of patients with resected PDAC could not receive adjuvant therapy because of inadequate recovery after surgery with surgical mortality or morbidity (9). Neither group of patients is included in trials for the adjuvant therapy due to ineligibility, so the impact of recent randomized, controlled trials (4–6) would be limited only for the per-protocol populations by upfront surgery. Neoadjuvant chemotherapy (NAC) offers several theoretical advantages over upfront surgery, including early delivery of systemic therapy for almost all patients intended for treatment, high tolerance of multi-agent regimens by patients and a higher negative-margin resection rate, leading to improve OS. A review of select trials for patients with localized PDAC has suggested increased OS, supporting the benefits (10,11). Randomized trials have not yet reported a comparison between the neoadjuvant approach and upfront surgery for potentially resectable PDAC. The comparative analyses all suffered from selection bias, because most non-randomized studies report survival data only for patients who underwent resection (12).

This phase II/III trial was designed to evaluate the superiority of NAC with gemcitabine and S-1 (GS) compared with upfront surgery in patients with resectable or borderline-resectable PDAC related to portal vein invasion. The rationale behind this regimen was based on a phase III trial that showed significantly longer progression-free survival (median 5.7 vs 4.1 months, $P < 0.001$) and a higher objective response rate (29.3% vs 13.3%, $P < 0.001$) for GS therapy than for gemcitabine monotherapy for unresectable PDAC patients (13). Although GS regimen could not be a standard for unresectable pancreatic cancer, failing to show an improvement of OS than each single agents (13), NAC need not necessarily yield longest OS but require high response in short course treatment. An exploratory phase II study of NAC with GS for resectable or borderline-resectable PDAC showed acceptable feasibility and a high R0 resection rate (14,15). Two major hypothetical risks have been pointed out for NAC. One is a possible increase in perioperative morbidity and mortality. Second is the possibility that disease may progress and become unresectable during the course of NAC (16). A nationwide survey suggested that neoadjuvant treatment might not worsen perioperative outcomes or might increase the chance for curative surgery (16). Accordingly, it was necessary to confirm the non-inferiority of NAC with respect to the resection rate and safety against upfront surgery by the phase II portion of this study before the start of the phase III portion. To date, there are no prospective data providing the superiority of neoadjuvant strategy over upfront surgery for resectable PDAC. The main objective of this trial is to determine whether NAC compared with upfront surgery can improve OS of patients with potentially resectable PDAC by intention-to-treat analysis.

Protocol digests of study PREP-02/JSAP05

Objectives

The primary objective of this study is to confirm the superiority of NAC with GS compared with the standard strategy of upfront surgery in patients with planned PDAC resection.

Study design

As a multicenter, two-arm, open-label, randomized phase II/III study, this trial is an intergroup cooperative study led by the Study Group of Preoperative Therapy for Pancreatic Cancer (PREP) and the Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer (JSAP); PREP-02/JSAP05, with participating institutions including 67 specialized centers at 20 December 2012. This study protocol was approved by the Institutional Protocol Review Board of Tohoku University (affiliation of the principal investigator) and other participating institutions.

Endpoints

The primary endpoint is the resection rate in the phase II part and OS in the phase III part. The secondary endpoints are adverse events in the phase II part and the resection rate, adverse events, recurrence-free survival and patterns of recurrence for resected cases, residual tumor status, nodal metastases, tumor marker kinetics, dose intensity and radiological and histological responses for the experimental arm (NAC-GS) in the phase III part. The resection rate is defined as the proportion of resected cases in the experimental or control arm (Upfront Surgery). OS is calculated from the day of randomization to the day of death from any cause and censored at the last day that the patient is documented to be alive.

Inclusion criteria

- Treatment-naïve PDAC with histological or cytological diagnosis.
- Localized tumor without distant metastasis (liver, peritoneum, lung, others) confirmed by radiological evaluation (enhanced computed tomography; CT).
- R0/1 resectable, without arterial abutment including the hepatic (HA) or celiac (CA) or superior mesenteric artery (SMA). T1–3, N0–1.
- Can tolerate curative surgery.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- Spared organ function satisfying the following laboratory data: white blood cell count $\geq 3000/mm^3$ and $< 12\,000/mm^3$; neutrophils $\geq 2000/mm^3$; platelet count $\geq 100\,000/mm^3$; hemoglobin, ≥ 9.0 g/dl; serum total bilirubin, ≤ 2.0 mg/dl; aspartate aminotransferase (AST) ≤ 150 IU/l; alanine aminotransferase (ALT) ≤ 150 IU/l; creatinine ≤ 1.2 mg/dl; creatinine clearance ≥ 50 ml/min.

- Adequate oral intake.
- Age 20–79 years.
- Written, informed consent.

Exclusion criteria

- Pulmonary fibrosis or interstitial pneumonia.
- Severe diarrhea.
- Synchronous malignancy except for carcinoma *in situ* or intramucosal tumor after adequate curative treatment.
- Metachronous malignancy except for disease having ≧3 relapse-free survivals.
- Active infection.
- Regular use of frucitocin, pheytoin or warfarin.
- Pregnancy, breastfeeding or desire of a woman to preserve fertility.
- Patients inappropriate for this study as judged by primary care physicians.

Registration and randomization

Eligible patients are registered centrally and assigned randomly to treatment at a non-profit organization, Japan Clinical Research Support Unit (J-CRSU), Tokyo, Japan. Randomization is performed by the minimization method to which the investigators are masked (Fig. 1). Patients are stratified according to institution and serum CA19-9 value (<370 ml vs ≥370 U/ml). The serum CA19-9 value must be measured without jaundice or after adequate biliary drainage (serum total bilirubin ≤3 mg/dl). Eligible patients are randomized (1:1) to receive either upfront surgery (control arm) or NAC-GS (experimental arm).

Treatment

Neoadjuvant chemotherapy

Patients allocated to the experimental arm (NAC-GS) to undergo chemotherapy receive intravenous gemcitabine at a dose of 1000 mg/m^2 on days 1 and 8, plus S-1 orally at a dose according to body surface area (BSA), as follows: BSA < 1.25 m^2, 40 mg; BSA 1.25–1.5 m^2, 50 mg; BSA > 1.50 m^2, 60 mg, twice daily on days 1–14 of a 21-day cycle (Fig. 1). Patients with a creatinine clearance of 50–60 ml/min receive a dose of S-1 that is reduced by 20 mg/day. The neoadjuvant treatment is repeated for two cycles unless unacceptable toxicity, such as Grade 4 evaluated by Common Toxicity Criteria (CTCAE, version 3.0), appears. In patients who develop Grade 3 hematological toxicity or Grade 2 non-hematological toxicity, both gemcitabine and S-1 are withheld until recovery. In patients who develop Grade 4 hematological toxicity or Grade 3 non-hematological toxicity, both gemcitabine (−200 mg/m^2/day) and S-1 (−20 mg/day) are reduced at treatment resumption. Restaging by CT is required before surgery. In cases of unexpected tumor progression (unresectable tumor extension or distant metastasis), patients receive palliative treatment including chemotherapy and/or radiotherapy as off-protocol care.

Surgery

Patients allocated to the control arm undergo primary surgery with curative intent at most within 8 weeks after enrollment. Patients allocated to the experimental arm undergo surgery 2–4 weeks after the last administration of oral S-1, at most within 6 weeks. Both study arms undergo, depending on the individual tumor site and its extension, curative-intent pancreatectomy with regional node

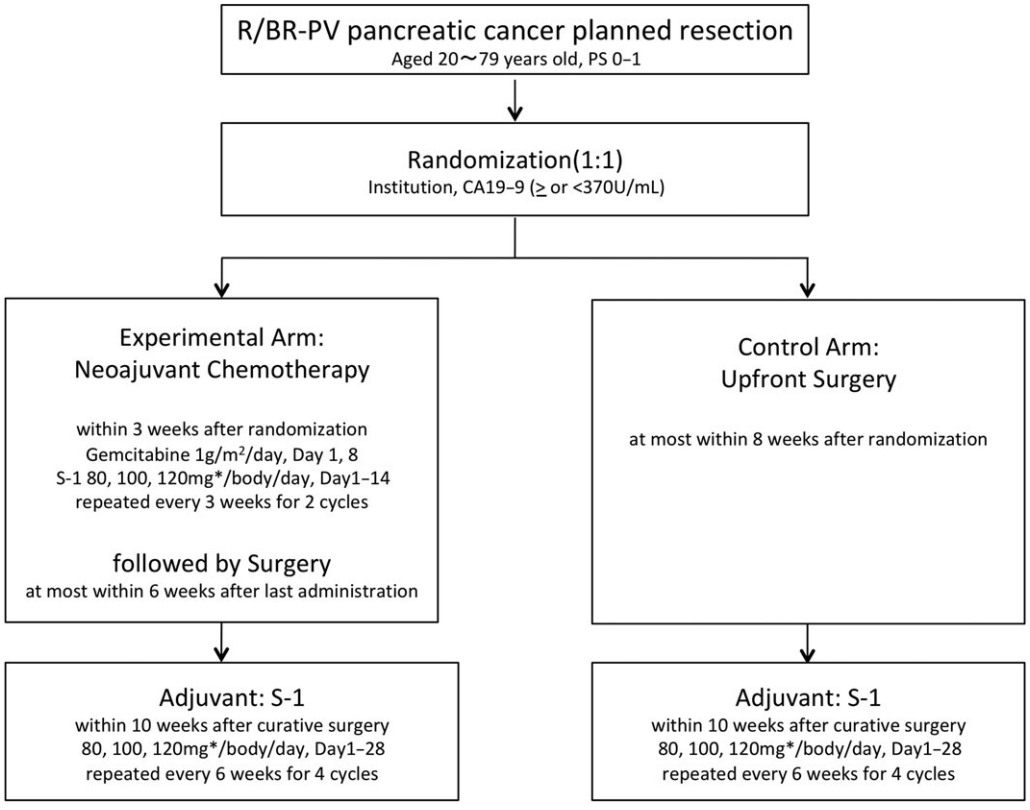

Figure 1. Schematic flowchart of the PREP-02/JSAP05 study. R: resectable, BR-PV: borderline resectable with portal vein invasion. *According to body surface area (BSA); BSA < 1.25 m^2, 1.25 ≤ BSA < 1.5 m^2, BSA ≥ 1.5 m^2.

dissection. Intra-operative peritoneal lavage cytology is required. In cases of unexpected intra-operative findings regarding unresectability, including distant metastasis or inseparable tumor extension into major arteries (HA, CA, SMA), the patients do not undergo resection but undergo a suitable bypass procedure if necessary.

Adjuvant chemotherapy

Radiological examination (CT) is required before the start of adjuvant treatment. The patients receive S-1 within 10 weeks after curative surgery in both arms as post-operative adjuvant therapy for 6 months (Fig. 1). The inclusion criteria for planned S-1 adjuvant therapy are as follows: macroscopically curative resection with histologic R0 or R1 residual disease; invasive ductal adenocarcinoma confirmed by histological examination of the resected specimen; peritoneal lavage cytology negative for cancer cells; absence of distant metastases, such as extra-regional nodal metastases; early recurrence detected by CT examination before planned adjuvant therapy; and insufficient recovery after surgery within 10 weeks.

Patients in the S-1 arm receive four cycles of oral S-1 twice daily for 4 weeks, followed by a 2-week rest period. The treatment is repeated unless unacceptable toxicity, such as Grade 4 evaluated using the Common Toxicity Criteria (CTCAE, version 3.0), appears. In patients who develop Grade 3 hematological toxicity or Grade 2 non-hematological toxicity, S-1 administration is withheld until recovery. In patients who develop Grade 4 hematological toxicity or Grade 3 non-hematological toxicity, the S-1 dose is reduced by 20 mg/day at treatment resumption. Ineligible patients receive palliative treatment including chemotherapy and/or radiotherapy as off-protocol care.

Follow-up

Patients are followed-up for 5 years after the completion of patient accrual. Enhanced CT or MRI of the upper abdomen and pelvis, chest CT and serum tumor marker levels are evaluated every 3 months until 2 years after surgery, and then every 6 months from 2 years after surgery. Diagnosis of recurrence is based on the CT findings. Physical and laboratory examinations are performed once every 2 weeks during protocol treatment. Subsequently, these examinations are performed every 3 months until 2 years, and then every 6 months until the end of 5 years after enrollment. Toxicities are evaluated according to the Common Terminology Criteria for Adverse Events, Version 3.0.

Study design and statistical analysis

This study is designed as a randomized phase II/III trial to confirm the superiority, in terms of OS, of NAC-GS followed by surgery and adjuvant S-1 over upfront surgery followed by adjuvant S-1 in patients with PDAC for whom surgery is planned. The sample size calculation is based on the assumption that the 2-year survival probability in the control arm (upfront surgery) is 35%. The control arm of this study was upfront surgery followed by adjuvant treatment. However, the survival data of the arm analyzed by intention-to-treat was limited for assumption (16). The reported 2-year survival probability for patients with PDAC curatively resected and who received adjuvant chemotherapy was 46% (14). With 30% exclusion of unexpected unresectable findings at surgery or ineligible for adjuvant treatment, such as peritoneal lavage cytology positive for cancer cells, extra-regional nodal metastases and insufficient recovery after surgery, 70% of all patients intended to undergo upfront resection would receive planned adjuvant therapy (7,9). The 2-year survival probability in the experimental arm (NAC-GS) is 50% according to the previous report (14,15). The planned total sample size was 360, to observe the required number of events (210) to detect 15% improvement in the 2-year OS in the experimental arm over 35% in the control arm, with a power of 80% and two-sided alpha level of 5%, the planned accrual period is 3 years, and follow-up period is 2 years for the primary analysis. The survival analyses are based on the intent-to-treat population, which includes all eligible patients enrolled in the study, with survival estimates calculated using the Kaplan–Meier method and compared using the stratified log-rank test. Survival estimates are presented with 95% confidence intervals (CIs). The hazard ratio of the treatment effect is presented for upfront surgery compared with that for NAC-GS.

The phase II part (n = 80) is planned to confirm if the experimental arm has a sufficient resection rate to proceed to the phase III part (n = 280), because the resection rate of the patients with PDAC receiving NAC has not yet been compared with those with PDAC receiving upfront surgery. According to data from a single-arm, multicenter, prospective study of NAC-GS for PDAC (PREP-01 study, submitted), the R0/1-resection rate was 60%, and the proportion of not resected patients was 40% (90% CI = 31.8–48.7%). If the 90% CI for the number of unresected patients in the experimental arm for the phase II part is within 50%, the study will proceed to phase III. The number of patients in phase II is planned to be 40 in both arms. The maximum number of permissible cases of no resection is 14; the proportion of not resected cases was 35% (90% CI = 22.6–49.2%). On September 2013, enrollment of the study was temporarily stopped after full enrollment of phase II part (n = 91) to proceed to phase III. On November 2013, it was decided to proceed to phase III, accepting the recommendation from the Independent Data and Safety Monitoring Committee, because the pre-specified criteria to proceed to phase III were met.

On September 2017, 1 year and 9 months after the final enrollment, 178 events were recorded in the total cohort (group-masking). On December 2017, the protocol was revised to prolong the follow-up period by 2–3 years after the final enrollment or recording 210 events to avoid decreasing the power of the trial without recruiting new participants according to the Independent Data and Safety Monitoring Committee.

Participant institutions (from north to south)

Asahikawa Medical University, Omagari Kousei Medical Center, Iwate Prefectural Central Hospital, Kesen-numa City Hospital, Japanese Red Cross Ishinomaki Hospital, Tohoku University, Sendai Open Hospital, Sendai Medical Center, Sendai Kousei Hospital, Yamagata Prefectural Central Hospital, Fukushima Medical University, Tochigi Cancer Center, Tsukuba University, Jichi Medical University Saitama Medical Center, Saitama Cancer Center, Chiba University, Chiba Cancer Center, Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital, Tokyo Medical University, National Cancer Center Hospital, National Cancer Center Hospital East, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo Women's Medical University, Kyorin University, Teikyo University, National Defense Medical College, Toho University Omori Hospital, Nippon Medical School, Showa University Northern Yokohama Hospital, Tokai University, Kanagawa Cancer Center, Toyama University, Shizuoka Cancer Center, Nagoya University, Aichi Cancer Center, Fujita Health University, Mie University, Shiga University of Medical

Science, Kyoto University, Kyoto Prefectural University of Medicine, Kansai Medical University, Osaka University, Osaka National Hospital, Kindai University Faculty of Medicine, Kansai Rousai Hospital, Kitano Hospital, Nara Medical University, Wakayama Medical University, Hyogo College of Medicine, Kobe University, Kawasaki Medical School, Hiroshima University, Kure Medical Center and Chugoku Cancer Center, Shikoku Cancer Center, Tokushima University, Kagawa University, Kurume University, Kyusyu University, University of Occupational and Environmental Health, Kitakyusyu Municipal Medical Center, Kyusyu Cancer Center, Nagasaki University, Saga-ken Medical Center Koseikan, Kumamoto University, Miyazaki University, Kagoshima University

Supplementary data

Supplementary data are available at *Japanese Journal of Clinical Oncology* online.

Conflict of interest statement

None declared.

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