News Release

Title

Multicentre phase I/II study of intravenous gemcitabine + nab-paclitaxel combined with intraperitoneal paclitaxel for patients with pancreatic cancer and peritoneal metastasis

Key Points

- There is no effective treatment against peritoneal metastasis in gastroenterological malignancies. In particular, it is an urgent issue to overcome this peritoneal metastasis in the area of pancreatic cancer with dismal survival outcomes.
- This study aimed to evaluate its clinical efficacy and safety for the combination of intravenous gemcitabine, intravenous nab-paclitaxel and intraperitoneal paclitaxel in patients with pancreatic cancer and peritoneal metastasis, with participation of domestic high-volume centers.
- This regimen exhibited promising clinical efficacy with acceptable tolerability in patients with pancreatic cancer and peritoneal metastasis. Especially, the treatment subsequent surgery was performed in 17% patients.

Summary 1

The research team led by Prof. Sohei Satoi (Kansai Medical University, Principal Investigator), Prof. Yasuhiro Kodera and Dr. Suguru Yamada (Nagoya University), and Prof. Tsutomu Fujii (Toyama University), including Tohoku University, Hokkaido University, Hiroshima University and Ehime University, conducted multicentre phase I/II study of their original intravenous gemcitabine + nab-paclitaxel combined with intraperitoneal paclitaxel treatment for patients with pancreatic cancer and peritoneal metastasis (Stage IV). The intravenous gemcitabine + nab-paclitaxel treatment is considered to be standard therapy for Stage IV patients, but the survival outcomes remain still poor. This study aimed to determine the recommended dose for the combination of intravenous gemcitabine, intravenous nab-paclitaxel and intraperitoneal paclitaxel in patients with pancreatic cancer and peritoneal metastasis, and evaluate its clinical efficacy and safety. The frequencies of dose-limiting toxicities were evaluated, and the recommended dose was determined in the phase I portion. The primary endpoint of the phase II portion was the overall survival rate at 1 year. The secondary endpoints were anti-tumour effects, symptom-relieving effects, safety and overall survival. Among 46 patients enrolled in the phase II portion, the median time to treatment failure was 6.0 months. The response and disease control rates were 49 and 95%, respectively. Ascites disappeared in 40% of patients, and cytology became negative in 39% of patients. The median survival time was 14.5 months, and the 1-year overall survival rate was 61%. Conversion surgery was performed in 17% patients, and those who underwent surgery survived significantly longer than those who were not surgically treated (not reached vs. 12.4 months). Grade 3/4 haematologic toxicities occurred

in 76% of patients, whereas non-haematologic adverse events occurred in 15% of patients. Adding intraperitoneal paclitaxel had clinical efficacy with acceptable tolerability.
This study has been published in British Journal of Surgery.

Summary 2

This multicentre phase I/II study aimed to determine the recommended dose for the combination of intravenous gemcitabine, intravenous nab-paclitaxel and intraperitoneal paclitaxel in patients with pancreatic cancer and peritoneal metastasis, and evaluate its clinical efficacy and safety. This regimen displayed promising clinical efficacy with acceptable tolerability in patients with pancreatic cancer and peritoneal metastasis.

Research Background

Pancreatic cancer has a poor prognosis, particularly for disseminated disease. The presence of peritoneal metastasis is often associated with ascites and intestinal obstruction, leading to malnutrition and poor performance status, which could deprive patients of the opportunity to receive chemotherapy. Intraperitoneal chemotherapy appears advantageous due to higher drug concentrations achieved in the peritoneal cavity, compared to systemic chemotherapy. Favourable clinical effects of intraperitoneal paclitaxel have been reported in clinical trials of patients with peritoneal metastasis, including ovarian cancer, gastric cancer and pancreatic cancer. A previous phase II study of intravenous and intraperitoneal paclitaxel combined with S-1 for patients with pancreatic cancer and peritoneal metastasis demonstrated good outcomes with favorable response and disease control rates. Also, the median survival time and 1-year overall survival rate were 16.3 months and 62 per cent, with conversion surgery performed in a quarter of the enrolled patients. Recently, nab-paclitaxel combined with gemcitabine was shown to be the standard treatment option for patients with pancreatic cancer and distant metastasis.

Research Results

A total of 50 patients were enrolled in this phase I/II study from seven Japanese centres, with 10 patients participating in the phase I portion and 46 patients (including six patients from the phase I portion) participating in the phase II portion. Based on dose-limiting toxicities, the recommended doses for intravenous gemcitabine, intravenous nab-paclitaxel and intraperitoneal paclitaxel were 800, 75, and 20 mg/m^2, respectively. Malignant ascites was observed in 30 (65%) patients on laparoscopy or laparotomy. All patients had positive intraperitoneal cytology, and 29 (63%) had pathological confirmation of peritoneal dissemination. The median treatment duration was 6.0 (range, 0–22.6) months. During treatment, the median primary tumour shrinkage was 20% (range, 0–100). The median percentage decrease of CA19-9 levels was 84% (range, 16.9–99.1), and normalisation of CA19-9 levels was observed in 12 patients (26%). The response rate and disease control rate were 49 and 95%, respectively. Peritoneal washing cytology turned negative in 18 of 46 (39%) patients,

and malignant ascites disappeared in 12 of 30 (40%) patients. Finally, conversion surgery was performed in eight (17%) patients. The median overall survival was 14.5 (range, 11.5–19.2) months, and the 1- and 2-year overall survival rates was 61 and 32%, respectively. The median time to surgery was 8.8 (range, 4.1–12.2) months after the initiation of chemotherapy. Finally, seven patients underwent R0 resection. The Evans grade was I in one patient, IIA in three patients and IIB and III in two patients each. Concerning overall survival, the patients who underwent conversion surgery survived significantly longer than those who did not undergo conversion surgery (not reached vs. 12.4 months, P = 0.004). Grade 3/4 haematologic adverse events occurred in 76% of patients, meanwhile, grade 3/4 non-haematologic adverse events occurred in 15% of patients.

Research Summary and Future Perspective

This trial demonstrated clinical efficacy with acceptable tolerability in patients with peritoneal metastasis from pancreatic cancer. Although the clinical response and survival data did not exceed that of an S-1 based regimen in a previous study, this strategy represents an option for treating peritoneal disease in countries where S-1 is not available. However, this study was conducted as a phase I/II study with a single-arm design; therefore, we must recognise the bias in its clinical implications. Hence, we plan to conduct a phase III study to compare survival outcomes between this intraperitoneal therapy and standard chemotherapy.

Publication

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