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Cost-Effectiveness of Adjuvant FOLFOX Therapy for Stage III Colon Cancer in Japan Based on the MOSAIC Trial

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A B S T R A C T

Objective: To evaluate the cost-effectiveness of adjuvant FOLFOX therapy versus 5-fluorouracil/leucovorin (FU/LV) for patients with stage III colorectal cancer. **Methods:** We performed the cost-effectiveness of FOLFOX compared with standard FU/LV treatment by the retrospective analysis of patient-level data from the randomized controlled Multicenter International Study of Oxaliplatin, 5-Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial. Predicted mean time spent in each disease state was calculated by our statistical model, which takes into account the cure rate and treats death from causes other than colon cancer as a competing risk. We performed this analysis from the perspective of the health-care payer. Using a time horizon of 30 years, both cost and effectiveness were discounted by 3% per year. **Results:** Estimated cure rates for colon cancer were 0.715 (FOLFOX) and 0.622 (FU/LV). Estimated medical costs of FOLFOX were JPY 3.1 million (USD 34,000) compared with JPY 1.9 million (USD 22,000) of FU/LV. The mean estimated quality-adjusted life-year was 9.83 with FOLFOX and 9.07 with that of FU/LV. The incremental cost-effectiveness ratio of FOLFOX was JPY 1.5 million (USD 17,000) per quality-adjusted life-year compared with FU/LV, which was supported by sensitivity analysis. Even if we assume that Japanese outcomes were better than those reported by the MOSAIC trial, which would reduce the difference between cure rates for each treatment to 5%, the incremental cost-effectiveness ratio remained below 5.0 million (USD 56,000) per quality-adjusted life-year. **Conclusions:** Adjuvant FOLFOX is a cost-effective treatment for stage III colon cancer in Japan compared with FU/LV therapy. Even when parameters were changed to reflect smaller improvements with FOLFOX, the conclusion is the same.

Keywords: adjuvant drug therapy, colon cancer, cost-effectiveness, FOLFOX regimen, oxaliplatin.

Introduction

After lung and stomach cancer, colon cancer is the third leading cause of death from malignant neoplasm in Japan. Age-adjusted mortality for colon cancer is 12.5 deaths per 100,000 for men and 8.6 deaths per 100,000 for women. Although this rate has decreased from its peak around 2000, more than 28,000 people died from colon cancer in 2009 [1]. Thus, colorectal cancer remains an important public health issue.

Surgery and radiation therapy are standard treatments for early-stage colon cancer; however, to reduce the risk of recurrence and extend survival, chemotherapy may be administered as adjuvant therapy to inhibit residual micrometastases in lymph nodes and elsewhere in the body [2]. A pooled analysis of randomized controlled trials (RCTs) showed that combined 5-fluorouracil/leucovorin (FU/LV) treatment reduced recurrence by 35% and death by 22% after potentially curative resection of colon cancer compared with no treatment [3]. FU/LV was shown to be superior to other regimens, such as the lomustine, vincristine, and 5-FU regimen [4] and the FU and levamisole regimen [5]; thus, FU/LV became the standard adjuvant chemotherapy regimen for colon cancer. FU/LV adjuvant therapy is also the standard care in Japan.

The FOLFOX regimen for metastatic colorectal cancer consists of oxaliplatin, a platinum-based anticancer drug, combined with FU/LV. RCTs have demonstrated that the FOLFOX regimen prolongs progression-free survival and overall survival (OS) compared with FU/LV for patients with metastatic disease [6]. In addition, FOLFOX is superior to FU/LV as an adjuvant therapy [7,8]. The Multicenter International Study of Oxaliplatin, 5-Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial reported that FOLFOX improves the adjuvant treatment of colon cancer [7]. In the MOSAIC trial, the 3-year disease-free survival (DFS) rate was 78.2% for patients receiving FOLFOX and 72.9% for those receiving FU/LV (hazard ratio for recurrence 0.77; $P = 0.002$). At 5 years, the DFS was 73.3% in the FOLFOX group and 67.4% in the FU/LV group. In patients with stage III cancer, the 6-year OS was 72.9% in the FOLFOX group and 68.7% in the FU/LV group (hazard ratio 0.80; $P = 0.023$) [9].

Some studies [10–12] have suggested that FOLFOX is a cost-effective treatment compared with FU/LV; however, some Japanese oncologists believe that the recurrence rate for colorectal cancer is lower in Japan than in European and North American countries. They therefore tend to be reluctant to use adjuvant FOLFOX therapy because they believe that Japanese patients will not benefit from adjuvant FOLFOX as much as patients who

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participated in the MOSAIC trial. This is complicated by the issue of heterogeneity of clinical outcomes or how to extrapolate results from a large multinational RCT to cost-effectiveness analyses in each country. If the results of a multinational RCT are applied to economic evaluations, then heterogeneity of clinical outcomes should be taken into account. The present study focused on this theme. To reflect heterogeneity of baseline outcomes and clinical benefit from FOLFOX and to extrapolate the survival curve more appropriately, we used an elaborated statistical model that can account for cure rate; few others have taken advantage of this model. With this statistical model, we performed an economic evaluation of adjuvant FOLFOX therapy for patients with stage III colorectal cancer based on patient-level data from the MOSAIC trial.

Methods

Chemotherapy regimens

We retrospectively analyzed patient-level data from the multinational randomized controlled MOSAIC trial. We used the data of patient characteristics, DFS, and OS at 3 years, as well as dose of oxaliplatin.

In the MOSAIC trial, stage II and stage III patients were randomized to one of two treatment groups: FOLFOX, which consisted of 12 cycles of oxaliplatin (85 mg/m^2 intravenous infusion) on day 1 of the 2-week cycle, LV (200 mg/m^2 intravenous infusion) on days 1 and 2, and 5-FU (400 mg/m^2 bolus intravenous injection followed by 600 mg/m^2 continuous infusion for 22 hours) on days 1 and 2, or FU/LV, which was the same regimen as FOLFOX treatment, but without oxaliplatin.

The MOSAIC trial enrolled patients with stage II and stage III colon cancer; however, we assumed that FOLFOX therapy would be used primarily for patients with stage III cancer in Japan. Therefore, we limited the target population to the stage III colon cancer intent-to-treat subpopulation, and patients who did not receive even a single dose of the predetermined chemotherapy protocol were excluded. The intent-to-treat subpopulation (stage III) from the MOSAIC trial used in our analysis was FOLFOX (n = 672) and FU/LV (n = 675). Demographic characteristics of our targeted population were the same as those reported by the MOSAIC trial; median age was 60 years, and the ratio of male and female was 1:1.

Framework of economic analysis

We performed a cost-effectiveness analysis of FOLFOX adjuvant chemotherapy compared with FU/LV for the treatment of stage III colon cancer. Our analysis was based on recommendations of the Panel on Cost-Effectiveness in Health and Medicine [13]. Quality-adjusted life-years (QALYs) were used to calculate the incremental cost-effectiveness ratio (ICER).

We considered three conditions: DFS, metastatic recurrence, and death. The mean time spent in each state was estimated by methods described in the "Statistical Analysis" section. Utility scores were 0.8 (DFS), 0.6 (metastatic recurrence), and 0 (death) based on a Japanese study that measured general population utility scores of colorectal cancer by using time trade-off and standard gamble methods [14].

This cost-effectiveness analysis was performed from the perspective of the health-care payer and included only direct medical costs, not indirect costs (e.g., productivity costs). Using a time horizon of 30 years, both cost and effectiveness were

Table 1 – Breakdown of chemotherapy costs.

	Unit cost (JPY)	Number (per month)		Price (JPY per month)	
		FOLFOX	FU/LV	FOLFOX	FU/LV
Outpatient chemotherapy				45,000	32,000
Granisetron 3 mg	5494	2	0	10,988	0
Dexamethasone 3.3 mg (vial)	195	6	6	1170	1170
Dexamethasone 3.3 mg (tablet)	6	64	0	378	0
Outpatient service fee	700	4	4	2800	2800
IV drip fee	980	4	4	3920	3920
Preparation in sterile environment	500	4	4	2000	2000
Outpatient chemotherapy	5500	4	4	22,000	22,000
Prescription fee	680	2	0	1360	0
Diagnositc imaging				4100	4100
Chest CT scan	6600	1 of 6	1 of 6	1100	1100
Abdominal CT scan	6600	1 of 6	1 of 6	1100	1100
Pelvic CT scan	6600	1 of 6	1 of 6	1100	1100
CT scan diagnostic fee	4500	1 of 6	1 of 6	750	750
Blood test				8700	8700
Blood drawing fee	180	2	2	360	360
Peripheral blood tests fee	210	2	2	420	420
Peripheral blood tests diagnostic fee	1250	1	1	1250	1250
Biochemical tests fee	1230	1	1	1230	1230
Biochemical tests diagnostic fee	1440	1	1	1440	1440
Tumor maker tests fee	4000	1	1	4000	4000
Pharmacy costs				1900	0
Pharmacist's fee	400	2	0	800	0
Dispensing fee	100	2	0	200	0
Management of drug history	300	2	0	600	0
Drug information providing fee	150	2	0	300	0

CT, computed tomography; FU/LV, 5-fluorouracil/leucovorin; JPY, Japanese yen; IV, intravenous.