




BMJ Open Study protocol of the HGCSG1803: a phase II multicentre, non-randomised, single-arm, prospective trial of combination chemotherapy with oxaliplatin, irinotecan and S-1 (OX-IRIS) as first-line treatment for metastatic or relapsed pancreatic cancer

Shintaro Nakano ¹, Yasuyuki Kawamoto,¹ Satoshi Yuki,² Kazuaki Harada,² Takuto Miyagishima,³ Susumu Sogabe,⁴ Masayoshi Dazai,⁵ Atsushi Sato,⁶ Atsushi Ishiguro,⁷ Michio Nakamura ⁸, Shinya Kajiura,⁹ Yasuo Takahashi,¹⁰ Miki Tateyama,¹¹ Kazuteru Hatanaka,¹² Yasushi Tsuji,¹³ Takahide Sasaki,¹⁴ Yoshiaki Shindo,¹⁵ Tomoe Kobayashi,¹⁶ Isao Yokota,¹⁷ Naoya Sakamoto,² Yuh Sakata,¹⁸ Yoshito Komatsu ¹

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For numbered affiliations see end of article.

Correspondence to

Professor Yoshito Komatsu; ykomatsu@ac.cyberhome.ne.jp

ABSTRACT

Introduction Combination chemotherapy with oxaliplatin, irinotecan, fluorouracil and leucovorin (FOLFIRINOX) has become one of the standard treatments for metastatic pancreatic cancer. However, the use of FOLFIRINOX requires prolonged infusion. Therefore, we planned to develop a new combination chemotherapy regimen with oxaliplatin, irinotecan and S-1 (OX-IRIS) for advanced pancreatic cancer. In the phase I study that was conducted previously, the safety and recommended dose of OX-IRIS were assessed. In this study, we will evaluate the efficacy and safety of OX-IRIS.

Methods and analysis The HGCSG1803 study started as a multicentre, non-randomised, single-arm, prospective, phase II study in December 2019. Eligible subjects were patients with untreated metastatic or relapsed pancreatic cancer. OX-IRIS is administered as follows: 30 min infusion of antiemetic; 2-hour infusion of oxaliplatin (65 mg/m²); 1.5-hour infusion of irinotecan (100 mg/m²) on day 1 and 15 of each 4-week cycle; and oral S-1 (40 mg/m²) twice daily from after dinner on day one to after breakfast on day 15, followed by a 14-day rest, to be repeated every 2 weeks until disease progression, unacceptable toxicity or patient refusal. The primary endpoint is response rate. The secondary endpoints are overall and progression-free survival, safety and dose for each drug. Using a binomial test, a sample size of 40 patients was set with a threshold value of 10% and expected value of 30%. Registration of 40 cases is planned from 18 institutions in Japan.

Ethics and dissemination All the procedures will be conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki of 1964 and its later versions. All the patients

Strengths and limitations of this study

- ⇒ This is a phase II study focusing on the efficacy and safety of oxaliplatin, irinotecan and S-1 (OX-IRIS) as a new combination chemotherapy regimen for advanced pancreatic cancer.
- ⇒ The primary endpoint is response rate of OX-IRIS.
- ⇒ Since this study is a single-arm study, it may include some bias.

will receive written information about the trial and will provide informed consent before enrolment. This trial was approved by the Hokkaido University Certified Review Board (approval No: 018-037).

Trial registration number jRCTs011190008.

INTRODUCTION

Pancreatic cancer is the fourth-leading cause of cancer-related deaths worldwide,¹ and its incidence is projected to increase. In the metastatic setting, intensive systemic chemotherapy such as with oxaliplatin, irinotecan, fluorouracil and leucovorin (FOLFIRINOX)² yields significantly longer survival rates than with gemcitabine monotherapy. However, FOLFIRINOX also has a relatively high toxicity, and therefore, the modified FOLFIRINOX (mFOLFIRINOX)³ is also used in general practice. In addition, gemcitabine plus nab-paclitaxel (GnP)⁴ showed significant improvement in overall survival (OS)

than gemcitabine monotherapy. Currently, both FOLFIRINOX and GnP are recommended as first-line chemotherapy regimens for metastatic pancreatic cancer.⁵

However, although both FOLFIRINOX and mFOLFIRINOX have shown good outcomes,^{2 3} they involve the continuous infusion of fluorouracil (5-FU) for 46 hours, which can cause patient discomfort. Further, many patients prefer oral anticancer drug regimens over intravenous drug regimens.⁶ Several clinical trials have shown that regimens that included oral drugs have had similar efficacies to established infusion regimens in other cancers.^{7–10} Thus, FU infusion-free regimens, in which orally administered FUs replace continuous infusions, have become a preferred treatment option. In pancreatic cancer, we reported previously that a 4-week IRIS regimen showed clinical benefits and an acceptable safety profile.^{11 12} In addition, S-1 monotherapy showed clinical benefits for both resected¹³ and advanced pancreatic cancer patients.¹⁴ Thus, S-1 is expected to be as effective as a continuous infusion of 5-FU. Therefore, we planned to develop a new combination chemotherapy regimen for advanced pancreatic cancer comprising oxaliplatin, irinotecan and S-1 (OX-IRIS). Previously, we conducted the phase I study for assessing the safety and determining the recommended dose of the OX-IRIS regimen.¹⁵ In this study, we will evaluate the efficacy and safety of OX-IRIS in metastatic pancreatic cancer patients.

METHODS AND ANALYSIS

Study setting

A multicentre, single-arm, open-label, phase II clinical study will evaluate the efficacy of OX-IRIS in metastatic pancreatic cancer.

Endpoints

The primary endpoint will be the objective response rate (best overall response of the confirmed complete response or partial response), defined as the proportion of patients who achieved an objective response among all eligible patients. The secondary endpoints will be progression-free survival (PFS), OS, disease control rates, adverse events and dose intensity. The disease control rate is defined as the best overall response of confirmed complete response, partial response or stable disease. OS is defined as the duration between the study registration and any-cause death, with data to be censored on the last day that the patient is alive. PFS is defined as the duration between the study registration and disease progression or any-cause death, with data to be censored on the last day that the patient is alive, without any evidence of progression.

Inclusion and exclusion criteria

Inclusion criteria

Patients with advanced/recurrent pancreatic cancer who meet the following eligibility criteria will be considered:

1. The presence of histologically or cytologically confirmed adenocarcinoma or adenosquamous carcinoma.
2. Distant metastasis or recurrence confirmed via chest and enhanced abdominal/pelvic CT.
3. Age 20–75 years.
4. Eastern Cooperative Performance Status of 0 or 1.
5. With measurable lesions based on the Response Evaluation Criteria in Solid Tumours (RECIST) V.1.1.
6. No prior chemotherapy or radiation therapy; for patients with previous neoadjuvant therapy, the interval between surgery and relapse must be ≥ 6 months; for patients with previous adjuvant therapy, the interval between the end of chemotherapy and relapse must be ≥ 6 months for S-1 therapy.
7. Can tolerate oral intake.
8. A life expectancy of at least 8 weeks.
9. With sufficient organ function defined as follows: absolute neutrophil count $\geq 1500/\text{mm}^3$; $100 \times 10^9/\text{g/L}$ platelet count $\geq 100\,000/\text{mm}^3$; haemoglobin $\geq 90\text{g/L}$; total bilirubin $\leq 2.0\text{mg/dL}$; aspartate aminotransferase $< 2.5 \times$ upper limit of normal (ULN) for the reference lab; alanine aminotransferase $< 2.5 \times$ ULN for the reference lab; serum creatinine $\leq 1.2\text{mg/dL}$; creatinine clearance $\geq 60\text{mL/min}$.
10. Able to provide written informed consent.

Exclusion criteria

1. A history of synchronous or metachronous malignancies within 5 years.
2. UGT1A1 *6 or *28 homozygous or double heterozygous.
3. Grade ≥ 2 peripheral neuropathy.
4. Received a transfusion, blood product or haematopoietic growth factor such as granulocyte colony-stimulating factor up to 7 days prior to enrolment.
5. With severe fluid accumulation in body cavities, such as pleural infusions and ascites, that continually requires treatment such as drainage.
6. With interstitial pneumonia or pulmonary fibrosis.
7. With poorly controlled diarrhoea.
8. With severe comorbidities (heart failure, renal failure, hepatic failure, paresis of the intestine or ileus).
9. With an active infection.
10. With active viral hepatitis; patients positive for the hepatitis B antigen will be eligible if they receive anti-viral drugs and are negative for the hepatitis B virus DNA.
11. With poorly controlled diabetes.
12. With severe psychological disorders.
13. With any central nervous system metastasis.
14. Receiving treatment with continuous systemic corticosteroid more than 10mg/day or immunosuppressants.
15. Women who are pregnant, nursing or possibly pregnant, or men trying to conceive with a partner.
16. With a history of hypersensitivity to any drugs in this study.
17. Receiving flucytosine or atazanavir sulfate.

OX-IRIS: Oxaliplatin + Irinotecan + S-1

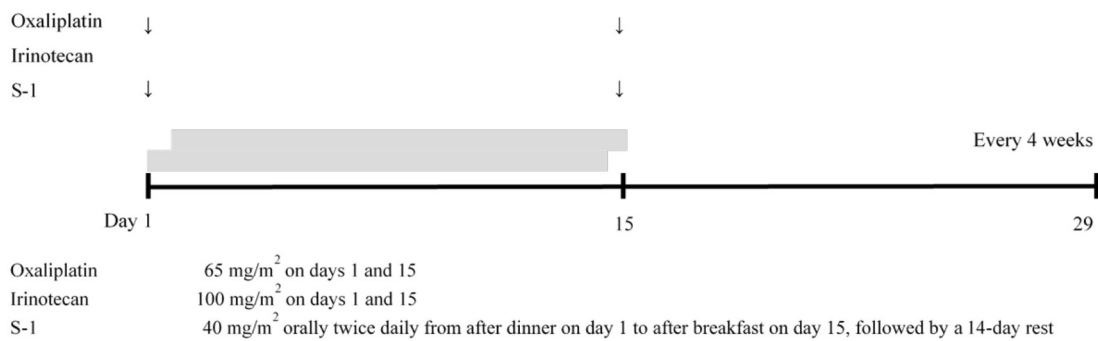


Figure 1 OX-IRIS regimen. The OX-IRIS regimen involves a 28-day cycle of oxaliplatin and irinotecan on days 1 and 15 and S-1 (80 mg/m²/day) on days 1–14. OX-IRIS, oxaliplatin, irinotecan and S-1.

18. Other patients who are considered to be ineligible for this study by the investigator.

Treatment

Previously, we conducted the phase 1 study (HGCSG1403)¹⁵ to determine the recommended dose of oxaliplatin and irinotecan. The maximum tolerated dose of oxaliplatin was 85 mg/m² and irinotecan 100 mg/m² while the recommended dose of oxaliplatin was 65 mg/m², and that of irinotecan was 100 mg/m². S-1 was fixed at 40 mg/m².

In the current study, the treatment protocol will be a 30 min intravenous infusion of antiemetic; a 2-hour intravenous infusion of oxaliplatin at 65 mg/m²; a 1.5-h intravenous infusion of irinotecan at 100 mg/m² on day one and day 15 of each 4-week cycle; and S-1 (40 mg/m²) orally twice daily, from after dinner on day 1 to after breakfast on day 15, and followed by a 14-day rest, to be repeated every 2 weeks until disease progression, unacceptable toxicity or patient refusal (figure 1). All the patients will receive routine doses of palonosetron, aprepitant and dexamethasone for emesis prophylaxis. Colony-stimulating factors will not be allowed for primary prophylaxis but will be allowed for treatment of febrile neutropenia. There will be no restrictions on any subsequent treatment.

Follow-up

Enhanced abdominal and pelvic CT or MRI, chest CT or MRI, and tumour markers (CEA and CA19-9) will be evaluated at least every 8 weeks until disease progression or death. The tumour response will be assessed every 8 weeks according to the RECIST criteria V.1.1.¹⁶ The response rate will require confirmation. Physical examinations, laboratory tests and the evaluation of adverse events will be performed according to the Common Terminology Criteria for Adverse Events V.5.0 on at least days 1, 8, 15 and 22 of the first treatment course and at least on days 1 and 15 of the second or subsequent treatment courses. All the registered patients will be followed up for at least 1 year after the completion of the patient enrolment. The

primary endpoint will be analysed 1 year after the completion of patient enrolment.

Data management, control of data consistency, quality control, monitoring and audits

Central monitoring will be performed by the Hokkaido Gastrointestinal Cancer Study Group Data Centre to ensure data submission, patient eligibility and protocol compliance. The monitoring reports will be submitted to the Hokkaido University Hospital Institute Review Board every 12 months with safety monitoring being performed by an independent committee (Effect Safety Committee), to which all the severe adverse events will be reported.

Participating institutions

Kitami Red Cross Hospital, Hokkaido University Hospital, Teine Keijinkai Hospital, Hokkaido Cancer Centre, Sapporo Medical Centre NTT EC, Sapporo City General Hospital, KKR Sapporo Medical Centre, Hokkaido Gastroenterology Hospital, Sapporo Higashi Tokushukai Hospital, Tonan Hospital, Tomakomai Nissho Hospital, Tomakomai City Hospital, Kushiro Rosai Hospital, Hakodate Municipal Hospital, Hirosaki University Hospital, Toyama University Hospital, Japanese Red Cross Akita Hospital and Nakadori General Hospital

Statistical analysis

FOLFIRINOX is reportedly superior to gemcitabine monotherapy for metastatic pancreatic cancer.² Therefore, we expect OX-IRIS to show similar efficacy with FOLFIRINOX in pancreatic cancer. Using a binomial test, a sample size of 33 patients is needed to maintain 80% power under the hypothesis that the overall response rate is expected to be 30%² with a threshold value of 10%² and a target one-sided alpha of 2.5%. With an allowance of 20% for ineligible patients and drop-outs, a sample size of 40 patients was set. If the primary endpoint is met, we will plan the phase 3 trial comparing OX-IRIS and FOLFIRINOX or GnP.

Patient and public involvement

Neither the patients nor the public will be involved in the design, conduct, reporting or dissemination plans of our research.

ETHICS AND DISSEMINATION

All the procedures will be conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki of 1964 and its later versions. All patients will receive information about the trial in written forms and will provide their informed consent before enrolment. The study was approved by the Hokkaido University Certified Review Board (approval No: 018-037). Patients have been enrolled since December 2019. As the study will complete accrual in September 2021, and results will be published by the end of 2023. The findings from the analysis of the trial will be disseminated in a variety of ways including abstracts, posters and presentations at conferences and published manuscripts in peer-reviewed journals.

DISCUSSION

Several mFOLFIRINOX regimens containing S-1 as an alternative to fluorouracil and leucovorin have been reported in first-line settings.^{17–20} Akahori *et al* conducted a phase 2 study of SOXIRI regimen¹⁸ in which patients received 80 mg/m² of S-1 twice a day for 2 weeks in an alternate-day administration, 150 mg/m² of irinotecan on day 1 and 85 mg/m² of oxaliplatin on day 1 of a 2-week cycle. The response rate was 22%, and the median OS and PFS were 17.7 and 7.4 months, respectively. However, 43% of the subjects had locally advanced pancreatic cancer, and the efficacy and safety of SOXIRI in patients with metastatic cancer were unclear. Sasaki *et al* conducted a phase 1 trial of S-IROX¹⁹ and found that S-IROX had tolerable toxicities and preliminary antitumour activity. Accordingly, a phase II/III trial (JCOG1611) comparing mFOLFIRINOX and S-IROX with GEM plus nab-PTX is underway (jRCTs031190009). This study may have several limitations. This study will not have a control arm, and a randomised trial will be required to determine the clinical efficacy of OX-IRIS. This trial will not involve a QOL analysis; we will conduct this in the phase 3 trial. We expect that the findings of this study will lead to the development of new treatment options for patients with advanced pancreatic cancer.

Author affiliations

- ¹Division of Cancer Centre, Hokkaido University Hospital, Sapporo, Japan
- ²Department of Gastroenterology and Hepatology, Hokkaido University Hospital, Sapporo, Japan
- ³Department of Medical Oncology, Kushiro Rosai Hospital, Kushiro, Japan
- ⁴Department of Medical Oncology, KKR Sapporo Medical Center, Sapporo, Japan
- ⁵Department of Gastroenterology, Sapporo Medical Center NTT EC, Sapporo, Japan
- ⁶Department of Medical Oncology, Hirosaki University Graduate School of Medicine, Hirosaki, Japan
- ⁷Department of Medical Oncology, Teine Keijinkai Hospital, Sapporo, Japan

- ⁸Department of Gastroenterology, Sapporo City General Hospital, Sapporo, Japan
- ⁹Department of Gastroenterology and Hematology, Faculty of medicine, University of Toyama, Toyama, Japan
- ¹⁰Department of Gastroenterology, Hokkaido Cancer Centre, Sapporo, Japan
- ¹¹Division of Internal Medicine, Tomakomai Nisshou Hospital, Sapporo, Japan
- ¹²Department of Gastroenterology, Hakodate Municipal Hospital, Hakodate, Japan
- ¹³Department of Medical Oncology, Tonan Hospital, Sapporo, Japan
- ¹⁴Department of Internal Medicine, Hokkaido Gastroenterology Hospital, Sapporo, Japan
- ¹⁵Department of Gastroenterological Surgery, Nakadori General Hospital, Akita, Japan
- ¹⁶Department of Gastroenterology, Tomakomai City Hospital, Tomakomai, Japan
- ¹⁷Department of Biostatistics, Hokkaido University Graduate School of Medicine, Sapporo, Japan
- ¹⁸CEO, Misawa City Hospital, Misawa, Japan

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s)

Provenance and peer review Not commissioned; externally peer reviewed.

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ORCID iDs

Shintaro Nakano <http://orcid.org/0000-0001-9630-572X>
 Michio Nakamura <http://orcid.org/0000-0002-1509-9811>
 Yoshito Komatsu <http://orcid.org/0000-0002-1570-6802>

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