

Phase II study of chemoradiotherapy combined with gemcitabine plus nab-paclitaxel for unresectable locally advanced pancreatic ductal adenocarcinoma (NUPAT 05 Trial): study protocol for a single arm phase II study

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ABSTRACT

The efficacy of nab-paclitaxel combined with gemcitabine (GnP) and of chemoradiotherapy (CRT) for unresectable locally advanced pancreatic ductal adenocarcinoma (UR-LA PDAC) is still unclear. We previously conducted a phase I study of CRT using GnP and determined the recommended dose and have now designed a phase II trial to evaluate the efficacy of CRT incorporating GnP for UR-LA PDAC. Eligibility criteria are chemotherapy-naïve patients with UR-LA PDAC as defined by the NCCN guidelines version 2. 2016. Study patients will receive 100 mg/m² nab-paclitaxel and 800 mg/m² gemcitabine on Days 1, 8, and 15 per 4-week cycle with concurrent radiation therapy (total dose of 50.4 Gy in 28 fractions of 1.8 Gy per day, 5 days per week). Treatment will be continued until disease progression or surgery, which is to be performed only for patients in whom the disease is well-controlled at 8 months from beginning the protocol treatment. Primary endpoint is 2-year overall survival rate and co-primary endpoint is resection rate. Secondary endpoints are overall survival, progression free survival, time to treatment failure, response rate, disease control rate, early tumor shrinkage, depth of response, reduction of SUV-max on PET-CT, serum tumor markers, relative dose intensity, safety, and Quality of life. This study will show the efficacy and safety of chemoradiotherapy combined with GnP.

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Abbreviations:

PDAC: pancreatic ductal adenocarcinoma

UR-LA: unresectable locally advanced disease

CRT: chemoradiotherapy

GnP: nab-paclitaxel with gemcitabine

CS: conversion surgery

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is the seventh leading cause of cancer-related death worldwide.¹ PDAC has increased in Japan during the past few years, and is the fourth largest cause of cancer-related mortality, with 31,866 deaths in 2015.^{2,3} PDAC is typically diagnosed at the advanced stage and the overall 5-year survival rate is extremely poor at 2%–7%.⁴ Thirty–40% of patients with PDAC present with unresectable locally advanced disease (UR-LA).^{5,6}

Two recent phase III trials have shown that either a combination of oxaliplatin, irinotecan, fluorouracil and leucovorin (FOLFIRINOX) or a combination of nab-paclitaxel with gemcitabine (GnP) achieve superior survival than gemcitabine alone in patients with metastatic PDAC.^{7,8} This is currently the standard treatment regimen for patients with metastatic PDAC and is also recommended by the National Comprehensive Cancer Network (NCCN) guidelines for UR-LA PDAC.⁹

Several prospective studies have reported that chemoradiotherapy (CRT) is more effective than chemotherapy or radiotherapy alone in patients with UR-LA PDAC.^{10–13} However, there are other trial results that support chemotherapy alone rather than CRT,^{14,15} and the optimal treatment strategy for this disease entity remains controversial.

In a previous phase I study exploring CRT in patients with UR-LA PDAC with a fixed dose of 50.4 Gy (1.8Gy /28fr) and escalating doses of GnP (NUPAT 02 Trial), we established a recommended dose of 800 mg/m² for gemcitabine and 100 mg/m² for nab-paclitaxel.¹⁶ We now plan to conduct a phase II trial (NUPAT 05 trial) to evaluate the safety and efficacy of this regimen in patients with UR-LA PDAC.

METHODS

Objectives

The NUPAT 05 trial is a phase II trial to be conducted by Nagoya University Pancreatic Tumor Board study group with the aim of evaluating safety and efficacy of CRT incorporating GnP in patients with UR-LA PDAC as defined by the NCCN resectability criteria.⁹

Study endpoints

The primary endpoint is 2-year overall survival rate by intention to treat. Resection rate will be evaluated as a co-primary endpoint. Secondary endpoints are overall survival, disease-free survival, time to treatment failure, overall response rate according to radiologic Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1,¹⁷ disease control rate, reduction in serum concentrations of tumor markers including carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), and PDAC-associated antigen (DUPAN2), early tumor shrinkage (ETS);

defined as a reduction > 20% of target lesions' diameters within 8 weeks of starting treatment), depth of response (DpR; defined as percentage of maximal tumor shrinkage at the nadir diameter compared with baseline), change in SUVmax of the primary tumor on PET/CT, safety according to Common Terminology Criteria for Adverse Event 4.0,¹⁸ relative dose intensity (RDI), and Quality of life (QoL) as assessed by the Functional Assessment of Cancer Therapy (FACT) and Patient Neurotoxicity Questionnaire (PNQ). This study will be performed in accordance with the declaration of Helsinki. The protocol has been approved by the Institutional Review Board of Nagoya University. All patients will provide written informed consent before enrollment in the study. The study is registered at UMIN-CTR (UMIN000028116).

Eligibility criteria

The inclusion and exclusion criteria for the NUPAT 05 trial are summarized in Table 1.

Statistical aspects

The primary endpoint of this study is the 2-year survival rate. In previous studies of patients with UR-LA PDAC, the 2-year survival rate after treatment with gemcitabine plus radiotherapy

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Unresectable locally advanced pancreatic cancer based on the resectability status of the NCCN guidelines	1. Distant metastasis
2. Age between 20 and 75 (at the time of informed consent)	2. History of severe drug hypersensitivity or allergy
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1	3. Invasion into gastrointestinal tract
4. No previous antitumor treatment	4. Obvious infection or inflammation
5. Within 10 × 10 cm radiation field for the primary lesion and regional lymph node	5. Serious medical or psychological condition interfere with treatment
6. Adequate biliary drainage if obstructive jaundice is present	6. Other concurrent or previous malignancy within the past 5 years, except a curative carcinoma in situ or mucosal cancer
7. No direct invasion into the gastrointestinal tract	7. Peripheral neuropathy > grade 2
8. No simultaneous cancer in the other organs	8. Ascites or pleural effusion
9. Adequate oral intake	9. Active gastrointestinal bleeding required blood transfusion
10. Expected more than 3 months survival	10. Diarrhea > grade 2
11. Adequate hematologic and major organ functions defined as; leukocyte count ≥ 3,500/mm ³ and < 12,000/mm ³ , neutrophil count ≥ 2,000/mm ³ , hemoglobin level ≥ 9.0 g/dL, platelet count ≥ 100,000/mm ³ , total bilirubin level ≤ 2.0 mg/dL, aspartate aminotransferase and alanine aminotransferase levels ≤ 150 U/L, serum creatinine level ≤ 1.2 mg/dL, and creatinine clearance ≥ 50 mL/min	11. Obvious fibroid lung or interstitial pneumonia
12. Written informed consent	12. Previous abdominal radiotherapy
	13. Uncontrolled severe cancer pain
	14. Radiation field included lung
	15. Pregnancy, or women who desire to have children
	16. Any reason why, in the opinions of the investigator, the patient should not participate

ranged from 12% to 15% and that after gemcitabine alone was 5%.^{12,13,19,20} In our department, CRT had also achieved better survival outcomes than chemotherapy alone (2-year survival rate: 47.1% vs. 19.1%). Additionally, better survival outcomes have been reported in patients with UR-LA PDAC receiving chemotherapy with GnP than in those receiving gemcitabine alone.⁹ We therefore hypothesized that, in patients with UR-LA PDAC, concurrent radiotherapy and GnP would achieve better survival outcomes than chemotherapy alone and assumed a 30% improvement in 2-year overall survival rate after CRT. We calculated that to prove an improvement in 2-year overall survival rate from 15% to 45% in a binominal test with alpha error of 0.05 and beta (power) of 0.817, assuming dropouts, a sample size of 25 patients was required. Resection rate will be also analyzed as co-primary endpoint.

Treatment

The study patients will receive 100 mg/m² nab-paclitaxel intravenously over 30 min followed by 800 mg/m² gemcitabine intravenously over 30 min. A total of 50.4Gy (1.8Gy/28fr) will be administered concurrently. GnP will be administered on Day 1, 8, and 15 per 4-week cycle. After two cycles of GnP have been administered, additional cycles will be continued until disease progression, an unacceptable level of adverse event(s), patient withdrawal, or conversion surgery (Fig. 1).

Conversion surgery (CS) may be considered in patients with stable disease or better, technically resectable tumors, normal tumor marker concentrations, decrease in SUVmax, and ECOG performance status of 0 or 1 8 months after starting the protocol treatment.

Follow-up

Follow-up will include physical examination, blood tests, and imaging. Tumor markers will be measured monthly and tumor responses evaluated according to RECIST version 1.117 using dynamic CT at 2 month intervals. PET/CT will be performed 3 monthly until disease progression or CS. Toxicities and adverse event will be evaluated in accordance with CTCAE version 4.0. Suspected unexpected life-threatening or fatal adverse events will be reported to our hospital's director and Ministry of Health, Labor and Welfare. A data and safety monitoring board will monitor the trial subjects' safety by qualitative assessment of feasibility, accrual rate, and toxicity/

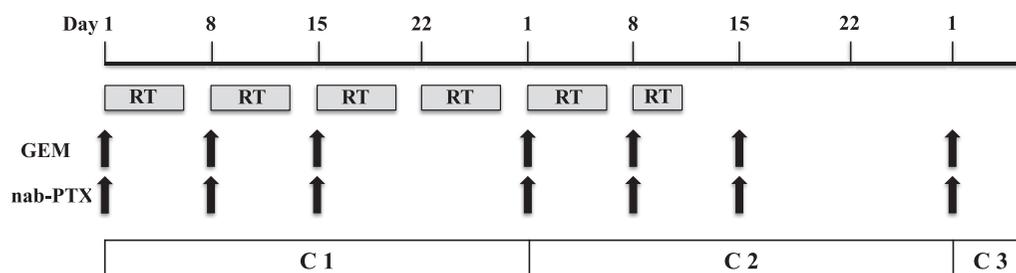


Fig. 1 Treatment schedule.

RT; radiation therapy, GEM; gemcitabine, nab-PTX; nab-paclitaxel.

morbidity.

DISCUSSION

The NUPAT 05 trial will investigate the survival benefit of CRT combined with GnP in patients with UR-LA PDAC. Some clinical trials have shown that chemotherapy with GnP is effective against primary pancreatic tumors. Exploratory analysis of a phase 3 MPACT trial for metastatic PDAC indicated that reduction in primary pancreatic tumor burden is an independent predictor of survival.²¹ More recently, the phase 2 LAPACT trial showed that induction chemotherapy with GnP in patients with UR-LA PDAC was well tolerated and effective, the median PFS being 10.8 months.²² These results support the effectiveness of GnP in patients with UR-LA PDAC.

Of note, the CS rate was 15% in the LAPACT trial but 40%–50% in other studies using CRT combined with FOLFIRINOX in patients with UR-LA PDAC.^{23,24} In our phase 1 NUPAT 02 trial of CRT with GnP, CS was performed in 6/12 patients (50%) and curative resection (R0) achieved in all six (100%). Furthermore, we documented extremely good pathological responses (two grade 4, two grade 3, one grade 2 and one grade 1b). CS for UR-LA PDAC patients reportedly improves long-term survival.²⁵ Some trials have also found an association between pathological response after CRT and long-term survival.^{26–28} Thus, we expect CRT incorporating GnP to improve resection rates and hence long-term survival and plan accordingly to evaluate resection rate statistically as a co-primary endpoint in this trial. A multicenter retrospective analysis of patients with UR-LA PDAC found that those who received chemo- or chemoradio-therapy for more than 8 months from diagnosis had better long-term survival.²⁵ Therefore, in the planned trial, we will consider CS if a response with normalization of tumor marker concentrations is maintained 8 months after starting the protocol treatment.

Thus, both the efficacy and safety of CRT incorporating GnP and the impact of multidisciplinary treatment including CS on long-term survival of patients with UR-LA PDAC will be evaluated in this trial.

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