A Study on the Tolerability of Capecitabine plus Oxaliplatin as Adjuvant Chemotherapy

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Abstract. *Aim: Tolerability, adverse events, and long-term outcomes were compared and analyzed between patients receiving oral anticancer agent-based adjuvant chemotherapy regimen (PO group) and those receiving combination adjuvant chemotherapy with oxaliplatin (OX group), after curative resection of colorectal cancer at our Department. Patients and Methods: The subjects included in the study were 169 patients with stage III colorectal cancer who underwent curative resection and received postoperative adjuvant chemotherapy between June 2007 and October 2014. Fifty-three patients were included in the OX group, while 116 patients were included in PO group. Results: No significant difference was observed in treatment completion rates. No significant difference in either the overall or relapse-free survival rates was observed between the two groups. Conclusion: Oxaliplatin has been shown to improve therapeutic outcomes after curative resection of colorectal cancer. Even compared to oral anticancer agents, oxaliplatin appears to be equal in tolerability and treatment completion rate.*

Since the results of the Multicentre International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) were reported (1), regimens including oxaliplatin have been recommended as adjuvant chemotherapy after curative resection of stage III colorectal cancer. However, because adverse events such as peripheral neuropathy and myelosuppression were reported, such regimens demonstrated a tolerability problem.

Meanwhile, in Japan, primarily oral anticancer agent-based adjuvant chemotherapy has been widely administered for some time, and reported to be safe, with high relapse-free survival rates (2, 3). Because the outcome is comparable to the results obtained from the oxaliplatin-treated group in the MOSAIC study, Japanese doctors are hesitant on administering oxaliplatin in some cases.

However, the usefulness of oxaliplatin has been reported in many studies abroad. If it is comparable to oral anticancer agents concerning tolerability and safety, administration of oxaliplatin should be actively adopted.

In the present study, tolerability, adverse events, and long-term outcomes were compared and analyzed between oral anticancer agent-based adjuvant chemotherapy regimen and combination adjuvant chemotherapy with oxaliplatin, after curative resection of colorectal cancer at our Department.

Patients and Methods

The subjects included in the study were 169 patients with stage III colorectal cancer who underwent curative resection and received postoperative adjuvant chemotherapy between June 2007 and October 2014. Fifty-three patients received the combination adjuvant chemotherapy with oxaliplatin (OX group), while 116 patients received only oral anticancer agents (PO group) for comparison and analysis.

Statistical analyses were performed with JMP12 (SAS Institute, Cary, NC, USA) Chi-square test was used to test for significance of differences, and the log-rank test was used to analyze survival rates. Adverse events were assessed by Common Terminology Criteria for Adverse Events version 4.0 (CTCAE) (4).

Results

The background of patients is summarized in Table I. No significant differences in age, sex, N1/N2 ratio, or colon/rectal cancer ratio were observed between the two groups.

Although the OX group included more patients who required dose reduction, discontinued treatment, or developed grade 3 or above adverse events, no significant difference was observed in treatment completion rates (Table II). The median relative dose intensity (RDI) of oxaliplatin was 82.5%.

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Table I. *Patients' characteristics.*

	OX group (n=53)	PO group (n=116)	*p*-Value
Age	61.1±10.2	63.2±12.2	0.27
Gender			
Male	32 (60.4%)	69 (59.5%)	1.00
Female	21 (39.6%)	47 (40.5%)	
N			
N1	36 (67.9%)	87 (75.0%)	0.59
N2	17 (32.1%)	31 (26.7%)	
Location			
Colon	39 (73.6%)	87 (75.0%)	0.99
Rectum	14 (26.4%)	29 (25.0%)	

Table II. *Comparison of completion rate, drug reduction, drug withdrawal and adverse events between OX group and PO group.*

	OX group (n=53)	PO group (n=116)	*p*-Value
Neutropenia	12 (22.6%)	5 (4.3%)	<0.001
Thrombocytopenia	16 (30.2%)	2 (1.7%)	<0.001
Liver dysfunction	3 (5.7%)	6 (5.2%)	1.00
Nausea	6 (11.3%)	7 (6.0%)	0.37
Peripheral neuropathy	6 (11.3%)	0 (0%)	0.001
Hand-foot syndrome	2 (3.8%)	6 (5.2%)	0.99

Table III. *The incidence of adverse events that caused drug reduction or withdrawal in OX group and PO group.*

	OX group (n=53)	PO group (n=116)	*p*-Value
Completion			
+	37 (69.8%)	95 (81.9%)	0.12
–	16 (30.2%)	21 (18.1%)	
Dose reduction			
+	26 (49.1%)	16 (13.8%)	<0.001
–	27 (50.9%)	100 (86.2%)	
Withdrawal			
+	32 (60.4%)	26 (22.4%)	<0.001
–	21 (39.6%)	90 (77.6%)	
Adverse events			
+	18 (34.0%)	7 (6.0%)	<0.001
–	35 (66.0%)	109 (94.0%)	

In the OX group, the significantly common reasons for dose reduction and discontinuation of treatment were myelosuppression and peripheral neuropathy (Table III).

No significant difference in either the overall or relapse-free survival rates was observed between the two groups (Figures 1 and 2).

Discussion

Various adjuvant chemotherapy regimens administered after resection of stage III colorectal cancer have been reported. Lembersky *et al*. reported that no significant difference in disease-free survival (DFS) or overall survival (OS) was observed between patients treated with oral uracil and tegafur plus leucovorin (UFT/LV), and those treated with weekly intravenous 5-fluorouracil plus leucovorin (5FU/LV) (5). They further reported that oral anticancer agents yielded effects comparable to the effects of 5FU/LV. Twelves *et al*. (6) reported that oral capecitabine yields therapeutic effects comparable to those of 5FU/LV. In Japan, oral anticancer agents have been widely used for some time. Shimada *et al*. (2) reported that no significant difference in either DFS or OS was observed between Japanese patients treated with UFT/LV and those treated with 5FU/LV. Furthermore, the 5-year OS rate was 87.5%, which was higher than that reported by Lembersky *et al*. (5) and comparable to that observed in the patients treated with FOLFOX (leucovorin, fluorouracil, and oxaliplatin) chemotherapy in the MOSAIC study (1). Grade 3/4 toxicity observed in the UFT/LV-treated group was alanine aminotransferase elevation in 8.7% of the patients. The tolerability of this regimen was very good. According to these reports, oral anticancer agents have a therapeutic effect comparable to that of 5FU/LV, are of high safety, and have the additional advantage of simple administration as they are oral preparations.

In recent years, the MOSAIC study (1) showed that the 5-year relapse-free survival rates were 73.3% for FOLFOX chemotherapy, and 67.4% for 5FU/LV chemotherapy, indicating that FOLFOX chemotherapy is significantly more effective. Furthermore, capecitabine plus oxaliplatin (XELOX) chemotherapy was reported to be superior to 5FU/LV chemotherapy (7, 8). According to the final results of the N016968 study (8), the 7-year relapse-free survival rates were 63% for XELOX chemotherapy, and 56% for 5FU/LV chemotherapy, showing that XELOX chemotherapy was significantly more effective. Presently, adjuvant chemotherapy regimens with oxaliplatin are considered the standard treatment for adjuvant chemotherapy after resection of stage III colorectal cancer. Furthermore, a pooled analysis of four large-scale clinical trials (9) showed no difference in survival time after relapse between patients receiving adjuvant chemotherapy with and without oxaliplatin. On the other hand, due to the occurrence of adverse events, primarily peripheral neuropathy and myelosuppression, adjuvant chemotherapy with oxaliplatin appears to have reduced completion rate and tolerability. Especially in patients without relapse, another reported problem is that

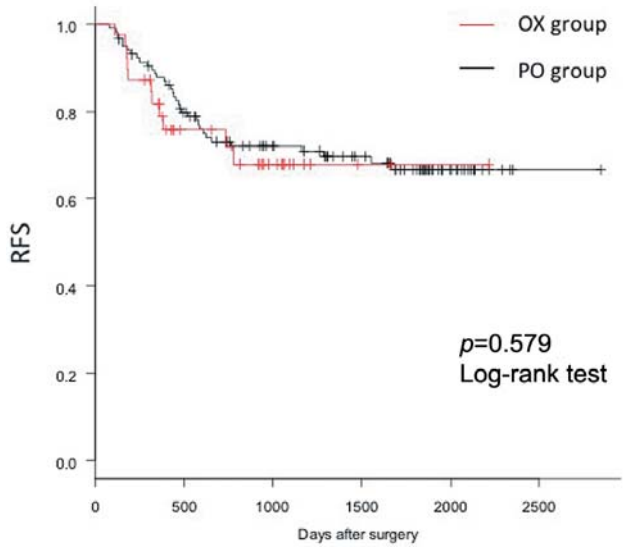

Figure 1. *Comparison of relapse-free survival rates in patients receiving combination adjuvant chemotherapy with Oxaliplatin (OX group), and those receiving oral anticancer agents (PO group).*

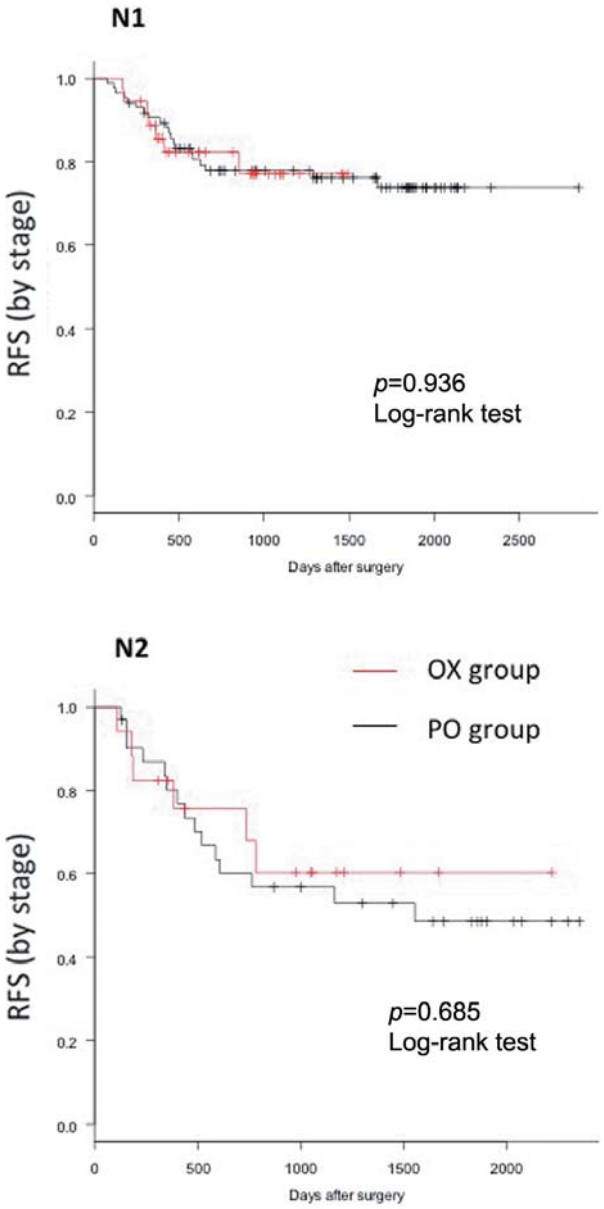

Figure 2. *Comparison of relapse-free survival rates in patients receiving combination adjuvant chemotherapy with Oxaliplatin (OX group), and those receiving oral anticancer agents (PO group).*

peripheral neuropathy persists for a considerably long period of time. In the MOSAIC study (1), grade 3 or above peripheral neuropathy remained in 1.3% of the patients 12 months after treatment and in 0.7% at 48 months. Resolution of persistent neuropathy is an important issue to be addressed.

In Japan, since Shimada *et al*. (2) reported an OS rate of 87.5% that was comparable to the outcome in the FOLFOX-treated group in the MOSAIC study (1), Japanese doctors hesitate to include oxaliplatin in certain cases. A major reason for this appears to be that compared to oral anticancer agents, the addition of oxaliplatin increases the incidence of adverse events and decreases the tolerability of treatment. Recently, several studies about efficacy and safety of adjuvant chemotherapy including oxaliplatin were reported from Japan (10, 11). However, they did not compare between 5-FU with oxaliplatin and without oxaliplatin. Therefore, we evaluated the incidence rates of adverse events, and the tolerability of adjuvant chemotherapy in patients who received a treatment regimen with or without oxaliplatin at our facility. No difference was observed in treatment completion rates. Although discontinuation of treatment or dose reduction is required, we considered that oxaliplatin could also be adequately administered as part of adjuvant chemotherapy in Japanese patients. However, because of the insufficient number of cases available at a single facility, no significant difference was observed in long-term outcomes.

Moreover, in an effort to prevent adverse events caused by oxaliplatin, the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) (12); a randomized controlled trial (RCT) comparing patients receiving 3- and 6-month courses of combination adjuvant chemotherapy with oxaliplatin, was established. Case registration has been completed, and patients are being followed-up at present. If the results of this trial show comparable outcomes between the two groups, this will indicate that a 3-month course of postoperative adjuvant chemotherapy is sufficient. Because a shorter duration can be expected to contribute towards the alleviation of adverse effects of oxaliplatin, this trial carries significant importance.

Oxaliplatin has been shown to improve therapeutic outcome after curative resection of colorectal cancer. Even compared to oral anticancer agents, oxaliplatin appears to be equal in tolerability and treatment completion rate. A certain limitation of our study was that we analyzed patients presented in only one hospital, therefore a greater number of patients should be included in future studies. Furthermore, this is historical study. Future studies should be conducted to develop methods for controlling adverse events resulting from oxaliplatin administration, as well as to determine optimal treatment duration that will allow adequate therapeutic outcome with minimal adverse effects.

References

1 Andre T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, Bonetti A, Clingan P, Bridgewater J, Rivera F and de Gramont A: Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol *27*: 3109-3116, 2009.

2 Shimada Y, Hamaguchi T, Mizusawa J, Saito N, Kanemitsu Y, Takiguchi N, Ohue M, Kato T, Takii Y, Sato T, Tomita N, Yamaguchi S, Akaike M, Mishima H, Kubo Y, Nakamura K, Fukuda H and Moriya Y: Randomised phase III trial of adjuvant chemotherapy with oral uracil and tegafur plus leucovorin *versus* intravenous fluorouracil and levofolinate in patients with stage III colorectal cancer who have undergone Japanese D2/D3 lymph node dissection: final results of JCOG0205. Eur J Cancer *50*: 2231-2240, 2014.

3 Yoshida M, Ishiguro M, Ikejiri K, Mochizuki I, Nakamoto Y, Kinugasa Y, Takagane A, Endo T, Shinozaki H, Takii Y, Mochizuki H, Kotake K, Kameoka S, Takahashi K, Watanabe T, Watanabe M, Boku N, Tomita N, Nakatani E and Sugihara K: S-1 as adjuvant chemotherapy for stage III colon cancer: a randomized phase III study (ACTS-CC trial). Ann Oncol *25*: 1743-1749, 2014.

4 Health USDOHAHSNIo and Institute NC: Common Terminology Criteria for Adverse Events v4.0(CTCAE). 2009.

5 Lembersky BC, Wieand HS, Petrelli NJ, O'Connell MJ, Colangelo LH, Smith RE, Seay TE, Giguere JK, Marshall ME, Jacobs AD, Colman LK, Soran A, Yothers G and Wolmark N: Oral uracil and tegafur plus leucovorin compared with intravenous fluorouracil and leucovorin in stage II and III carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project Protocol C-06. J Clin Oncol *24*: 2059-2064, 2006.

6 Twelves C, Wong A, Nowacki MP, Abt M, Burris H, 3rd, Carrato A, Cassidy J, Cervantes A, Fagerberg J, Georgoulias V, Husseini F, Jodrell D, Koralewski P, Kroning H, Maroun J, Marschner N, McKendrick J, Pawlicki M, Rosso R, Schuller J, Seitz JF, Stabuc B, Tujakowski J, Van Hazel G, Zaluski J and Scheithauer W: Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med *352*: 2696-2704, 2005.

7 Schmoll HJ, Cartwright T, Tabernero J, Nowacki MP, Figer A, Maroun J, Price T, Lim R, Van Cutsem E, Park YS, McKendrick J, Topham C, Soler-Gonzalez G, de Braud F, Hill M, Sirzen F and Haller DG: Phase III trial of capecitabine plus oxaliplatin as adjuvant therapy for stage III colon cancer: a planned safety analysis in 1,864 patients. J Clin Oncol *25*: 102-109, 2007.

8 Schmoll HJ, Tabernero J, Maroun J, de Braud F, Price T, Van Cutsem E, Hill M, Hoersch S, Rittweger K and Haller DG: Capecitabine Plus Oxaliplatin Compared With Fluorouracil/Folinic Acid As Adjuvant Therapy for Stage III Colon Cancer: Final Results of the NO16968 Randomized Controlled Phase III Trial. J Clin Oncol *33*: 3733-3740, 2015.

9 Schmoll HJ, Twelves C, Sun W, O'Connell MJ, Cartwright T, McKenna E, Saif M, Lee S, Yothers G and Haller D: Effect of adjuvant capecitabine or fluorouracil, with or without oxaliplatin, on survival outcomes in stage III colon cancer and the effect of oxaliplatin on post-relapse survival: a pooled analysis of individual patient data from four randomised controlled trials. Lancet Oncol *15*: 1481-1492, 2014.

10 Kotaka M, Yoshino T, Oba K, Shinozaki K, Touyama T, Manaka D, Matsui T, Ishigure K, Hasegawa J, Inoue K, Goto K, Sakamoto J, Saji S, Ohtsu A and Watanabe T: Initial safety report on the tolerability of modified FOLFOX6 as adjuvant therapy in patients with curatively resected stage II or III colon cancer (JFMC41-1001-C2: JOIN trial). Cancer Chemother Pharmacol *76*: 75-84, 2015.

11 Osawa H, Handa N and Minakata K: Efficacy and Safety of Capecitabine and Oxaliplatin (CapOX) as an Adjuvant Therapy in Japanese for Stage II/III Colon Cancer in a Group at High Risk of Recurrence in Retrospective Study. Oncol Res *22*: 325-331, 2015.

12 Andre T, Iveson T, Labianca R, Meyerhardt JA, Souglakos I, Yoshino T, Paul J, Sobrero A, Taieb J, Shields AF, Ohtsu A, Grothey A and Sargent DJ: The IDEA (International Duration Evaluation of Adjuvant Chemotherapy) Collaboration: Prospective Combined Analysis of Phase III Trials Investigating Duration of Adjuvant Therapy with the FOLFOX (FOLFOX4 or Modified FOLFOX6) or XELOX (3 *versus* 6 months) Regimen for Patients with Stage III Colon Cancer: Trial Design and Current Status. Curr Colorectal Cancer Rep *9*: 261-269, 2013.

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