Feasibility of Oxaliplatin and Infusional Fluorouracil/Leucovorin (FOLFOX4) for Japanese Patients with Unresectable Metastatic Colorectal Cancer

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Background: A combination of oxaliplatin and infusional fluorouracil/leucovorin (FOLFOX4) is one of the standard regimens for palliative and adjuvant chemotherapy for colorectal cancer. However, the feasibility of FOLFOX4 for Japanese patients has not been determined. We conducted this prospective study to evaluate the feasibility of FOLFOX4.

Methods: Previously treated or untreated patients with unresectable metastatic colorectal cancer were enrolled. The primary endpoint was the rate of completion which was defined as completion of the first 4 cycles with relative dose-intensity of oxaliplatin of 80% or higher.

Results: Of the 32 enrolled patients, 31 received FOLFOX4. Twenty-four patients (75%) had received prior chemotherapy. The rate of completion of the first four cycles was 87% (27/31; 95% CI, 70.2–96.4%). With the median number of cycles of nine (range, 1–26), grade 3 or 4 hematological toxicity and non-hematological toxicity were seen in 12 (39%) and 5 (16%) patients, respectively. Grade 1 or 2 sensory neuropathy was seen in 28 patients (90%), but no grade 3 or 4 neuropathy was seen. Grade 1 or 2 allergic reaction was seen in five patients (16%). One patient developed fatal interstitial pneumonitis and died of respiratory failure. Objective response rate was 28.6% (6/21; 95% CI, 11.3–52.2%) in the patients with measurable lesions. Median progression-free survival was 6.5 months (95% CI, 4.6–8.5 months) in all patients.

Conclusions: The completion rate of the first four cycles was as high as expected with manageable toxicity, although fatal pneumonitis developed in one case. FOLFOX4 is feasible for Japanese patients.

Key words: FOLFOX – oxaliplatin – feasibility study – colorectal cancer – interstitial pneumonitis

INTRODUCTION

Oxaliplatin is a cytotoxic agent from the dianimocyclohexane platinum family that was first synthesized by Kidani in Japan in 1976 (1). However, its clinical development has mainly been conducted in Europe. Oxaliplatin and infusional fluorouracil (5-FU)/leucovorin (LV; LV5FU2) regimen was compared with infusional 5-FU/LV (LV5FU2) in a randomized-controlled trial, and patients treated with FOLFOX4 showed significantly prolonged progression-free survival (PFS) and better response rate (RR) (2). In a US randomized study, FOLFOX4 proved superior to irinotecan and bolus 5-FU/LV (IFL) in terms of overall survival (OS), time to progression (TTP) and RR (3). Furthermore, FOLFOX4 improved the disease-free survival for patients with completely resected stage II and III colon cancer compared to LV5FU2 in a randomized-controlled trial (4). FOLFOX4 is one of the
standard regimens both for palliative and adjuvant chemotherapy for colorectal cancer.

In Japan, phase I and II studies of oxaliplatin as a single agent were conducted (5,6). Recommended dose (RD) was determined to be 130 mg/m² in a tri-weekly regimen, toxicity was tolerable and RR was 8.8% (5/57, 95% CI, 2.9–19%) for patients refractory to fluoropyrimidine-based regimen. After the single agent studies, a phase I/II study of oxaliplatin with bolus 5-FU/levofolinate (I-LV) was conducted because only a bolus 5-FU/I-LV regimen (Roswell Park Memorial Institute regimen) was available at that time in Japan. In that study, RR was 64% (9/14; 95% CI, 35–87%) in patients who received the RD, median TTP was 171 days and median survival time was 603 days in all patients (7).

In March 2005, oxaliplatin (Elplat, Yakult Honsha Co. Ltd., Tokyo, Japan) was approved in Japan. The prescribing information for Elplat recommends that oxaliplatin should be administered in a FOLFOX4 regimen referring to that of the USA, because it has the most reliable evidence of safety and efficacy.

However, little is known about the feasibility of FOLFOX4 in Japanese. We therefore conducted a feasibility study of FOLFOX4 in Japan. The primary endpoint was completion rate of the first four cycles. Secondary endpoints were incidence and grade of adverse events, RR, PFS and OS. This study was a prospective single-arm study conducted in a single institution.

PATIENTS AND METHODS

PATIENT SELECTION

At the time of study enrollment, patients were required to fulfill the following criteria: histologically confirmed adenocarcinoma, unresectable metastatic colorectal cancer, age ≥20 and ≤75 years, performance status (ECOG) of 0 or 1, no prior treatment with oxaliplatin, leukocyte count ≥3000 and ≤12 000/mm³, absolute neutrophil count ≥1500/mm³, platelet count ≥100 000/mm³, total bilirubin ≤1.5 mg/dl, aspartate aminotransferase (AST) ≤100 IU/l, alanine aminotransferase (ALT) ≤100 IU/l, serum creatinine ≤1.5 mg/dl, written informed consent, life expectancy ≥3 months and prior therapy completed at least 2 weeks before enrollment. Exclusion criteria were co-existence of cancers other than colorectal cancer, active infection with fever higher than 38°C, sensory neuropathy, watery diarrhea, symptomatic brain metastasis, blood transfusion or administration of granulocyte colony-stimulating factor 14 days before enrollment, abnormality in electrocardiogram that required treatment, severe complication and current pregnancy or lactation.

TREATMENT PLAN

FOLFOX4 consisted of oxaliplatin at a dose of 85 mg/m² on day 1 and I-LV at 100 mg/m² as a 2-h infusion followed by bolus 5-FU at 400 mg/m² and a 22-h infusion of 5-FU at 600 mg/m² on days 1 and 2 every 2 weeks. A 5-hydroxytryptamine-3 antagonist and dexamethasone were administered as routine antiemetic prophylaxis. An implanted central venous port and disposable pump were used for administrations on an outpatient basis.

Physical examinations and laboratory tests were performed weekly during the first two cycles and bi-weekly thereafter. Toxicity was graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 in Japanese (8). Subsequent cycles were repeated if the following were met: an absolute neutrophil count ≥1500/mm³, platelet count ≥75 000/mm³, all non-hematological toxicity (except for fatigue, anorexia, nausea and vomiting if can be controlled by antiemetics) had resolved to grade 1 and no infection with fever over 38°C. Patients were allowed to have a maximum of additional 2-week suspension from the planned administration date.

The dose of 5-FU was reduced for grade 3 or 4 leukopenia, neutropenia, thrombocytopenia, neutropenic fever and other non-hematological toxicity except for fatigue, anorexia, nausea/vomiting that can be controlled by antiemetics and transient abnormality in electrolytes. In the case of treatment suspension over 8 days due to toxicity, the dose of 5-FU was reduced. The dose of oxaliplatin was reduced for neutropenic fever, other grade 4 non-hematological toxicity, grade 2 neuropathy persistent between cycles and grade 3 neuropathy. In the case of grade 3 neuropathy persistent between cycles, administration of oxaliplatin was discontinued. If the patient required dose reduction more than twice, treatment was discontinued. Treatment was continued until disease progression, unacceptable toxicity or withdrawal of consent.

ENDPOINTS

We evaluated the feasibility of FOLFOX4 with the rate of completion. Completion was defined as completion of the first four cycles with relative dose-intensity (RDI) of oxaliplatin of 80% or higher. The rate of completion was calculated by the ratio of number of patients who achieved completion to all treated patients. Dose-intensity (DI) of the first four cycles was calculated as total cumulative dose of the first four cycles divided by the duration of dosing ([(initial date of fourth cycle)−(initial date of first cycle)]/7) (9). RDI was calculated as the dose-intensity divided by the planned DI, multiplied by 100. Planned DIs of oxaliplatin, bolus 5-FU and infusional 5-FU were 42.5 mg/m²/week, 400 mg/m²/week and 600 mg/m²/week, respectively.

Response rate was calculated for the patients who had measurable lesions using Response Evaluation Criteria in Solid Tumor (RECIST) (10). Tumor measurements were performed every 8 weeks during therapy with computed tomography. PFS was defined as the time between the date of enrollment and the date of disease progression or death from any cause when no progression was recorded. Survival was defined as the time between the date of enrollment and the date of death.
STATISTICAL CONSIDERATION

The primary endpoint was completion rate of the first four cycles. Enrollment of 30 patients provided reasonable width of the 95% CI to estimate completion rate. The Kaplan–Meier method was used to describe the distribution of PFS, OS and the cumulative incidence of neuropathy with Dr SPSS II for windows, release 11.0.1J.

This study was approved by the National Cancer Center Institutional Review Board in adherence with provisions set forth in the Helsinki Agreement.

RESULTS

PATIENT CHARACTERISTICS

Between April 2005 and July 2005, 32 patients were enrolled. Baseline patient characteristics are listed in Table 1. Twenty-four patients (75%) had received prior chemotherapy. Eleven patients received one regimen and 13 patients received two or more regimens. One patient never received FOLFOX4 because of rapid disease progression after enrollment and was excluded from the analysis.

TOXICITY

With a median follow-up period of 15.4 months (range: 2.1–18.8 months), all patients discontinued the protocol treatment. The median number of cycles was nine (range: 1–26). Twenty-three patients (74%) discontinued FOLFOX4 owing to disease progression and seven patients (23%) discontinued FOLFOX4 owing to toxicity, mainly neuropathy and allergic reaction. The incidence of toxicity is shown in Table 2. Grade 3 or 4 hematological toxicity and non-hematological toxicities are summarized in Table 2.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>No. of patients</th>
<th>All grades (%)</th>
<th>Grade 3/4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucocytes</td>
<td>11</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>7</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>11</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Platelets</td>
<td>13</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Creatinine</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>9</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>AST</td>
<td>15</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>ALT</td>
<td>16</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Fever</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>15</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>3</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>6</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>15</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Hand–foot skin reaction</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>19</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

AST, aspartate aminotransferase; ALT, alanine aminotransferase.
non-hematological toxicity were seen in 12 (39%) and 5 (16%) patients, respectively.

 Almost all patients except those who withdrew early presented sensory neuropathy. Nineteen patients (61%) and nine patients (29%) suffered from grade 1 neuropathy and grade 2 neuropathy, respectively, and four patients refused to continue FOLFOX4 owing to neuropathy. No grade 3 neuropathy was seen. Cumulative incidence of neuropathy is shown in Fig. 1.

 Allergic reaction occurred in five patients (16%). The median number of cycles when the first allergic reaction occurred was 8 (range: 6–10). All patients recovered from allergic reaction after suspending the infusion of oxaliplatin and administration of steroid. Two other patients discontinued FOLFOX4 after the first presentation of allergic reaction, regardless of prophylactic administration of steroid and an antihistamine agent. Two other patients discontinued FOLFOX4 5 months after progression with irinotecan therapy and that patient continued 4 cycles with premedications until disease progression.

 Five patients (16%) were hospitalized owing to toxicity (Table 3). One patient was admitted to hospital after 11 cycles, complaining of shortness of breath. He was diagnosed as interstitial pneumonitis and received steroid pulse therapy and assisted ventilation; however, he died of respiratory failure 33 days after onset.

 **COMPLETION RATE**

 DIs in first four cycles of oxaliplatin, bolus 5-FU and infusional 5-FU were 39.2 mg/m² (RDI: 92%), 367 mg/m² (RDI: 92%) and 551 mg/m² (RDI: 92%), respectively. Completion rate was 87% (27/31; 95% CI, 70.2–96.4%). Four patients could not complete the first four cycles with DI of oxaliplatin of 80% or higher. DIs of oxaliplatin were under 80% in 3 patients (73.7, 74.7 and 77.8%) because treatment suspension was required owing to hematological toxicity and fever. One patient discontinued FOLFOX4 after the first cycle because of disease progression.

 **EFFICACY**

 Objective response rates were 28.6% (6/21; 95% CI, 11.3–52.2%) in all the patients with measurable lesions and 60.0% (3/5; 95% CI, 14.7–94.7%) in the first-line treatment patients. All responses observed were partial response. Median progression-free survival was 6.5 months (95% CI, 4.6–8.5 months) and median survival time has not been reached yet (Figs 2 and 3).

 **DISCUSSION**

 In this prospective trial, we evaluated the feasibility of FOLFOX4. However, there is no clear definition of feasibility in chemotherapy. Because the protocol allowed inclusion of patients with prior chemotherapy in this trial, efficacy was not a good primary endpoint. We reviewed some reports of FOLFOX4 and searched for the most appropriate primary endpoint in this feasibility study. RDis of oxaliplatin for FOLFOX4 as first-line chemotherapy were reported to be 88% and 73% (2). In other studies, RDis of oxaliplatin for FOLFOX4 as second-line treatment and third-line treatment in all cycles were 87.8 and 80%, respectively (9,11). In this study, we considered FOLFOX4 to be feasible if the patient completes the first four cycles of FOLFOX4 with DI of

Table 3. Admission due to toxicity

<table>
<thead>
<tr>
<th>Case</th>
<th>Toxicity</th>
<th>Cycles</th>
<th>Period (day)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Grade 3 AST, ALT and anorexia</td>
<td>4</td>
<td>10</td>
<td>FOLFOX4 was continued after dose reduction</td>
</tr>
<tr>
<td>2</td>
<td>Grade 2 allergic reaction</td>
<td>6</td>
<td>2</td>
<td>FOLFOX4 was discontinued</td>
</tr>
<tr>
<td>3</td>
<td>Grade 3 infection with normal ANC</td>
<td>7</td>
<td>14</td>
<td>FOLFOX4 was continued</td>
</tr>
<tr>
<td>4</td>
<td>Grade 3 hemorrhage, stomach</td>
<td>10</td>
<td>10</td>
<td>FOLFOX4 was continued</td>
</tr>
<tr>
<td>5</td>
<td>Grade 5 pneumonitis</td>
<td>11</td>
<td>28</td>
<td>Dead</td>
</tr>
</tbody>
</table>

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ANC, absolute neutrophil count.
oxaliplatin of 80% or higher. Twenty-seven patients completed four cycles of oxaliplatin with DI of oxaliplatin of 80% or higher and the completion rate was 87% (95% CI, 70.2–96.4%). This completion rate was satisfactory. Although this endpoint was limited to evaluating early treatment compliance, FOLFOX4 is feasible for Japanese patients.

RR and median PFS (or TTP) in patients who received the first-line and second- or third-line treatment were 45–50.7% and 8.7–9.0 months and 9.9–13% and 4.6–4.8 months, respectively (2,3,9,11). It is difficult to evaluate the efficacy of FOLFOX4 from the results of this study because the enrolled patients were heterogeneous in terms of prior treatments. However, considering that three-quarters of the patients received prior chemotherapy, RR of 28.6% and median PFS of 6.5 months seem promising.

In this study, the incidence of grade 3 or 4 neutropenia was relatively low (23%) compared with those (41.1–50%) in Western and US phase III trials (2–4,9). The lower incidence of neutropenia might have been due to the fact that younger patients with better PS were enrolled in this study than in other studies. Although most patients suffered from sensory neuropathy, no neuropathy of grade 3 or higher was observed. One of the reasons for this might be that the time to treatment discontinuation was shorter and cumulative dose of oxaliplatin was lower because three-quarters of the patients had received prior chemotherapy.

We experienced five cases of grade 1 or 2 allergic reactions, but there was no case of grade 3 or higher. All patients presented skin rashes during infusion of oxaliplatin. After suspending the infusion of oxaliplatin and administration of an intravenous steroid, all of the patients recovered from allergic reactions. Allergic (or hypersensitivity) reactions to oxaliplatin have been described in the literature and their clinical features are skin rashes, urticaria, erythema, pruritus, hypotension and dyspnea. The exact mechanisms of allergic reactions are not clear, but they are thought to correlate to type I immunoglobulin E mediated allergy (12). In the largest FOLFOX4 trial, the incidences of all grade and grade 3 or 4 allergic reaction were 10.3 and 2.9%, respectively (4).

The median number of oxaliplatin cycles was 7–9 in some studies (13–15). The number of cycles when allergic reaction occurred in this trial and clinical symptoms are in accordance with those in previous studies. Standard prophylactic treatment has not been established, and the usefulness of prophylactic antihistamines and steroids is controversial (13–15). If previous reaction is not life-threatening, extending the infusion duration of oxaliplatin may be worthwhile in subsequent cycles (13,14). In this study, three of the four patients who received re-challenge of FOLFOX4 could continue FOLFOX4 with premedications, but one patient presented allergic reaction again and discontinued FOLFOX4. Close monitoring is therefore required in the case of re-exposure to oxaliplatin.

Fatal pneumonitis, which might have been caused by oxaliplatin, developed in one patient during the treatment. Pulmonary toxicity as a result of oxaliplatin is rare (16), but acute lung diseases, including eosinophilic lung disease and interstitial pneumonitis, have been described in the literature (17–19). The incidence of acute lung injury owing to gefitinib, a tyrosine kinase inhibitor of epidermal growth factor receptor, was reported to be higher in Japan (2%) than in the USA (0.3%) (16). We have to carefully observe whether the incidence of pneumonitis as a result of oxaliplatin in Japan is higher or not.

In conclusion, this feasibility study of FOLFOX4 demonstrated high completion rate of the first four cycles. Toxicity was mild except for in one case of interstitial pneumonitis and could be managed almost on an outpatient basis. In Japan, FOLFOX4 can be a standard regimen as well as irinotecan and infusional 5-FU/LV (FOLFIRI). Overseas, bevacizumab, a recombinant, humanized monoclonal antibody targeting vascular endothelial growth factor, with chemotherapy has proved to have a survival benefit, and FOLFOX or
FOLFIRI with bevacizumab is the standard of care for most patients with unresectable metastatic colorectal cancer (20,21). The combination of FOLFOX4 and bevacizumab is now being investigated in Japan. This combination would be one of the standard treatments even for Japanese in the near future.

**Conflict of interest statement**
None declared.

**References**