A Randomized Phase II Trial to Test the Efficacy of Intra-peritoneal Paclitaxel for Gastric Cancer with High Risk for the Peritoneal Metastasis (INPACT Trial)

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Owing to its peculiar pharmacological characteristics, paclitaxel attains substantial intra-peritoneal concentration for a prolonged period when delivered intra-peritoneally, and is active against peritoneal metastasis of ovarian cancer. It is also considered promising against disseminated gastric cancer. However, the fact that the intra-peritoneal paclitaxel has not been approved in Japan has rendered its evaluation by a formal clinical trial impossible. The authors designed a randomized phase II trial using the Kodo Iryo Hyoka system, a new system to legally test an yet unapproved mode of treatment. It is hoped that this trial will result in a breakthrough in the treatment of peritoneal carcinomatosis from gastric cancer.

Key words: paclitaxel – clinical trial – gastric cancer

TRIAL BACKGROUNDS AND RATIONALE

Curatively resected gastric cancer patients often suffer from recurrence as peritoneal carcinomatosis. This could be caused by cancer cells that had already been shed from the serosal surface at the time of surgery, sometimes detectable by examining the peritoneal washes, or those that were disseminated during surgical procedures. In addition to extensive irrigation of the peritoneal cavity (1), intra-peritoneal (IP) instillation of effective anticancer drugs could eliminate these cells to the extent that the recurrences could be prevented. Repeated IP administration of paclitaxel (PTX) has been shown to be safe and effective for disseminated ovarian cancer, another cancer type where peritoneal disease often turns out to be a major cause for disease failure (2). Since its efficacy when administered intravenously (DIV) against gastric cancer has been proved (3) and its potential advantage when given intra-peritoneally has been robustly shown pharmacologically (4,5), IP PTX has been considered promising also to eliminate peritoneal metastasis from gastric cancer.

Formal clinical trials to prove the efficacy of this approach have been hindered by the fact that the IP administration of PTX has not been approved by the Ministry of Health, Labour and Welfare in Japan. When using such drugs outside of the medical insurance system, all other expenses such as the cost of medical services at the outpatient clinic, including drugs such as steroids, H2 blockers and anti-emetics will have to be covered also by the individual researcher or the patient. The authors attempted to overcome this problem by making an official request to conduct a multi-institutional trial by using a system known as the ‘Kodo Iryo Hyoka’ system. Using this system, unapproved or experimental medical practice whose cost is covered by the individuals can be delivered simultaneously with general medical procedures that are covered by the insurance. To use this system, the study protocol will have to be scrutinized and approved by a committee appointed by the Ministry. Furthermore, a trial thus performed is expected to be designed so as to generate an evidence for future approval of
the treatment by the Ministry. A one-arm single-institutional phase II trial to confirm the efficacy of a regimen that includes IP PTX (6) has already been approved and is ongoing using the ‘Kodo Iryo Hyoka’ system. To add further evidence in support of the IP treatment and to ultimately establish a basis for the future approval by the Ministry, a head-to-head comparison of IP and DIV of the same drug under the same schedule was considered mandatory. Since the patients so allocated will then have to be treated by IP PTX alone for a fixed period of time, patients who are deemed eligible for the trial had to have a significant risk to develop peritoneal carcinomatosis, while harbouring no gross lesions that immediately call for systemic administration of the anticancer drugs.

The authors held a few meetings to finally compile a protocol for a clinical trial to evaluate IP PTX, as described in the following section. The study is called INPACT, in which INPACT is an abbreviation for ‘IP administration of chemotherapeutic agent’.

**PROTOCOL DIGEST OF THE STUDY**

**PURPOSE**

The purpose of this study is to show a prognostic impact of repeated IP of PTX over the DIV on the identical treatment schedule, among patients who are considered to have a high risk of developing peritoneal carcinomatosis. In the event of detecting a survival advantage, this study should be one of valuable evidence based on which to request the Ministry of Health, Labour and Welfare for approval of the IP administration. The establishment of various combinations incorporating IP PTX to combat all types of metastatic gastric cancer and a subsequent randomized trial to prove their survival benefits would then be expected.

**RESOURCES**

Data centre services and statistical supervision are funded by a non-profit organization, the Epidemiological and Clinical Research Information Network (ECRIN), Kyoto, Japan. All treatments with the exception of PTX-administered IP have been approved as a general practice within the scope of general medical insurance. IP administration of PTX has been approved by the Ministry of Health, Labour and Welfare as of July 2010, exclusively for the participants of this trial, using the Kodo Iryo Hyoka system. Bristol- Myers Squibb has kindly agreed to supply PTX to be given intra-peritoneally.

**ENDPOINTS**

The primary endpoint is the 2-year overall survival (OS) rate. The secondary endpoints are the incidence of adverse events, progression-free survival time, and OS time.

**ELIGIBILITY FOR PARTICIPATING IN THE TRIAL**

Approval of the protocol by the institutional review board is a prerequisite to participate in the trial. In addition, each participating institution is requested to fill in and send an application form to the Ministry of Health, Labour and Welfare via Nagoya University to obtain final approval by the government to join the Kodo Iryo Hyoka system.

**ELIGIBILITY CRITERIA FOR THE ENROLLMENT**

Inclusion criteria for primary registration:

(i) Histologically confirmed adenocarcinoma of the stomach.

(ii) Either macroscopically defined as Type 3 with a diameter >8 cm or Type 4 (linitis plastica), or defined as the other macroscopic type, but is considered highly suspicious for serosal invasion or peritoneal seeding.

(iii) Patients without the following findings on computerized tomography: cervical or mediastinal lymphadenopathy, bulky metastasis to suprapancreatic or retroperitoneal lymph nodes, distant organ metastasis, thoracic effusion, ascites spreading beyond the pelvic cavity.

(iv) No previous history of chemotherapy or radiation.

(v) Eastern Cooperative Oncology Group performance status of 0 or 1.

(vi) Age ≥20.

(vii) Adequate organ function is defined as follows: a white blood cell count of 3000–12 000/m³, neutrophil count of >1500/m³, platelet count of >100 000/m³, AST and ALT ≤100 IU/l, total bilirubin ≤1.5, serum creatinine level ≤1.5 mg/dl, serum albumin level ≥3.0 g/dl.

(viii) Surgery planned within 1 month of registration.

(ix) Written informed consent.

Exclusion criteria for primary registration:

(i) Serious comorbidities include the following:

(a) Ischemic heart disease and arrhythmia needing treatment.

(b) Myocardial infarction within 6 months of onset.

(c) Liver cirrhosis.

(d) Interstitial pneumonitis.

(e) Gastrointestinal bleeding in need of repeated blood transfusion.

(f) Uncontrolled diabetes mellitus.

(ii) Bowel obstruction rendering treatment with oral drugs impractical.

(iii) Active synchronous cancer or disease-free metachronous cancer within 5 years of onset.

(iv) Signs of acute infection or inflammatory disease

(v) Systemic treatment with corticosteroids

(vi) Hypersensitivity to Cremophor EL.
(vii) Women who are pregnant, contemplating pregnancy or amid breast-feeding.
(viii) Mental disorders which may affect ability or willingness to provide informed consent.
(ix) History of severe hypersensitivity to any drugs.
(x) History of alcoholic anaphylaxis.
(xi) Peripheral neuropathy.
(xii) Patients otherwise considered inappropriate for inclusion in the study.

Inclusion criteria for secondary registration:
(i) Considered resectable either at laparotomy or laparoscopy.
(ii) If the macroscopic type was not Type 3 with a diameter >8 cm or Type 4 (limitis plastica), peritoneal seeding or positive cytology of the peritoneal washes need to be confirmed during surgery.
(iii) Placement of the IP reservoir is possible.

**Registration**

Participating investigators are instructed to send an eligibility criteria report to the data centre at the non-profit organization ECRIN for the primary registration within 1 month of the scheduled surgery. Investigators are then requested to proceed to the secondary registration by telephone upon laparotomy or laparoscopy, when the eligibility criteria such as resectability, peritoneal metastasis and peritoneal washing cytology findings were confirmed. Patients are randomized during surgery to one of the two treatment groups by a centralized dynamic method using the following factors as balancing variables: macroscopical Type (Types 3 and 4/others), curability of surgery (R0 and R1/R2), age (≤75 years/≥75 years) and institution. Follow-up data including compliance to the treatment, adverse reactions and survival are to be reported to the data centre through clinical report forms.

The first 10 cases are to receive the IP PTX exclusively as a feasibility test, which will be evaluated only for toxicity and will be not included in the survival analysis. If more than four successful IP deliveries are conducted in less than 5 of the 10 patients, the study will either be terminated or modified appropriately.

The study has been registered in the University hospital Medical Information Network (UMIN) as No. 000002957.

**Treatment Methods**

Patients enrolled in this study are randomized to receive one of the following regimens of chemotherapy after gastrectomy.

**Group A: IP administration group:**
PTX: 60 mg/m² IP on the day of surgery (day 1) and on days 15, 22, 29, 43, 50 and 57. The dose of IP PTX is based on a phase I trial performed in the USA for ovarian cancer patients, and its safety when given weekly has been confirmed by a phase II trial (2).

**Group B: Intravenous administration group:**
PTX: 80 mg/m² DIV on the day of surgery (day 1) and on days 15, 22, 29, 43, 50, and 57.

These regimens of treatment are to be followed after 2–3 weeks by a standard systemic chemotherapy for advanced gastric cancer which, at the time the trial started, would be either S-1 monotherapy or a combination of S-1 and cisplatin (CDDP) (7). S-1 is generally recommended after R0/R1 resection and S-1/CDDP after R2 resection, but the selection is left to the discretion of the physician in charge. When patients randomized into Group A failed to receive IP chemotherapy for reasons other than allergic reaction to PTX, they are expected to continue with intravenous PTX according to the predetermined schedule, so that the subsequent systemic chemotherapy will be started at the same time as in other patients.

**Study Design and Statistical Methods**

The current study is a randomized phase II trial applying selection design as proposed by Simon et al. with selection probability of around 80% (8). The primary analysis in this study is aimed to select an appropriate treatment arm for further evaluation, and the sample size was calculated on the hypothesis that the 2-year OS rate of the DIV arm, estimated to be 30–40%, could be improved by 10% in the IP arm. The selection probability is estimated to be 82–83% when a total sample size is 80 and 84–85% when a sample size is 100. Since the first 10 cases will be treated by IP therapy as a feasibility phase and will be excluded from the survival analysis, the total sample size will be 90–110 and 50–60 patients will receive IP therapy.

**Interim Analysis and Monitoring**

The Data and Safety Monitoring Committee (DSMC) independently review the report of trial monitoring regarding efficacy and safety data. The first interim analysis will be performed at 1 year after registration of the last patient and DSMC will decide whether or not to publish the results based on futility analysis and safety data.

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**Conflict of interest statement**

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References


