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Effectiveness of oral fluoropyrimidine monotherapy as adjuvant chemotherapy for high-risk stage II colon cancer

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Purpose: The benefit of adjuvant chemotherapy for stage II colon cancer has not been clearly demonstrated even in cases with high-risk factors. This study aimed to compare the effectiveness of oral fluoropyrimidine monotherapy as adjuvant chemotherapy with that of intravenous fluoropyrimidine-based chemotherapy for high-risk stage II colon cancer.
Methods: This single-institution, retrospective study included patients who underwent curative resection for high-risk stage II colon cancer between 2003 and 2014. Patients were classified into 3 postoperative treatment groups: observation, oral fluoropyrimidine monotherapy group (OG), or intravenous fluoropyrimidine-based chemotherapy group (IVG).
Results: We identified 356 patients, including 87 (24.4%) in the observation group, 172 (48.3%) in the OG, and 97 (27.2%) in the IVG. Patients in the OG were older (63.8 ± 10.7 *vs*. 56.5 ± 10.8, P < 0.001) and had a lower number of T4 lesions (12.8% *vs*. 35.1%, P < 0.001) than those in the IVG. Regarding survival outcomes, the 5-year overall and disease-free survival rates were not different between the OG and IVG (91.2% *vs*. 92.6% [P = 0.090] and 85.1% *vs*. 81.9% [P = 0.535], respectively). In multivariate analysis, age over 70 years and no adjuvant chemotherapy were associated with poor overall survival and disease-free survival. Fewer chemotherapy-related adverse events of grade ≥3 were observed in the OG than in the IVG (12.2% *vs*. 34.0%, P < 0.001).
Conclusion: In high-risk stage II colon cancer, adjuvant oral fluoropyrimidine monotherapy can be an effective and convenient alternative to intravenous fluoropyrimidine-based chemotherapy as it has comparable oncological outcomes and reduced chemotherapy-related complications.
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Key Words: Adjuvnat chemotherapy, Capecitabine, Colonic neoplasms

INTRODUCTION

Colorectal cancer is the third most common type of cancer worldwide and in Korea [1,2]. Surgical resection with curative intent is the mainstay of treatment for patients with locoregional colon cancer. For stage III colon cancer, the benefit of adjuvant chemotherapy following curative resection is well-established [3-5]. However, the effectiveness of adjuvant

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chemotherapy for stage II colon cancer has not been clearly proven, and the expected absolute survival benefit of adjuvant treatment is in the range of 2%–5% at best [4-7].

According to previous large-scaled phase III trials and current clinical guidelines, including the National Comprehensive Cancer Network (NCCN), the addition of oxaliplatin to 5-fluorouracil (5-FU)/leucovorin in adjuvant chemotherapy following resection of stage II colon cancer has not been demonstrated, even in the cases with high-risk factors such as pathologic T4 lesion or bowel perforation [4,7]. However, oxaliplatin can induce cumulative dose-dependent grade 3 or 4 neurotoxicity in about 8%–12% of patients, and this neurotoxicity lasts for 4 years in 15.5% of patients, especially those older than 70 years [8,9]. Chemotherapy-induced peripheral sensory neuropathy is associated with a poor quality of life [10].

Patients with cancer prefer oral chemotherapy over intravenous (IV) administration if the drug efficacy is not compromised [11]. In stage III colon cancer, oral capecitabine achieved similar survival outcomes but significantly fewer adverse events than IV 5-FU plus leucovorin [12]. However, the efficacy of oral fluoropyrimidine monotherapy as adjuvant chemotherapy in stage II colon cancer has not been widely investigated. Therefore, in this study, we compared the effectiveness of adjuvant oral fluoropyrimidine monotherapy with IV fluoropyrimidine-based chemotherapy for high-risk stage II colon cancer.

METHODS

Ethical statement

The Institutional Review Board at Seoul National University Bundang Hospital approved this retrospective study before the commencement of data collection and analysis, and the requirement for informed consent was waived (No. B-1905-540-102).

Patients and treatments

This single-institution, retrospective, observational study included patients who underwent curative-intent resection for histologically proven stage II colonic adenocarcinoma with high-risk features at Seoul National University Bundang Hospital in Seongnam, Korea between 2003 and 2014. All data were retrospectively extracted from an electronic medical record. The data items included patient demographics such as age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status (PS) classification, tumor location (right-sided, ascending to the transverse colon; left-sided, splenic flexure to the sigmoid colon), and microsatellite instability (MSI) status. Patients with high-risk stage II colon cancer had at least one of the following features: poorly differentiated histology, lymphatic invasion, venous invasion, perineural invasion, harvested lymph node less than 12, bowel obstruction, tumor perforation, or pathologic T4 lesion. Patients with high MSI were excluded as they have a better prognosis and gain little benefit from adjuvant therapy based on the guidelines by NCCN and the European Society for Medical Oncology (ESMO) [7,13].

After resection of colon cancer, patients were classified into 3 groups according to their postoperative management: (1) observation group; (2) oral fluoropyrimidine monotherapy group, such as capecitabine (starting dose of 1,250 mg/m^2 twice daily for 14 days repeated every 21 days for 8 cycles) or tegafur/uracil (UFT; administered at a dose of 300 mg/m^2 daily for 5 cycles, each cycle comprising 4 weeks of oral chemotherapy administration followed by 1-week rest period); and (3) IV fluoropyrimidine-based chemotherapy group, including fluorouracil plus leucovorin (FL; 5-FU 400 mg/m^2 plus leucovorin 20 mg/m^2 daily for 5 days repeated every 28 days for 6 cycles) or FL with oxaliplatin (FOLFOX; oxaliplatin 85 mg/m^2 on day 1, leucovorin 400 mg/m^2 on day 1, 5-FU bolus 400 mg/m^2 on day 1 followed by 2,400 mg/m^2 for 46 hours, repeated every 2 weeks for 12 cycles) [7,12,14-16]. The choice of adjuvant chemotherapy regimen and dosage modification during the chemotherapy period was determined by experienced medical oncologists.

Outcome measures

To compare the effectiveness of postoperative management for each group, long-term oncologic outcomes such as 5-year overall survival (OS) and disease-free survival (DFS) were analyzed. OS was defined as the time between operation date and death from any cause or the date when the patient was last confirmed to be alive. DFS was defined as the time between the date of operation and first relapse, the occurrence of a second primary colorectal cancer, death from any cause, or the last date when the patient was confirmed to be disease-free [17]. All adverse events during chemotherapy were evaluated and graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 of the National Cancer Institute [18], and the most severe grade in each event category was considered the representative one. In addition, the number of patients with dose-reduced chemotherapy due to chemotherapy-induced toxicity and the rate of chemotherapy discontinuation were assessed.

Statistical analysis

One-way analysis of variance or independent-samples t-tests were performed to compare continuous variables, and the chi-square tests were used to compare categorical data. Continuous data are expressed as mean with standard deviation, and categorical variables are expressed as the number with the percentage. The probabilities of OS and DFS were estimated using the Kaplan-Meier method and compared using log-

rank tests. Multivariate analyses with the Cox regression hazard model were conducted to identify the factors that were independently associated with survival. A stepwise backward elimination technique, including variables initially with a P-value less than 0.1 in the univariate analysis, was used. All statistical tests were 2-sided, and P-values of <0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics ver. 22 (IBM Corp., Armonk, NY, USA).

RESULTS

Patients and treatments

Among 706 patients with pathologic stage II colon cancer at our institution from 2003 to 2014, 350 patients were excluded from analysis due to high MSI status, no high-risk features, or follow-up loss after surgical resection. Finally, 356 patients were included in the analysis. They were classified into 3 groups according to their postoperative management: 87 patients (24.4%) in the observation group, 172 (48.3%) in the oral fluoropyrimidine monotherapy group, and 97 (27.2%) in the IV fluoropyrimidine-based chemotherapy group. The

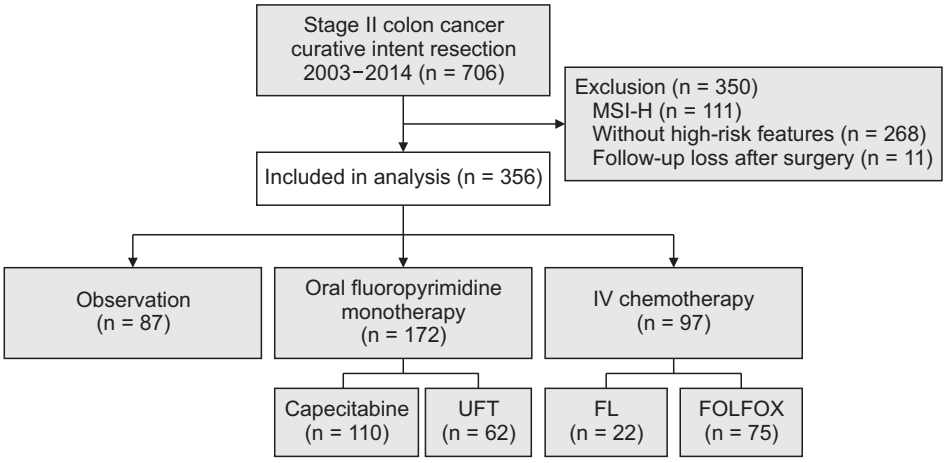

Fig. 1. Flowchart depicting the patient selection criteria. MSI-H, high-frequency microsatellite instability; IV, intravenous; UFT, tegafur/uracil; FL, 5-fluorouracil/leucovorin; FOLFOX, FL with oxaliplatin.

Table 1. Baseline characteristics according to postoperative treatment groups (n = 356)

Characteristic	Observation	OG	IVG	P-value	P-value, OG *vs.* IVG
No. of patients	87 (24.4)	172 (48.3)	97 (27.2)		
Age (yr)	74.5 ± 11.1	63.8 ± 10.7	56.5 ± 10.8	<0.001[a]	<0.001[b]
Female sex	32 (36.8)	67 (39.0)	41 (42.3)	0.742[c]	0.607[c]
Body mass index (kg/m^2)	22.5 ± 3.6	23.4 ± 3.2	22.7 ± 3.2	0.082[a]	0.095[b]
ASA PS grade					
I, II	63 (72.4)	163 (94.8)	94 (96.9)	<0.001[c]	0.546[c]
III–V	24 (27.6)	9 (5.2)	3 (3.1)		
Tumor location[d]					
Right-sided	38 (43.7)	47 (27.3)	32 (33.0)	0.030[c]	0.333[c]
Left-sided	49 (56.3)	125 (72.7)	65 (67.0)		
Operative method					
Open[e]	41 (47.1)	45 (26.2)	39 (40.2)	0.002[c]	0.020[c]
Laparoscopy	46 (52.9)	127 (73.8)	58 (59.8)		
Harvested LNs	42.5 ± 19.9	41.7 ± 20.2	47.9 ± 22.9	0.058[a]	0.023[b]
Emergency					
No	79 (90.8)	157 (91.3)	86 (88.7)	0.775[c]	0.522[c]
Yes	8 (9.2)	15 (8.7)	11 (11.3)		

Values are presented as number (%) or mean ± standard deviation.
OG, oral fluoropyrimidine monotherapy group; IVG, intravenous fluoropyrimidine-based chemotherapy group; ASA, American Society of Anesthesiologists; PS, physical status; LNs, lymph nodes.
[a]One-way analysis of variance; [b]independent 2 samples t-test; [c]chi-square test. [d]Tumor location is divided into right-sided (ascending to transverse colon) and left-sided (splenic flexure to the sigmoid colon). [e]Conversion to open surgery during laparoscopy was included.

oral fluoropyrimidine monotherapy group was subdivided into those receiving capecitabine (n = 110, 64.0%) and those receiving UFT (n = 62, 36.0%). The IV fluoropyrimidine-based chemotherapy group was subdivided into FL (n = 22, 22.7%) and FOLFOX (n = 75, 77.3%) (Fig. 1).

According to the baseline characteristics, the observation group had the highest mean age (74.5 ± 11.1 years) (Table 1). The mean age of the oral fluoropyrimidine monotherapy group was higher than that of the IV chemotherapy group (63.8 ± 10.7 *vs.* 56.5 ± 10.8, P < 0.001). The proportion of ASA PS classification III or IV was higher, and right-sided tumor location was more common in the observation group than in the adjuvant chemotherapy groups, but similar between the oral fluoropyrimidine monotherapy group and the IV chemotherapy group. The number of harvested lymph nodes was not significantly different among the 3 groups.

Table 2 shows the high-risk features of stage II colon cancer according to the treatment groups. The proportion of pathologic T4 lesions was higher in the IV chemotherapy group than in the other groups (P < 0.001). The IV chemotherapy group had more multiple high-risk features than the other groups.

Survival outcomes

The median follow-up time was 47.7 months (range, 2–133 months). The 5-year OS and DFS rates of all patients were 85.5% and 78.0%, respectively. The 5-year OS rate was 62.9% for the observation group, 91.2% for the oral fluoropyrimidine monotherapy group, and 92.6% for the IV fluoropyrimidine-based chemotherapy group (log-rank, P < 0.001). The 5-year DFS rates for patients in the observation, oral fluoropyrimidine monotherapy, and IV chemotherapy groups were 57.2%, 85.1%, and 81.9%, respectively (log-rank, P < 0.001) (Fig. 2). Between the oral fluoropyrimidine monotherapy group and the IV chemotherapy group, the 5-year OS and DFS rates were not different (log-rank, P = 0.090 and P = 0.535, respectively). In multivariate analysis, age over 70 years and no adjuvant

Table 2. High-risk pathology of stage II colon cancer according to postoperative treatment groups

Variable	Observation (n = 87)	OG (n = 172)	IVG (n = 97)	P-value	P-value, OG *vs.* IVG
T4 lesion	10 (11.5)	22 (12.8)	34 (35.1)	<0.001	<0.001
Poorly differentiated	7 (8.0)	4 (2.3)	7 (7.2)	0.073	0.061
Lymphatic invasion	22 (25.3)	55 (32.0)	34 (35.1)	0.344	0.686
Venous invasion	8 (9.2)	11 (6.4)	13 (13.4)	0.155	0.073
Perineural invasion	28 (32.2)	71 (41.3)	45 (46.4)	0.140	0.443
Harvested LNs <12	1 (1.1)	3 (1.7)	1 (1.0)	0.869	0.999
Bowel obstruction	33 (37.9)	52 (30.2)	27 (27.8)	0.301	0.781
Tumor perforation	17 (19.5)	27 (15.7)	11 (11.3)	0.305	0.366
No. of high-risk features					
1	60 (69.0)	119 (69.2)	46 (47.4)	0.001	0.001
≥2	27 (31.0)	53 (30.8)	51 (52.6)		

Values are presented as number (%).
OG, oral fluoropyrimidine monotherapy group; IVG, intravenous fluoropyrimidine-based chemotherapy group; LNs, lymph nodes.

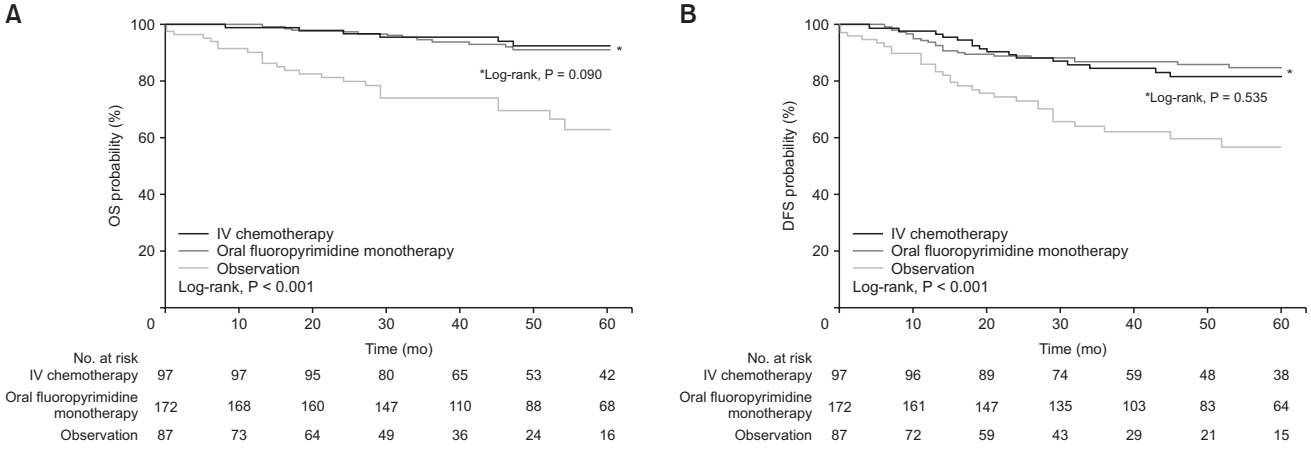

Fig. 2. Analysis of survival (Kaplan-Meier) according to the postoperative management for high-risk stage II colon cancer. (A) Overall survival (OS) and (B) disease-free survival (DFS). IV, intravenous.

Table 3. Univariate and multivariate hazard ratio for overall survival and disease-free survival

Variable	Overall survival				Disease-free survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (yr)								
<70	-		-		-		-	
≥70	5.019 (2.935–8.582)	<0.001	2.229 (1.132–4.391)	0.020	2.976 (1.917–4.620)	<0.001	1.773 (1.023–3.072)	0.041
Sex								
Male	-				-		-	
Female	1.333 (0.773–2.296)	0.301			0.661 (0.413–1.056)	0.083	0.705 (0.440–1.129)	0.146
Body mass index (kg/m^2)								
<25	-				-			
≥25	1.180 (0.670–2.078)	0.566			1.192 (0.736–1.931)	0.476		
Tumor location[a]								
Right-sided	-				-			
Left-sided	0.966 (0.554–1.683)	0.902			1.123 (0.697–1.808)	0.634		
Differentiation								
Well to moderate	-				-			
Poor	2.134 (0.768–5.932)	0.146			1.612 (0.650–3.998)	0.303		
T stage								
T3	-				-			
T4	1.209 (0.654–2.236)	0.545			1.505 (0.917–2.471)	0.106		
Perforation								
Absent	-				-			
Present	0.646 (0.258–1.618)	0.351			0.594 (0.273–1.291)	0.188		
Obstruction								
Absent	-		-		-			
Present	1.716 (1.031–2.855)	0.038	1.292 (0.763–2.188)	0.341	1.389 (0.895–2.154)	0.143		
Adjuvant chemotherapy								
Observation	-		-		-		-	
OG	0.190 (0.106–0.342)	<0.001	0.306 (0.156–0.603)	0.001	0.284 (0.173–0.468)	<0.001	0.388 (0.219–0.688)	0.002
IVG without oxaliplatin	0.038 (0.009–0.167)	<0.001	0.078 (0.016–0.385)	0.002	0.120 (0.038–0.378)	<0.001	0.196 (0.058–0.660)	0.010
IVG with oxaliplatin	0.156 (0.064–0.375)	<0.001	0.302 (0.109–0.833)	0.021	0.310 (0.164–0.587)	<0.001	0.471 (0.222–1.000)	0.050

Median follow-up time was 47.7 months.
HR, hazard ratio; CI, confidence interval; OG, oral fluoropyrimidine monotherapy group; IVG, intravenous fluoropyrimidine-based chemotherapy group.
[a]Tumor location is divided into right-sided (ascending to transverse colon) and left-sided (descending to the sigmoid colon).

chemotherapy were associated with poor OS and DFS (Table 3).

Adverse events of adjuvant chemotherapy

The incidence of adverse events was different between the oral fluoropyrimidine monotherapy and the IV chemotherapy groups (69.8% *vs.* 99.0%, P < 0.001). Adverse events except hand-foot syndrome were more frequent in the IV chemotherapy group than in the oral fluoropyrimidine monotherapy group. Severe adverse events of grade ≥3 were more frequent in the IV chemotherapy group than in the oral fluoropyrimidine monotherapy group (Table 4).

Chemotherapy discontinuation rates were comparable between the oral fluoropyrimidine agent and IV chemotherapy groups (9.9% *vs.* 10.3%, P = 0.911). The number of cases requiring dose reduction during chemotherapy due to toxicity was lower in the oral fluoropyrimidine agent group than in the IV chemotherapy group (15.7% *vs.* 58.8%, P < 0.001).

Table 4. Adverse events during adjuvant chemotherapy

Variable	OG (n = 172)	IVG (n = 97)	P-value
Overall	120 (69.8)	96 (99.0)	<0.001
Neutropenia	5 (2.9)	35 (36.1)	<0.001
Diarrhea	30 (17.4)	30 (30.9)	0.011
Nausea/vomiting	52 (30.2)	71 (73.2)	<0.001
Hand-foot syndrome	79 (45.9)	4 (4.1)	<0.001
Stomatitis	22 (12.8)	30 (30.9)	<0.001
Neuropathy	1 (0.6)	62 (63.9)	<0.001
CTCAE grade ≥3	21 (12.2)	33 (34.0)	<0.001
Neutropenia	2 (1.2)	19 (19.6)	<0.001
Diarrhea	7 (4.1)	6 (6.2)	0.437
Nausea/vomiting	1 (0.6)	8 (8.2)	0.001
Hand-foot syndrome	13 (7.6)	0 (0)	0.006
Stomatitis	1 (0.6)	2 (2.1)	0.267
Neuropathy	0 (0)	4 (4.1)	0.007

Values are presented as number (%).
OG, oral fluoropyrimidine monotherapy group; IVG, intravenous fluoropyrimidine-based chemotherapy group; CTCAE, Common Terminology Criteria for Adverse Events.

Adjuvant chemotherapy according to the administration of oxaliplatin

In additional analysis, patients who received adjuvant chemotherapy were divided into 2 groups based on whether oxaliplatin was included or not. The group without oxaliplatin (capecitabine, UFT, or FL; n = 194) was older and had more left-sided tumor location than the group with oxaliplatin (FOLFOX; n = 75) (Table 5). The group without oxaliplatin had less T4 lesion and poorly differentiated histology than the group with oxaliplatin (Table 6).

The 5-year OS and DFS rates were not different between the 2 groups (without oxaliplatin *vs.* with oxaliplatin: 92.4% *vs.* 89.6% [P = 0.937] for OS and 85.2% *vs.* 80.3% [P = 0.535] for DFS, respectively) (Fig. 3). Adverse events were less frequent in the group without oxaliplatin than in the group with oxaliplatin (73.2% *vs.* 98.7%; P < 0.001) (Table 7). Similarly, medication persistence was not different between the 2 groups (90.7% *vs.* 88.0%, P = 0.505). However, dose reduction of chemotherapeutic agents during adjuvant chemotherapy was less frequent in the

Table 5. Baseline characteristics according to administration of oxaliplatin

Characteristic	Without oxaliplatin (n = 194)	With oxaliplatin (n = 75)	P-value
Age (yr)	62.7 ± 11.2	57.3 ± 10.5	<0.001[a]
Female sex	75 (38.7)	33 (44.0)	0.423[b]
Body mass index (kg/m^2)	23.3 ± 3.2	22.7 ± 3.3	0.160[a]
ASA PS grade			
I, II	184 (94.8)	73 (97.3)	0.375[b]
III–V	10 (5.2)	2 (2.7)	
Tumor location[c]			
Right-sided	50 (25.8)	29 (38.7)	0.037[b]
Left-sided	144 (74.2)	46 (61.3)	
Operative method			
Open[d]	58 (29.9)	26 (34.7)	0.449[b]
Laparoscopy	136 (70.1)	49 (65.3)	
Harvested LNs	41.6 ± 20.3	50.0 ± 23.0	0.004[a]
Emergency			
No	177 (91.2)	66 (88.0)	0.420[b]
Yes	17 (8.8)	9 (12.0)	

Values are presented as mean ± standard deviation or number (%).
ASA, American Society of Anesthesiologists; PS, physical status; LNs, lymph nodes.
[a]Independent 2 samples t-tests; [b]chi-square test. [c]Tumor location is divided into right-sided (ascending to transverse colon) and left-sided (descending to the sigmoid colon). [d]Conversion to open surgery during laparoscopy was included.

Table 6. High-risk pathology of stage II colon cancer according to administration of oxaliplatin

Variable	Without oxaliplatin (n = 194)	With oxaliplatin (n = 75)	P-value
T4 lesion	26 (13.4)	30 (40.0)	<0.001
Poorly differentiated	4 (2.1)	7 (9.3)	0.007
Lymphatic invasion	67 (34.5)	22 (29.3)	0.416
Venous invasion	16 (8.2)	8 (10.7)	0.533
Perineural invasion	81 (41.8)	35 (46.7)	0.466
Harvested LNs <12	3 (1.5)	1 (1.3)	0.897
Bowel obstruction	61 (31.4)	18 (24.0)	0.229
Tumor perforation	29 (14.9)	9 (12.0)	0.534
No. of high-risk features			
1	127 (65.5)	38 (50.7)	0.036
≥2	67 (34.5)	37 (49.3)	

Values are presented as number (%).
LNs, lymph nodes.

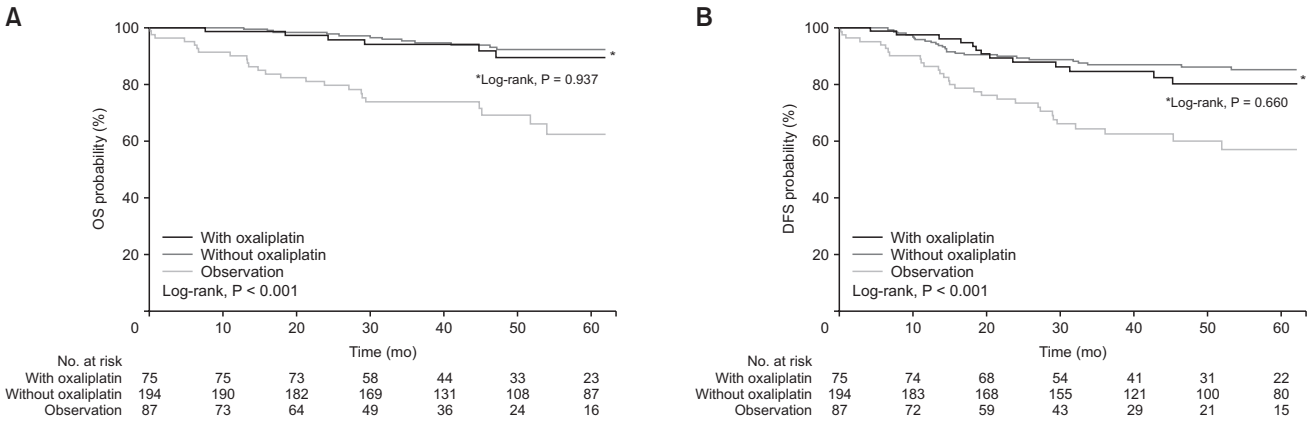

Fig. 3. Analysis of survival (Kaplan-Meier) with the inclusion of oxaliplatin as part of adjuvant chemotherapy for high-risk stage II colon cancer. (A) Overall survival (OS) and (B) disease-free survival (DFS).

Table 7. Adverse events during adjuvant chemotherapy according to administration of oxaliplatin

Variable	Without oxaliplatin (n = 194)	With oxaliplatin (n = 75)	P-value
Overall	142 (73.2)	74 (98.7)	<0.001
Neutropenia	12 (6.2)	28 (37.3)	<0.001
Diarrhea	44 (22.7)	16 (21.3)	0.812
Nausea/vomiting	65 (33.5)	58 (77.3)	<0.001
Hand-foot syndrome	79 (40.7)	4 (5.3)	<0.001
Stomatitis	38 (19.6)	14 (18.7)	0.864
Neuropathy	2 (1.0)	61 (81.3)	<0.001
CTCAE grade ≥3	29 (14.9)	25 (33.3)	0.001
Neutropenia	3 (1.5)	18 (24.0)	<0.001
Diarrhea	11 (5.7)	2 (2.7)	0.303
Nausea/vomiting	4 (2.1)	5 (6.7)	0.060
Hand-foot syndrome	13 (6.7)	0 (0)	0.022
Stomatitis	3 (1.5)	0 (0)	0.279
Neuropathy	0 (0)	4 (5.3)	0.001

Values are presented as number (%).
CTCAE, Common Terminology Criteria for Adverse Events.

group without oxaliplatin than in the group with oxaliplatin (16.5% *vs.* 69.3%, P < 0.001).

DISCUSSION

Our study results suggest that adjuvant chemotherapy using oral fluoropyrimidine monotherapy in patients with high-risk stage II colon cancer is beneficial with fewer severe adverse events but similar long-term survival outcomes compared to IV fluoropyrimidine-based chemotherapy.

Existing evidence on the effectiveness of adjuvant chemotherapy for patients with stage II colon cancer is not confirmative. Some studies reported better survival outcomes in the adjuvant chemotherapy group than in the observation group, whereas other studies reported that adjuvant chemotherapy was not beneficial even in patients with high-risk stage II colon cancer [3-6,19,20]. In our study, the adjuvant chemotherapy group had better survival outcomes than the observation group. However, age could be a confounding factor in the determination of OS and DFS. The observation group had higher mean age and more patients with ASA PS grade ≥III than the adjuvant chemotherapy groups. The natural course of these patients would be poor; hence, these patients were not ideal candidates for adjuvant chemotherapy.

The adjuvant chemotherapy regimen for high-risk stage II colon cancer varies according to the administration route and the combination of therapeutic agents. While a conclusive randomized controlled trial has not been conducted, NCCN guidelines recommend adjuvant chemotherapy with drugs such as capecitabine, FL, FOLFOX, or capecitabine plus oxaliplatin as a treatment option for high-risk stage II colon cancer [7]. In our study, patients who received IV chemotherapy were younger but had more T4 lesions than those who received oral fluoropyrimidine monotherapy. Furthermore, oxaliplatin-treated patients were younger and had more T4 lesions, right-sided colon cancer, and poorly differentiated histology than those who did not receive this treatment. In general, patients with T4 lesions, right-sided colon cancer, poorly differentiated histology, and multiple high-risk features were expected to have poor survival outcomes; however, there was no difference in survival outcomes between the oral fluoropyrimidine monotherapy and IV chemotherapy groups. The multivariate analysis results were also comparable. According to the ESMO guidelines, T4 stage is considered a major prognostic parameter for risk assessment of stage II colon cancer [13]. Among the patients with T4 lesions in this study, more than half received IV chemotherapy, including oxaliplatin. In other words, IV chemotherapy with oxaliplatin may improve survival outcomes in these patients. Future prospective research will be required

to confirm our findings.

Most patients with cancer prefer oral chemotherapy to IV chemotherapy when the treatment efficacy is similar [11,21,22]. In previous studies, the use of oral capecitabine monotherapy as adjuvant or palliative treatment in stage III or metastatic colon cancer showed similar efficacy and fewer adverse events compared with IV 5-FU/leucovorin chemotherapy [12,14]. However, data on adjuvant oral fluoropyrimidine monotherapy for stage II colon cancer is insufficient. In this study, OS and DFS were not different between the oral fluoropyrimidine monotherapy and IV chemotherapy groups. The incidence of treatment-related adverse events was much less in the oral fluoropyrimidine monotherapy group than in the IV chemotherapy group (69.8% *vs.* 99.0%, $P < 0.001$). Only the hand-foot syndrome was more frequent in the oral fluoropyrimidine monotherapy group (45.9% *vs.* 4.1%, $P < 0.001$), which is consistent with previous studies [23,24]. Severe adverse events of grade ≥3 were almost 3-fold higher in the IV chemotherapy group than in the oral fluoropyrimidine monotherapy group (34.0% *vs.* 12.2%, $P < 0.001$). Adverse events trigger a reduction of the initially planned therapeutic dose of the chemotherapeutic agents. Moreover, uncontrolled or severe adverse events can lead to the early termination of adjuvant chemotherapy. In this study, adjuvant chemotherapy was completed with initially scheduled cycles in 90% of patients in both oral fluoropyrimidine monotherapy and IV chemotherapy groups. However, the number of dose reduction cases during the treatment period due to adverse events was 4-fold higher in the IV chemotherapy group than in the oral fluoropyrimidine monotherapy group (58.8% *vs.* 15.7%, $P < 0.001$). Consequently, patients who received oral fluoropyrimidine monotherapy had a lower risk of adverse events and dosage reduction than those who received the IV fluoropyrimidine-based chemotherapy.

The IV chemotherapy in this study mainly comprised oxaliplatin-containing regimen (75 of 97, 77.3%). The severity of oxaliplatin-induced peripheral neuropathy increases by the dosage and duration of oxaliplatin administration [8-10,25-27]. In this study, patients who did not receive oxaliplatin had fewer severe adverse events than those who did, but no difference in survival outcomes was observed. Our observations are generally consistent with the results of the MOSAIC study, in which there were no differences in DFS and OS outcomes in patients with high-risk stage II colon cancer between FOLFOX and FL (10-year DFS rate, 72.7% *vs.* 67.0% [hazard ratio, 0.79; 95% confidence interval, 0.55–1.13; $P = 0.194$] and 10-year OS rate, 75.4% *vs.* 71.7% [hazard ratio, 0.89; 95% confidence interval, 0.60–1.32; $P = 0.579$], respectively) [4]. This suggests that oral fluoropyrimidine monotherapy can be used preferentially for most patients with high-risk stage II colon cancer.

The limitations of this study are as follows. First, this was a retrospective, single-center study with small number of enrolled patients. Minor adverse events are sometimes overlooked because chemotherapy toxicity is often underestimated in outpatient clinics in the real world. Furthermore, a small sample size is insufficient to detect minor changes in survival following IV or oxaliplatin chemotherapy. In this study, no subgroup benefited more from oxaliplatin-containing combination therapy compared to fluoropyrimidine monotherapy. Therefore, we acknowledge that further well-designed prospective studies are warranted to generalize the result of our study to various populations and investigate whether there are patients with high-risk stage II colon cancer who can benefit more from oxaliplatin-containing combination therapy than from fluoropyrimidine monotherapy. Second, during the 12-year period (2003–2014) in which adjuvant chemotherapy was administered in this study, the Korean National Health Insurance coverage criteria were changed. In January 2006, FOLFOX and capecitabine monotherapy were added to the National Health Insurance as adjuvant chemotherapy for colon cancer, and this has consequently led to a significant decrease in the use of UFT and an increase in the number of patients receiving adjuvant FOLFOX or capecitabine monotherapy. Therefore, we cannot rule out the potential bias in our results due to the medical policy changes.

In conclusion, our study suggests that oral fluoropyrimidine monotherapy is an effective and convenient adjuvant treatment for patients with high-risk stage II colon cancer, with similar survival outcomes and fewer chemotherapy-related adverse events than IV fluoropyrimidine-based chemotherapy. Therefore, oral fluoropyrimidine monotherapy may be considered the preferential therapy for most patients with high-risk stage II colon cancer. Future prospective studies are needed to confirm our observations.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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