Phase I Study of Single-Dose Oxaliplatin in Japanese Patients with Malignant Tumors

Kuniaki Shirao1, Yasuhiro Matsumura1, Yasuhide Yamada1, Kei Muro1, Masahiro Gotoh1, Narikazu Boku2, Atsushi Ohtsu2, Fumio Nagashima2, Yasushi Sano2, Manabu Mutoh2 and Yusuke Tanigawara3

1Gastrointestinal Oncology Division, National Cancer Center Hospital, Tokyo, 2Division of Gastrointestinal Oncology/Digestive Endoscopy, National Cancer Center Hospital East, Kashiwa, Chiba and 3Department of Pharmacy, Keio University School of Medicine, Tokyo, Japan

Received February 6, 2006; accepted March 23, 2006; published online May 15, 2006

INTRODUCTION

Oxaliplatin (trans-L-diaminocyclohexane oxalatoplatinum) is a platinum coordination complex. In preclinical studies, oxaliplatin has shown significant activity against a broad spectrum of tumors: murine leukemia, lymphoma, melanoma, lung and colon carcinoma, and fibrosarcoma, and human ovarian cancer, non-small cell lung cancer, neuroblastoma, non-semionomatoe germ cells, erythroleukemia, and breast and colon cancer (1–9).

The pharmacokinetic properties, tolerability and maximum tolerated dose of oxaliplatin have been studied primarily in Western countries (10–11). Additional phase II and phase III studies of oxaliplatin in Western countries demonstrated significant activity for metastatic colorectal cancer, both as a single agent (12) and in combination with 5-fluorouracil and leucovorin (13–18). The FOLFOX regimen of oxaliplatin and infused fluorouracil plus leucovorin should be considered as the standard therapy for patients with advanced colorectal cancer.

In early clinical trials, a phase I study of single-dose oxaliplatin was conducted in Japan (19). However, the criteria for the evaluation of clinical toxicity and the measurement techniques for the pharmacokinetic analysis of oxaliplatin in that study were different from those used in recent trials. Therefore, we conducted another phase I study of oxaliplatin in Japan using the more recent criteria for evaluation of toxicity and new measurement techniques for pharmacokinetic analysis (Inductively Coupled Plasma Mass Spectrometry; ICP-MS), thereby allowing valid comparisons with data from Western
countries. This study was conducted to clarify the safety and pharmacokinetic profile of single-dose oxaliplatin for Japanese patients.

PATIENTS AND METHODS

PATIENT SELECTION

Patients were entered into the study only if they met the following eligibility criteria: histological or cytological confirmation of a malignant tumor, a malignant tumor that was refractory to standard therapy or for which there was no effective therapy, a solid tumor, age between 20 and 74 years, performance status ≤2 on the Eastern Cooperative Oncology Group scale, adequate bone marrow function (absolute white blood cell count 3000–12 000/μl, hemoglobin levels ≥9.0 g/dl and platelet count ≥100 000/μl), adequate liver function (serum total bilirubin level ≤1.5 mg/dl and serum transaminase and alkaline phosphatase levels less than 2.5 times the upper standard limits), adequate renal function (serum creatinine level less than the upper standard limit), normal electrocardiogram, life expectancy of at least 9 weeks and provision of written informed consent. Furthermore, at least 4 weeks must have elapsed since the completion of any previous therapy and patients must have recovered from the toxic effects of any previous therapy. Exclusion criteria include the following: pregnancy, lactation, hepatitis B or C virus infection, human immunodeficiency virus infection, a history of hypersensitivity reaction and patients must have recovered from the toxic effects of any previous therapy. Exclusion criteria include the following: pregnancy, lactation, hepatitis B or C virus infection, human immunodeficiency virus infection, a history of hypersensitivity reaction to any drugs, neurological symptoms, brain metastasis, severe pleural effusion and ascites and any serious medical condition.

TREATMENT SCHEDULE, STARTING DOSE AND DOSE-ESCALATION SCHEDULE

Oxaliplatin was provided by Yakult Honsha Company (Tokyo, Japan) in a 100-mg vial. Oxaliplatin was administered in 250 ml of 5% glucose solution as a 2-h intravenous infusion. Needles or infusion sets containing aluminum components were not used for the preparation or administration of oxaliplatin due to the risk of degradation of the agent. Granisetron was routinely administered by 30 min intravenous infusion as an antiemetic treatment before the administration of oxaliplatin. No other prophylactic premedication was administered. This treatment was repeated every 3 weeks until disease progression or severe toxicity was observed or until 6 cycles were completed.

The starting dose (level 1) of oxaliplatin was 90 mg/m², corresponding to 70% of the previously reported standard dose (130 mg/m²) for oxaliplatin monotherapy. The dose of oxaliplatin at level 2 was 130 mg/m². No more dose escalation was planned, as the objective of this study was to estimate the safety of the standard dose of oxaliplatin. Initially, three patients were treated at each dose level. Three additional patients were entered at a given dose if dose-limiting toxicity (DLT) was observed in 0–2 of the initial three patients. The maximum tolerated dose (MTD) was defined as the dose level at which three of 3–6 patients experienced DLT during the first cycle. If the level 2 dose was not found to be the MTD, the dose at level 2 was defined as the recommended dose. The definition of DLT was as follows: (i) grade 4 hematological toxicities or (ii) grade 3 or 4 non-hematological toxicities except for nausea. No intrapatient dose-escalation was allowed.

In patients receiving the initial cycle of treatment, a subsequent cycle was started after recovery from the toxic effects of the previous cycle. Before the next cycle was started, the leukocyte count had to be 3000–12 000/μl, the platelet count ≥100 000/μl, and the liver and renal function had to satisfy the eligibility criteria. Patients requiring more than 6 weeks to recover from the toxicity of a cycle were withdrawn from the study.

EVALUATION

Patients were evaluated by appropriate investigation, including physical examination, chest X-ray, and computed tomography of the abdomen and chest, before entry into the study to determine the extent of disease. A complete blood cell count, liver function tests, renal function tests and urinalysis were performed for all patients before the study entry, on days 8 and 15 of the initial treatment cycle and before each subsequent treatment cycle. Appropriate investigations were repeated as necessary to evaluate the sites of marker lesions before every other course.

The toxicities were evaluated using the National Cancer Institute common toxicity criteria (20) regarding toxicities other than peripheral sensory neuropathy and by following the Oxaliplatin-specific scale. The definition of the Oxaliplatin-specific scale, which developed as a specific scoring scale for oxaliplatin-inducing peripheral sensory neuropathy, was as follows: grade 1—transient dysesthesia and/or paresthesia lasting less than 7 days; grade 2—transient dysesthesia and/or paresthesia lasting more than 7 days or longer; and grade 3—proprioceptor impairment inducing functional discomfort in everyday life (difficulty fastening buttons, writing, etc). Antitumor activity was evaluated in accordance with the World Health Organization scale (21).

PHARMACOKINETICS

Blood was collected to determine the total platinum concentration in plasma, the ultrafiltrate platinum concentration in plasma and the platinum concentration in blood cells. Blood specimens were obtained immediately before infusion, just before the end of infusion and at 0.25, 0.5, 0.75, 1, 3, 6, 9, 24, 48, 168, 336 and 504 h after the infusion during the initial cycle of the treatment. Furthermore, blood samples were taken before infusion, just before the end of infusion and at 504 h after the infusion for the second and subsequent cycles. Blood samples were collected into polyester tubes (VP-H070; Terumo Co., Tokyo, Japan) containing sodium heparin and immediately centrifuged (1000 g, 10 min, 4°C). From the
upper layer, an aliquot of plasma was preserved for total platinum determination. The remainder of the supernatant was processed for ultrafiltrate platinum separation (1000 g, 60 min, 4°C using Amicon CentriFree™ ultrafiltration filters, cut-off: 30 kD; Millipore Co., Bedford, MA, USA). The red blood cells in the lower layer were washed twice with equal volumes of 4°C saline. All samples (each about 1 ml) were frozen until analysis. Fractionated urine was collected in glass containers before infusion and from the start of infusion to 24 h after administration of the drug. The total volume of each fraction was recorded and a 100-ml aliquot was obtained and frozen at −20°C until analysis.

All of the samples were analyzed by ICP-MS (Inductively Coupled Plasma Mass Spectrometry). Samples were diluted 1/20 (for plasma and red blood cells) and 1/10 (for free platinum) in an aqueous solution containing 1% nitric acid and 100 μg/l of europium used as an internal standard.

The plasma concentration–time data following administration was analyzed by a noncompartmental method using the computer program WinNonlin (Ver.3.1, Pharsight Co., Mountain View, CA, USA). The peak plasma concentration, C_{max}, and the time to reach the peak concentration, T_{max}, were recorded directly from the experimental observations. The area under the plasma concentration–time curve (AUC) from time 0 to T, AUC_{(0-T)}, where T is the time of the last measurable concentration, was calculated by the trapezoidal method.

ETHICS

This trial was approved by the institutional review board of the clinical oncology program at all hospitals participating in this study and conducted in accordance with the Japanese Good Clinical Practice guidelines.

This study was supported by Yakult Honsha Co., Ltd.

RESULTS

PATIENT CHARACTERISTICS

From June 1999 to January 2000, nine patients were enrolled in this study. Their characteristics are listed in Table 1. The four men and five women had a median age of 51 years (range, 31–61 years). Four patients had a performance status of 0, while the other five had a performance status of 1. All tumors were colorectal cancer; four were specifically colon cancer and the other five had a performance status of 1. All tumors were previously undergone surgical resection for primary tumors, and three had also received radiation therapy and all had received prior chemotherapy. The mean number of previous chemotherapy regimens was 2.8 (range: 2–3).

Three patients were entered at dose level 1 and 6 patients at dose level 2. A total of nine cycles at dose level 1 was given (median cycles per patient: 3; range: 2–4) and a total of nine cycles at dose level 2 was given (median cycles per patient: 1.5; range: 1–2).

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Total no. of patients</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
</tr>
<tr>
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</tr>
<tr>
<td>Female</td>
<td>5</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>51 (31–61)</td>
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<td>ECOG* performance status</td>
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<tr>
<td>0</td>
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</tr>
<tr>
<td>1</td>
<td>5</td>
</tr>
<tr>
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</tr>
<tr>
<td>Colon</td>
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</tr>
<tr>
<td>Rectum</td>
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<tr>
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</tr>
<tr>
<td>Radiation</td>
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</tr>
<tr>
<td>Chemotherapy</td>
<td>9</td>
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</table>

*Eastern Cooperative Oncology Group.

TOXICITY

Toxicity was assessed in all nine patients. At dose level 1, none of the patients exhibited toxicities of grades 2, 3 or 4 during the first cycle. At dose level 2, none of the patients exhibited grade 4 toxicity, while grade 3 toxicity was seen as a decline in serum sodium and grade 2 toxicity was evident as anemia, neurotoxicity, anorexia, nausea, vomiting, fatigue and ALT elevation during the first cycle. The level 2 dose was not found to be the MTD, but dose level 2 (130 mg/m²) was judged to be the recommended dose.

Table 2 shows the highest grade of toxicities during all treatment courses according to patients. At dose level 1, grade 4 neutropenia and grade 2 leukopenia were observed in one of three patients, and another patient developed grade 2 fatigue. At dose level 2, grade 2 anemia (2/6), neurotoxicity (1/6), anorexia (2/6), nausea (3/6), vomiting (3/6), diarrhea (1/6), fatigue (3/6) and ALT elevation (1/6) were observed, and grade 3 decreases in serum sodium (1/6) and potassium (1/6) were observed.

In all nine patients and all 18 cycles of treatment, neurotoxicity developed. Neurotoxicity in all patients receiving nine cycles of the level 1 dose (90 mg/m²) was grade 1. Neurotoxicity in patients receiving the level 2 dose (130 mg/m²) was seen as grade 1 in seven cycles and grade 2 in two cycles. This neurotoxicity was evident as a transient peripheral neuropathy manifesting as paresthesia and dysesthesia in the extremities and perioral area, triggered or enhanced by exposure to cold. There was no evidence of grade 3 neurotoxicity such as fine movement disturbance (difficulty fastening buttons, writing, etc) or moderately sensitive ataxia. These symptoms lasted between a few hours and a few days (grade 1: <7 days, grade 2: ≥7 days) and were reversible. Cumulative neurologic toxicity was not definitively observed in this study.

Major adverse reactions included neurotoxicity, myelosuppression and gastrointestinal toxicities; most cases were grades 1 or 2. No serious renal toxicity or hepatotoxicity,
Table 2. Toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>90 mg/m² (n = 3)</th>
<th>130 mg/m² (n = 6)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>G1</td>
<td>G2</td>
</tr>
<tr>
<td>Leukopenia</td>
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<td>1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
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<td>0</td>
</tr>
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<td>Thrombocytopenia</td>
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</tr>
<tr>
<td>Neurotoxicity</td>
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<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
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<td>0</td>
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<tr>
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<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
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<td>0</td>
</tr>
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<td>1</td>
</tr>
<tr>
<td>Alopecia</td>
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</tr>
<tr>
<td>ALT</td>
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<td>0</td>
</tr>
<tr>
<td>Creatinine</td>
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<td>0</td>
</tr>
<tr>
<td>Decline of serum sodium</td>
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<td>0</td>
</tr>
<tr>
<td>Decline of serum potassium</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

G, grade; ALT, alanine aminotransferase.

which usually occurs with other platinum agents, was observed. No patients discontinued the oxaliplatin regimen due to toxicity. No dose reduction was required in any patient in any administration. No treatment-related deaths occurred during the study.

RESPONSE

Response was assessed in all nine patients. No objective responses were seen. No change occurred in two of the three patients at dose level 1 and in three of the six patients at dose level 2, while the remaining four patients showed signs of progressive disease.

PHARMACOKINETICS

Pharmacokinetic analysis was performed on blood and urine specimens from all nine patients. The pharmacokinetic parameters are summarized in Table 3. Each parameter showed relatively small inter-individual variability.

The mean plasma concentration–time profiles are shown in Fig. 1. A bi-exponential open model best described the disappearance of platinum in the plasma at both dose levels, and a tri-exponential open model best described the disappearance of ultrafilterable platinum in the plasma at both dose levels.

The peak plasma concentration ($C_{\text{max}}$) and the AUC for platinum and ultrafilterable platinum in the level 2 patients (130 mg/m²) were larger than those in the level 1 patients (90 mg/m²) (Table 3). In the second cycle, the trough values of the platinum and ultrafilterable platinum in the plasma were higher, although by less than 2-fold, than in the first cycle ($P < 0.05$) (Table 4). Furthermore in the second cycle, the trough value of the platinum concentration in the red blood cells was higher, although by less than 2-fold, than that in the first cycle ($P < 0.001$) (Table 4). These findings on the platinum accumulation in the plasma and the red blood cells were observed at both dose levels.

The mean urinary excretion of oxaliplatin for 24 h was $28.4 \pm 7.6\%$ of the level 1 administered dose (90 mg/m²) and $33.9 \pm 8.8\%$ of the level 2 administered dose (130 mg/m²).

DISCUSSION

Oxaliplatin is recognized as one of the key drugs for the treatment of colorectal cancer, and in particular the FOLFOX regimen of oxaliplatin and infusional fluorouracil plus leucovorin is the standard therapy for patients with metastatic colorectal cancer in Western countries (17,18). We conducted this phase I study in Japanese patients to confirm the safety and pharmacokinetics profile of oxaliplatin monotherapy administered as 130 mg/m² in a 2-h infusion every 3 weeks as recommended worldwide.

In our trial, the major adverse reactions included myelosuppressive, neurological and gastrointestinal toxicities, although most were grades 1 and 2 at both dose levels of 90 and 130 mg/m². The incidence and degree of toxicity did not differ much from those of other phase I studies in Western countries (10,11). Earlier phase I (10,11) and phase II (13–16) studies in Western countries indicated that peripheral neuropathy, the most severe result of toxicity from oxaliplatin therapy, can be maintained at or below grade 2 at the recommended dose of 130 mg/m², and the toxicity profile is particular in its reversibility, as well as in its rapid onset, location and intensity of sensory disturbance with the absence of a motor component. Our results regarding neurotoxicity were almost the same as those of the Western phase I and II studies (10,11,13–16). However, the cumulative neurological toxicity reported in Western phase II studies (13–16) was not clearly observed in our study. Extra et al. (11) reported that grade 3 neurotoxicity has been observed at cumulative doses greater than 540 mg/m². Because the patients were given at most 360 mg/m² (median dose: 270 mg/m²) in this study, we did not expect to observe this cumulative phenomenon.

A bi-exponential open model best described the disappearance of platinum in the plasma at both dose levels of 90 and 130 mg/m², and a tri-exponential open model best described the disappearance of ultrafilterable platinum in the plasma at both dose levels. The same findings were observed in other studies (10,19). In their assessment of dose proportionality for total plasma platinum, Taguchi et al. (19) reported that the mean $C_{\text{max}}$ and AUC$_{0-24}$ for single 1-h infusion increased in a dose-related manner over the dose range of 20–180 mg/m². Our result was not inconsistent with the manner of dose proportionality.

Pharmacokinetic parameters showed relatively small inter-individual variability in our data. These parameters of platinum...
in plasma and plasma ultrafiltrate taken from Western patients administered 2-h oxaliplatin infusion of 130 mg/m² were previously reported, and the values were measured by ICP-MS (Inductively Coupled Plasma Mass Spectrometry), which we used in our study. These values of the $C_{\text{max}}$, AUC, terminal $t_{1/2}$ and CL were very similar to our data in the patients given the 130 mg/m² dose (10).

The elimination of platinum occurs mainly in urine rather than in feces (10). In this study, mean urinary excretion of oxaliplatin for 24 h was 33.9% of the level 2 administered dose (130 mg/m²). This value was almost identical to the value of 35.9% in Western patients given a dose of 135–150 mg/m² (11).

Graham et al. (10) reported that limited platinum accumulation was observed in plasma and blood cells, but not in plasma ultrafiltrate. Our data on the platinum accumulation in Japanese patients was the same as that in Western patients, except for the data on the plasma ultrafiltrate. However, the degree of accumulation was less than 2-fold in both studies.

In conclusion, the worldwide standard dose of 130 mg/m²/q3w for oxaliplatin monotherapy is also acceptable for treating...
Japanese patients, with only mild myelosuppression, neurotoxicity and gastrointestinal toxicities. No racial difference was suggested in the pharmacokinetics of oxaliplatin. A phase II study of oxaliplatin monotherapy and a phase I/II study of the combination of oxaliplatin with fluorouracil plus leucovorin have finished in Japanese patients with metastatic colorectal cancer. Further large clinical trials on oxaliplatin are warranted to evaluate the toxicity profiles and the clinical antitumor activity in Japanese patients.

Acknowledgments

We are grateful to Drs Y. Sakata, Y. Sasaki, I. Hyodo and T. Yamao for their kind advice, and many other participants of this study. We also thank S. Sugimoto, M. Matsuo, N. Sekine and H. Ogawa for their assistance in data management. This study was supported by the Yakult Honsha Co., Ltd., Tokyo, Japan.

References