Clinical and Economic Evaluation of First-line Therapy with FOLFIRI or Modified FOLFOX6 for Metastatic Colorectal Cancer

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Objective: Recently, significant progress in treatment of metastatic colorectal cancer has been achieved. Either FOLFIRI (fluorouracil, leucovorin and irinotecan) or modified FOLFOX6 (fluorouracil, leucovorin and oxaliplatin, oxaliplatin dose 85 mg/m²) is selected as first-line therapy in clinical practice in Japan. However, economic burden of colorectal cancer is considerable.

Methods: Analysis was made for all patients who were treated with FOLFIRI or modified FOLFOX6 for metastatic colorectal cancer. Regimen of FOLFIRI was compared with modified FOLFOX6 under consideration from clinical and economic standpoints. Progression free survival, response, toxicity and cancer care cost in patients with metastatic colorectal cancer was analyzed. Direct costs based on the fee schedule of the Japanese national health insurance were calculated.

Results: Median progression free survival was 7.7 months for FOLFIRI versus 8.4 months for modified FOLFOX6 (P = 0.48). Overall cost for first four cycles was ¥756 284 for FOLFIRI and ¥1 081 162 for modified FOLFOX6 (P < 0.0001). All grade alopecia was significantly more frequent with FOLFIRI than with modified FOLFOX6 (P = 0.04). All grade neuropathy was more observed with modified FOLFOX6 than FOLFIRI (P = 0.0002).

Conclusions: FOLFIRI is inexpensive in the initial stage of treatment which a number of patients can receive chemotherapy than modified FOLFOX6 as first-line therapy for metastatic colorectal cancer in Japanese national insurance system.

Key words: costs and cost analysis – FOLFIRI protocol – FOLFOX-6 protocol – colorectal neoplasms

INTRODUCTION

Cancer is a major public health problem in Japan as well as the USA and European countries. Currently, one of three deaths in Japanese is due to cancer. Especially, the incidence of colorectal cancer (CRC) is rapidly increasing and CRC is the highest cause of cancer deaths in women, and the third highest cause in men (1). In addition, almost half of patients diagnosed with CRC will develop metastatic disease (2). Recently, significant progress in treatment of metastatic colorectal cancer (mCRC) has been achieved with development of chemotherapy regimens containing fluorouracil (5-FU), irinotecan and oxaliplatin (3). Additionally, targeted monoclonal antibodies, including bevacizumab and cetuximab, have improved treatment outcome (4–6). In Japan, however, bevacizumab and cetuximab were approved for metastatic or recurrent CRC in 2007 and in 2009, respectively. Either FOLFIRI (fluorouracil, leucovorin and irinotecan) or modified (m) FOLFOX6 (fluorouracil, leucovorin and oxaliplatin, oxaliplatin dose 85 mg/m²) has been selected as first-line therapy in clinical practice until 2009. The result of
GERCOR study, comparing FOLFIRI with FOLFOX6 (fluorouracil, leucovorin and oxaliplatin, oxaliplatin dose 100 mg/m²), indicated that there was no statistically significant difference in median progression free survival (PFS) as first-line therapy (7). The choice of first-line therapy has been mainly decided according to physician’s favor and toxicity profiles of these regimens.

Although development of chemotherapy for mCRC has prolonged overall survival, new therapeutic options dramatically increased the cost of treatment (8,9). Elevating cost of cancer care, especially cancer drug costs has been recognized as serious problem based on long recession in Japanese society. There are few researches for cost of cancer chemotherapy in Japan and most of the pharmacoeconomic reports are carried out based on model analysis. To make decision in clinical practice, however, it is necessary to take not only cost of anticancer drugs but also cost of supportive care into consideration. The objective of our analysis is to compare FOLFIRI with mFOLFOX6 in mCRC patients under consideration from clinical and economic standpoints in the context of Japanese clinical practice.

PATIENTS AND METHODS

This was a retrospective study of all patients who were treated for mCRC at Saitama Medical University International Medical Center-Comprehensive Cancer Center (SMU-CC) between April 2007 and January 2009. This analysis was approved by the Institutional Review Board of Saitama Medical University International Medical Center.

SELECTION OF PATIENTS

All patients received as first-line therapy either FOLFIRI or mFOLFOX6 at SMU-CC in clinical practice were included. Patients were required to have histologically proven adenocarcinoma of the colon or rectum; metastatic or recurrent disease; to be between 20 and 75 years of age; and a World Health Organization (WHO) performance status of 0–2. Patients receiving fewer than four cycles of chemotherapy for a reason other than disease progression or death and having already received initial chemotherapy as first-line therapy for CRC at other hospital were excluded from this analysis.

CHEMOTHERAPEUTIC REGIMENS

FOLFIRI regimen consisted of l-leucovorin (l-LV) 200 mg/m² as a 2-h infusion, and irinotecan 180 mg/m² given as a 90-min infusion, followed by bolus 5-FU 400 mg/m² and a 46-h infusion 5-FU 2,400 mg/m². mFOLFOX6 regimen consisted of the same l-LV plus 5-FU regimen, with the addition of oxaliplatin 85 mg/m² given as a 2-h infusion, concurrent with l-LV. Granisetron and dexamethasone were administered to prevent acute emesis. These regimens were repeated every 2 weeks. In all cases, 5-FU continuous infusion was given using a portable disposable pump on outpatient basis. Each oncologist considering of patient’s preference decided the choice of regimen. Treatment was continued until unacceptable toxicity, patient refusal to continue chemotherapy, tumor progression or death.

CLINICAL ASSESSMENT

PFS was defined as time duration from the start date of Cycle 1 to tumor progression. We also assessed tumor response by using Response Evaluation Criteria in Solid Tumors (RECIST) (10). Toxicity was evaluated according to Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) (11). Relative dose intensity was calculated based on the ratio of the drug doses actually delivered in the originally expected time over the expected dose in the expected time.

ECONOMIC ANALYSIS

We carried out cost-minimization analysis based on the assumption that effectiveness of FOLFIRI and mFOLFOX6 was similar (7). Generally, costs were collected over the total duration of patient survival. However, it is difficult to evaluate costs of overall survival because the choice of second- and third-line therapies for mCRC is differ widely in individuals. Therefore, we collected costs during PFS to evaluate two regimens as first-line therapy. Primary outcome of this cost analysis was costs for first four cycles (8 weeks) because first evaluation of chemotherapy was performed after four cycles and almost all patients were likely to receive full-dose chemotherapy in four cycles.

This analysis was conducted from the perspective of the health care payer. We calculated direct costs based on the fee schedule of the Japanese national health insurance. Hospital and outpatient resources related to chemotherapy and adverse events were collected until unacceptable toxicity, patient refusal to continue chemotherapy, tumor progression or death. Overall costs included all direct costs associated with hospitalization for chemotherapy or for management of adverse events, anticancer drugs and antiemetics, additional prescribed drugs for adverse events, infusions on out-patient basis, visits to health professionals due to adverse events or follow-up and all examinations. Additional prescribed drugs for adverse events contained outpatient drug costs, estimated based on the fee schedule of the Japanese national health insurance. We did not include traveling costs of each patient.

STATISTICAL ANALYSIS

Differences in quantitative parameters, including economic data, were tested using the non-parametric Mann–Whitney test. Differences in qualitative parameters were tested using the χ² test or Fisher’s exact test. PFS was estimated by the Kaplan–Meier method, and values were compared using the
log-rank test. *P* value of <0.05 was considered as statistically significant. All statistical analyses were carried out using the SPSS statistical software (version 17.0).

**RESULTS**

From April 2007 to January 2009, 247 patients with metastatic or recurrent CRC visited department of medical oncology at SMU-CC to receive first-line chemotherapy. A total of 193 patients were excluded, 161 patients had already received initial chemotherapy at other hospital, 18 patients did not receive FOLFIRI or mFOLFOX6, 14 patients received fewer than four cycles of chemotherapy. In total, 54 patients were included in this analysis, 30 patients received FOLFIRI and 24 patients received mFOLFOX6. Characteristics of 54 included patients were reported in Table 1. The patients were well balanced between two regimens, except for performance status and primary site.

**Clinical data were shown in Table 2.** Median PFS was 7.7 months for FOLFIRI versus 8.4 months for mFOLFOX6 (*P* = 0.48). Overall response rates were 47% with FOLFIRI versus 42% with mFOLFOX6. There were no statistically significant difference in number of treatment cycles and visits between two regimens. One patient received FOLFIRI was hospitalized for febrile neutropenia. Relative dose intensity for irinotecan was 68% and for oxaliplatin was 62%. Frequency of common toxicities was shown in Table 3. All grade alopecia was significantly more frequent with FOLFIRI than with mFOLFOX6. All grade neuropathy was more observed with mFOLFOX6.

**Economic Analysis**

Cancer care costs were compared in Table 4. Overall cost for first four cycles of FOLFIRI and mFOLFOX6 were ¥756284 and ¥1081162, respectively (*P* < 0.0001). Overall cost until disease progression was ¥1867377 for FOLFIRI.
and ¥2 064 952 for mFOLFOX6 (P = 0.22). Chemotherapy cost accounted for more 80% of overall cost in each regimen. Other economic parameters had no statistically difference between two groups.

**DISCUSSION**

Incidence of CRC is increasing and CRC as well as lung cancer and gastric cancer is one of the most important malignancies in Japan. Regardless with prolonged survival in patients with CRC, economic burden of CRC is considerable around the world (8,9). On the other hand, Japan has been maintained excellent national health insurance system for all the people, however, substantial increase in cost of heart care, especially cancer care cost causing a serious financial problem to Japanese society.

SMU-CC is newly established hospital in April 2007. SMU-CC is only one cancer center that belong to medical school in Japan and 330 beds are available in the treatment of cancer patients. We carried out clinical and economic evaluation of first-line chemotherapy for patients with CRC in SMU-CC in clinical practice setting. Although current analysis was performed retrospectively, all the patients who met selection criteria were covered. In addition, we calculated direct costs based on the Japanese national health insurance record, which also covers all the direct cost for each patient except traveling cost.

To make clinical decision, medical oncologist must take into account for several factors, such as efficacy, toxicity and cost of the treatment. Especially, cancer drug cost has received increasing attention. However, not only drug cost but also other medical fee including supportive care such as antiemetics, granulocyte colony stimulating factor and

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<tr>
<th>Toxicity</th>
<th>FOLFIRI (n = 30)</th>
<th>mFOLFOX6 (n = 24)</th>
<th>P value (all grade)</th>
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<tbody>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
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<tr>
<td>Neutropenia</td>
<td>6</td>
<td>4</td>
<td>6</td>
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<tr>
<td>Thrombocytopenia</td>
<td>1</td>
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<tr>
<td>Nausea</td>
<td>14</td>
<td>9</td>
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<tr>
<td>Vomiting</td>
<td>11</td>
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<tr>
<td>Diarrhea</td>
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<td>Mucositis</td>
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<td>Alopecia</td>
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<td>Neuropathy</td>
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<th>Table 4. Cancer care cost</th>
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<tr>
<td>Hospitalization</td>
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<td>Visits</td>
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<td>Additional prescribed drug</td>
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<td>Laboratory test</td>
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<td>Chemotherapy</td>
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<td>For first four cycles</td>
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<td>Until disease progression</td>
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<tr>
<td>Overall</td>
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<td>For first four cycles</td>
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<td>Until disease progression</td>
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Data are median (range).
antibiotics, radiographic diagnostics, blood cell counts, serum biochemistry and hospitalization fee, which induced by selected chemotherapeutic regimen must be took into account. In our analysis, there was no significant difference in PFS between two regimens. This result is similar to the result of GERCOR study (7). Drug induced toxicity is also the important factor whether patient can continue chemotherapy. Frequency of visits is similar between two groups, but there was difference of toxicity profiles between two regimens. Alopecia was more frequently observed with FOLFIRI than mFOLFOX6. This difference of toxicity profiles between two regimens, however, did not have influence on total cost, because there exist no established supportive treatment for both alopecia and neuropathy.

For first four cycles, mFOLFOX6 was clearly more expensive than FOLFIRI ($P < 0.0001$) in Japanese health care insurance system. However, in overall cost, there was no statistically significant difference between two regimens ($P = 0.22$). We consider the fact that the decrease of chemotherapy cost with mFOLFOX6 was greater than FOLFIRI as main reason for this result because chemotherapy cost accounted for more 80% of overall cost in each regimen. Relative dose intensity for irinotecan was 68% and for oxaliplatin was 62%. Neuropathy is the major toxicity with oxaliplatin. When neuropathy is appeared and patients complain the severity, oncologists tend to reduce oxaliplatin dose or omit oxaliplatin administration from regimen (12,13). Therefore, the decrease of chemotherapy cost with mFOLFOX6 will become pronounced over time. This result indicates that FOLFIRI is inexpensive in the initial stage of treatment which a number of patients can receive chemotherapy than mFOLFOX6 as first-line therapy for CRC.

We have several limitation of this analysis as follows; the data of this analysis is retrospectively obtained from clinical practice, relatively small sample size may result in a lack of statistical power, selection of treatment regimen was left to oncologist and patient’s choice and there may exist selection bias, costs of expensive targeting agents including cetuximab and bevacizumab were not prescribed in the patients cohorts, we analyzed only first-line chemotherapy and no information of the drug and supportive care cost by salvage treatment and palliative care, which are too complicated to analyze, and we collected only direct costs, not including indirect costs.

In Japan, medical oncologists have not really recognized cost of cancer care. Obviously, we have stressed efficacy priority over cost to improve patient’s quality of life. However, we should also consider efficacy, toxicity and cost of chemotherapy. Recently, American Society of Clinical Oncology (ASCO) published ‘Guidance Statement: The Cost of Cancer Care’ addressing that patient—physician discussions regarding the cost of care are an important component of high-quality care (14). We calculated cancer management cost based on clinical practice. We must also make prospective cost-effective analysis in Phase III trial in the future.

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Conflict of interest statement
None declared.

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