



# Pharmacokinetic evaluation of intrapleural perfusion with hyperthermic chemotherapy using cisplatin in patients with malignant pleural effusion

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## ABSTRACT

**Objectives:** Malignant pleural effusion (MPE) has a poor prognosis. Most patients are treated with tube thoracostomy and sclerotherapy, although its success rate is around 64%. We have investigated intrapleural perfusion with hyperthermic chemotherapy (IPHC) using cisplatin in a study with a pharmacokinetic evaluation.

**Methods:** Patients with MPE, performance status of 0–1, possibility of good lung expansion and Cr < 1.2 mg/dL were treated with IPHC. The circuit was filled with 2000 mL of normal saline containing cisplatin at a dose of 80 mg/m<sup>2</sup>. Under video-assisted thoracoscopic surgery, the thoracic cavity was filled and perfused at a speed of approximately 1 L/min at a temperature of 43 °C for 1 h. Perfusion solution and plasma samples were periodically collected, and concentrations of protein-unbound (free) platinum, which was the active derivative of cisplatin, and total platinum were determined by flameless atomic absorption spectrometry.

**Results:** Twenty patients with MPE (8 lung cancers, 7 mesotheliomas, and 5 others) were enrolled in this study. Rate of free platinum concentration relative to total platinum concentration in perfusion solution after 1 hr IPHC at 43 °C was 61.1 ± 12.9%. Area under curve (AUC) of free platinum in the pleural space was calculated to be 26.3 µg/mLh, resulting in complete control of pleural effusion for 3 months after IPHC in all cases (95% confidence interval: 83–100%). While, absorption rate of total platinum from the pleural space was 33.8 ± 17.0% (27.4 ± 13.6 mg/m<sup>2</sup>), and the maximum concentration of total platinum in serum was low, 0.66 ± 0.31 µg/mL, resulting in controllable side effects; grade 1 renal toxicity: 6 patients, grade 1 emesis: 7 patients.

**Conclusions:** IPHC with cisplatin showed favorable pharmacokinetic profiles for an optional treatment to control malignant pleural effusion.

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## 1. Introduction

Although malignant pleural effusion (MPE) is not a rare occurrence, the preferred treatment for patients with MPE and pleural dissemination has not been determined. Lung cancer is the most common primary neoplasm that metastasizes to the pleura, but although pleural mesothelioma is rare, it is also an important cause of MPE. Current treatment options for malignant pleural effusion are limited; we usually use minocycline, OK432 and talc for pleurodesis. But the success rate of pleurodesis using these agents was

reported to be around 64% [1], indicating insufficient control by this modality.

Hyperthermia was found to increase the cytotoxicity of chemotherapeutic agents, including cisplatin (CDDP), in vitro [2,3] and in vivo. [4] Wallner KE et al. [2] and Hettinga JV et al. [3] reported that the hyperthermia reinforces the cytotoxicity reaction of CDDP synergistically, and heated CDDP at 43 °C was effective in both CDDP hypersensitive and hyposensitive tumors. Urano et al. [4] observed that the cytotoxic effect of CDDP was enhanced at elevated temperatures in vivo. In humans, hyperthermic intraperitoneal chemotherapy (HIPEC) with CDDP was first developed in peritoneal mesothelioma [5] followed by ovarian carcinoma. [6] It was suggested that HIPEC with CDDP might improve the treatment outcome of patients with peritoneal mesothelioma or ovarian cancer as salvage therapy, which let researchers investigate whether

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intrapleural perfusion with hyperthermic chemotherapy (IPHC) worked in subjects with malignant pleural effusion.

In order to obtain adequate control of MPE, IPHC using CDDP has been reported and introduced [7–9]. Matszaki et al. [7] performed IPHC with CDDP for 2 h at 43 °C, and reported that the control of pleural effusion of lung cancer was 100% in 12 cases. Ratto GB et al. [8] showed that IPHC with CDDP 100 mg/m<sup>2</sup> at a temperature of 41.5 °C for 1 h had feasible to 10 patients with pleural mesothelioma. Ried M et al. [9] reported that extended thymoma resections, including adjacent structures and pleurectomy/decortication, with IPHC using CDDP provided a low recurrence rate and acceptable median survival, 11% (1 out of 9 patients) and 25 months, respectively.

These reports for IPHC using CDDP employed limited number of patients. And, although a few reports investigated pharmacokinetics (PK) of CDDP, pharmacodynamics (PD) was considered not to be enough. In this study for cases with MPE, we have investigated the PK of IPHC using CDDP with a focus on side effects and effectiveness. And we make a comparison of PK/PD of CDDP between IPHC and intravenous administration measured in our previous study.

## 2. Patients and methods

### 2.1. Study protocol and actual methods of IPHC

This open-label prospective study investigated pharmacokinetics, safety and effectiveness of IPHC using CDDP at a dosage of 80 mg/m<sup>2</sup> for 1 h in patients with MPE. This study was performed in accordance with the Helsinki Declaration (1964, amended in 2004) of the World Medical Association, and the study protocol was approved by the institutional review board of Saitama Medical University (#329). The main eligibility criteria included inpatients with MPE, who were 20 years or older, had performance status (PS) of 0–1 and had ALT < 100 IU/L and AST < 100 IU/L, serum creatinine < 1.2 mg/dL and body temperature < 37 °C Celsius. Furthermore, they should be expected to have high possibility for good lung expansion after removing MPE. After obtaining informed consent was obtained, they underwent IPHC using CDDP.

After investigating the pleural space under video-assisted thoracoscopic surgery (VATS), perfusion was performed with a roller pump and heat exchanger (Fig. 1). The circuit was filled with 2000 mL of normal saline, the thoracic cavity was filled and perfused with the saline solution, which was heated by the heat exchanger, under general anesthesia with both-lung ventilation. CDDP at a dose of 80 mg/m<sup>2</sup> was added to the circuit fluid when the temperature stabilized at 42.5 °C (range 42.0–43.5 °C). IPHC was then performed for 60 min with a pump flow rate of 1 L/min. Subsequently, all fluid containing CDDP was removed from the thoracic cavity.

Patients were systematically given hydration of 2000 mL/day on the day when IPHC was done, and continued the hydration of 2000 mL/day for 4 days. Patients were also given antiemetic treatments, such as 5HT<sub>3</sub> antagonist. Chest drainage was maintained during one week.

### 2.2. Pharmacokinetics and analytical method

Heparinized blood samples (5 mL) for the pharmacokinetic study were obtained before and at 0.5, 1, 24, and 48 h (h) after adding CDDP. The blood was centrifuged immediately, and plasma samples to measure total platinum concentrations were stored at –20 °C. In addition, 5 mL of the perfusion solution was collected after completion of IPHC. In order to measure protein-unbound (free) platinum in the perfusion solution, 1 mL of the solution was centrifuged using an Amicon Centrifree 4104 (Amicon Corporation,

Mass.) at 1980 g for 20 min. The concentrations of free platinum and total platinum were determined by flameless atomic absorption spectrometry. [10]

Maximum peak concentrations ( $C_{max}$ ) of CDDP in blood were obtained directly from the serum concentration–time data. The area under concentration (AUC) of total platinum in plasma from 0 to 1 h ( $AUC_{0-1}$ ) and the AUC from 1 h to the last measurable sampling point ( $AUC_{1-48}$ ) was calculated by the trapezoidal rule. To calculate systemic absorption rates of total platinum from the pleural space, the following formula was used;

Systemic absorption rate = (administered total platinum – total platinum concentration in the perfusion solution × solution volume after IPHC)/administered total platinum × 100.

The rate of free platinum per total platinum in the perfusion solution after 1 h of IPHC was calculated.

### 2.3. Adverse events and effectiveness

To evaluate patients' morbidity, we evaluated changes in body temperature in the rectum and the esophagus. All adverse events were reported, and severity was graded by the National Cancer Institute Common Toxicity Criteria (version 3.0). Routine clinical and laboratory assessments were performed on days 2, 4, 6, and 8 during the inpatient period, then, at least on day 15 at the outpatient clinic.

As to the treatment's effectiveness, we evaluated the complete control of pleural perfusion, which was defined as no pleural effusion 3 months after IPHC.

### 2.4. Statistical analysis

Statistical significance of differences among 3 groups was determined by Kruskal–Wallis one-way analysis of variance on ranks. Multiple comparisons for all the paired groups were further performed by Dunn's method.

## 3. Results

### 3.1. Patient characteristics

Between August 2005 and March 2008, 20 patients with MPE were enrolled in this study. The demographic features of these patients are summarized in Table 1. The patients comprised 13 males and 7 females, 38–78 years old, with PS 0–1. There were 8 patients with lung carcinoma, and 7 patients with pleural mesothelioma. Of the other 5 patients, 2 patients had thymic malignancy, 1 had renal cell carcinoma, and 1 had ovarian carcinoma. One patient's primary site was unknown. Mean body surface area was 1.62 m<sup>2</sup>.

### 3.2. Pharmacokinetics of CDDP under IPHC

Systemic absorption rates of total platinum from the pleural space were measured and calculated in all patients. (Table 2A) The systemic absorption rates of patients with lung cancer and mesothelioma were higher than those with other malignancies of thymic malignancies, renal cell carcinoma, and ovarian carcinoma. The mean and SD of the systemic absorption rate was 33.8 ± 17.0%. The serum concentration–time curves of total platinum after administering CDDP into the circuit fluid is shown in Fig. 2. The maximum concentration of total platinum in serum was 0.66 ± 0.31 µg/mL at the end of IPHC, but total platinum in serum was detected for a long time; 0.28 ± 0.12 µg/mL and 0.21 ± 0.11 µg/mL at 24 h and 48 h, respectively, after adding CDDP into the circuit fluid.  $AUC_{0-1}$  and  $AUC_{1-48}$  of total platinum in serum

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