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ORIGINAL ARTICLE

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Randomized controlled trial of the efficacy of adjuvant immunochemotherapy and adjuvant chemotherapy for colorectal cancer, using different combinations of the intracutaneous streptococcal preparation OK-432 and the oral pyrimidines 1-hexylcarbamoyl-5-fluorouracil and uracil/tegafur

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Abstract
Background. We investigated the efficacy and safety of adjuvant immunochemotherapy and adjuvant chemotherapy for colorectal cancer, using different combinations of the intracutaneous streptococcal preparation OK-432 and the oral pyrimidines 1-hexylcarbamoyl-5-fluorouracil (carmofur, HCFU) and uracil/tegafur (UFT).
Methods. Patients with stage II, III, or IV (Dukes' B, C) colorectal cancer were enrolled and randomly assigned to one of three groups: an immunochemotherapy group (mitomycin C [MMC] + 5-fluorouracil [5-FU] + HCFU + OK-432), a chemotherapy group (MMC + 5-FU + HCFU), and a control group (surgery alone) for those with colon cancer (study 1); and an immunochemotherapy group (MMC + 5-FU + UFT + OK-432), a chemotherapy group (MMC + 5-FU + UFT), and a control group (surgery alone) for those with rectal cancer (study 2).
Results. A total of 760 patients with colon cancer and 669 patients with rectal cancer were entered into this randomized clinical trial (RCT). The incidence of side-effects was in the order of: immunochemotherapy group > chemotherapy group > control group in both the cohort of patients with colon cancer and the cohort with rectal cancer. In particular, the frequency of leucopenia and skin disorders was significantly higher than control groups. There were no severe adverse events such as death related to the adjuvant therapy. In both the colon cancer and rectal cancer cohorts, no significant difference in the 5-year survival rate and disease-free survival rate was noted among the three groups.
Conclusion. The results of an RCT demonstrated that the combination of MMC + 5-FU + HCFU + OK-432 for colon cancer and that of MMC + 5-FU + UFT + OK-432 for rectal cancer could not prolong the survival of patients with surgically resected colorectal cancer, but that both combinations were well tolerated as adjuvant therapy.

Key words Colorectal cancer · Adjuvant immunochemotherapy · OK-432 · HCFU · UFT

Introduction

Recurrence of colon cancer is often found as hepatic metastasis, and the proportions of hepatic metastases and local recurrences are still high in rectal cancer. The prevention and treatment of recurrence pose major problems in the treatment of colorectal cancer. Clinical trials of various adjuvant chemotherapies have been conducted vigorously worldwide with the aim of improving the clinical results of curative resection of colorectal cancer.[1–3]

The JFMC07-8601 trial conducted by the Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC) is one of the largest scale clinical trials in Japan.[4,5] The results showed a significant improvement in the survival rate in the mitomycin C (MMC) + 1-hexylcarbamoyl-5-fluorouracil (carmofur, HCFU) group for stage IV or V

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colon cancer compared with the group treated by surgery alone.[4] In rectal cancer, the disease-free survival rate of the MMC + uracil/tegaur (UFT) group was significantly higher than that of the group having surgery alone.[5] Based on the results of the JFMC07-8601, in the current study, we investigated a new adjuvant chemotherapy using two kinds of oral anticancer drugs, the pyrimidine fluoride HCFU for colon cancer and UFT for rectal cancer, with the aim of improving the clinical results. HCFU, an oral derivative of 5-fluorouracil (5-FU), is reported to have improved the survival rate and disease-free survival rate as adjuvant chemotherapy for colorectal cancer.[4,6,7] UFT, a compound prepared by mixing tegafur, a 5-FU derivative, and uracil (which inhibits the degradation of 5-FU) at the molecular weight ratio of 1:4 is reported to have improved the disease-free survival rate in rectal cancer.[5,8]

Immediately before this study was planned, promising results in the treatment of colon cancer using levamisole (LEV) as an immunoactivator and 5-FU were reported.[9] In the current study, a streptococcal agent (OK-432), a nonspecific immunoactivator, instead of LEV, was added to the regimen of JFMC07-8601 in order to reinforce the efficacy of chemotherapy. Accordingly, OK-432 was added to MMC + 5-FU + HCFU in patients with colon cancer and it was added to MMC + 5-FU + UFT in patients with rectal cancer in order to clarify the efficacy of adjuvant immunochemotherapy.

Patients and methods

Patients

This study, conducted as JFMC15-8901, consisted of two studies; namely, study 1 for colon cancer and study 2 for rectal cancer. The protocol was prepared by the JFMC15-8901 Committee and then approved by the Scientific Screening Committee of the JFMC. Hospitals participating in the study were recruited through medical journals, and 262 hospitals were selected by the Scientific Screening Committee.

This study adhered to the guidelines set out in *The general rules for clinical and pathological studies on cancer of colon, rectum and anus (4th edition)*,[10] which were applicable in Japan at the time. These rules for the classification of staging differ from the TNM classification of the International Union Against Cancer (UICC) as follows: stage II refers to cases in which lymph node metastasis is negative and the tumor spreads beyond the proper muscle, but does not invade other organs. Stage III refers to cases in which metastasis to paracolic lymph nodes is positive or the tumor directly invades other organs. Stage IV refers to cases in which metastasis to intermediate lymph nodes or main lymph nodes is positive. Therefore, stage II corresponds to Dukes' B, and stages III and IV to Dukes' C.

Cases meeting the following criteria: (1) stage II, III, or IV (Dukes' B, C) colorectal cancer and (2) patient age less than 75 years were registered from January 1989 to the end of December 1989. Consent to participate in this study was obtained from patients in advance. A central telephone registration system was adopted. The registered cases were randomly assigned to the treatment groups according to the assignment table.

Methods

In both study 1 and study 2, there were three treatment groups; namely, an immunochemotherapy group (group A and group D), a chemotherapy group (group B and group E), and a control group (group C and group F).

In study 1, for colon cancer, MMC (Kyowa Hakko Kogyo, Tokyo, Japan), 6 mg/m^2, was administered intravenously on the day of surgery, 1 week after surgery, and 1, 2, 3, 4, 5, and 6 months after surgery; 5-FU, 250 mg/day, was administered intravenously for 1 week from postoperative day 1, HCFU (Nihon Schering, Osaka, Japan) 300 mg/day was administered orally for 1 year from 2 weeks after surgery; and OK-432, 1 KE, 3 KE, and 5 KE, was administered intracutaneously on the day of surgery and on postoperative days 3 and 7, and 5 KE was administered every 2 weeks after the postoperative day 14 up to 6 months after surgery in group A. In group B, OK-432 was not administered, but MMC + 5-FU + HCFU were administered as in group A. In group C, surgery alone was performed.

In study 2, on rectal cancer, UFT (Taiho Pharmaceutical, Tokyo, Japan) 400 mg/day (in place of HCFU in group A) was administered orally for 1 year from the second postoperative week in group D, and the other drugs were administered by the same administration method as in group A. In group E, no OK-432 was administered, and MMC + 5-FU + UFT were administered as in group D. In group F, surgery alone was performed (Fig. 1).

The accumulation of cases began in January 1989. Because the indication of OK-432 for colorectal cancer was deleted from the list of drugs covered by the Japanese Medical insurance system in December 1989, due to a lack of evidence of an effect on colorectal cancer, the accumulation in groups A and D, using OK-432, was terminated on December 31, 1989. Clinical trials conducted during the period from January to December 1989 were designated as the first-term trial of JFMC15-8901. Registration of cases continued up to the end of December 1990 in groups B and C of study 1 and in groups E and F of study 2. This was designated as the second-term trial of JFMC15-8901. This article reports the results of the first-term trial of JFMC15-8901.

All the registered cases were followed-up for 5 years after surgery. The contents of reports were verified by a data manager. When the accuracy of the information entered was in doubt, an inquiry was made with the physician in charge.

Statistical analysis

The required sample size was calculated on the basis of the following assumptions: a 5-year survival rate of 70% for the

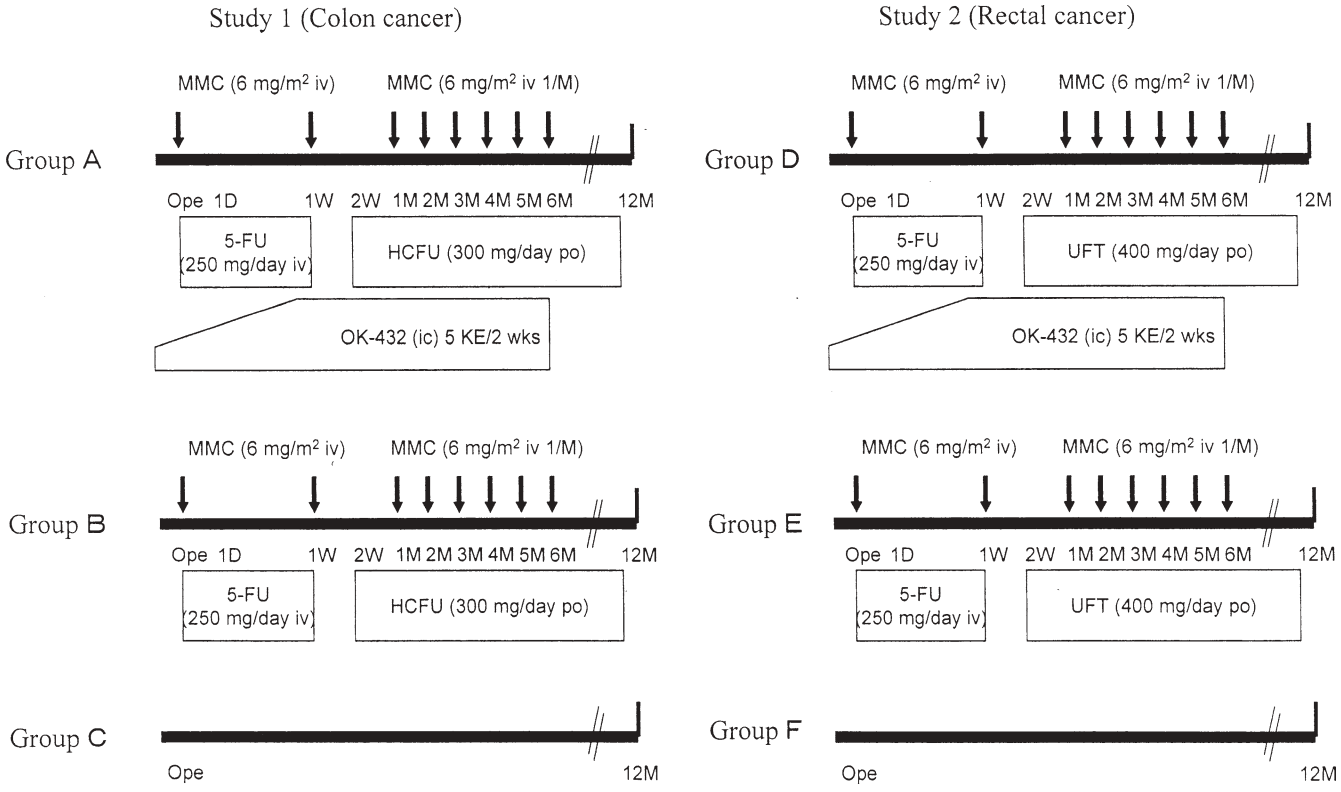

Fig. 1. Medication schedule. *MMC*, mitomycin C; *5-FU*, 5-fluorouracil; *HCFU*, 1-hexyl-carbamoyl-5-fluorouracil; *UFT*, uracil/tegafur; *D*, day; *W*, week(s); *M*, month(s); *ope*, operation

control group, and 75% for the drug treatment groups with colon cancer, and a 5-year survival rate of 60% for the control group, and 65% for the drug treatment groups with rectal cancer. The number of patients required for a group was estimated to be 600 for colon cancer and 700 for rectal cancer.

Statistical analysis was performed with Statistical Analysis System (SAS version 6.12, SAS Institute, Cary, NC, USA) software at the data center, and the procedure for the analysis and the results of this study were approved by the Clinical Trial Committee of the JFMC. The χ^2 test and Kruskal-Wallis test were used to evaluate the clinical characteristics. The survival rate and disease-free survival rate were estimated by the Kaplan-Meier method, and statistical significance was evaluated by the log-rank test and generalized Wilcoxon test (g-Wilcoxon test). The final report of this study was approved by the Clinical Trial Committee of the JFMC.

Results

Study 1 (colon cancer)

A total of 760 registered patients with colon cancer were randomly assigned to treatment in group A (5-FU + MMC + HCFU + OK-432; 254 patients); group B (5-FU + MMC + HCFU; 259 patients); or group C (control; 247 patients). In this study, 12 cases were ineligible (Table 1). No significant differences in the main clinicopathological background factors were found among the three groups (Table 2).

The compliance rate, based on the prescribed administration of 100 ± 20%, was 57.1% for MMC (group A, 56.3%; group B, 57.9%), 92.8% for 5-FU (group A, 92.9%; group B, 92.7%); 59.6% for HCFU (group A, 59.4%; group B, 59.8%) and 47.6% for OK-432 (Table 3). No significant difference in compliance was found between the groups with respect to MMC, 5-FU, and HCFU.

The toxicity profiles of these treatments are presented in Table 4. The incidence was in the order of group A > group B > group C. The most common significant toxicities were hematological disorders. Parameters showing significant differences in groups A and B compared with group C were stomatitis, anorexia, nausea, vomiting, increased blood urea nitrogen (BUN) and creatinine, skin disorders, dizziness, and feeling hot. The parameter showing a significantly high incidence in group A compared with groups B and C was fever. There were no severe adverse events such as death related to the adjuvant therapy.

The 5-year follow-up rate was 98.4%. No statistically significant difference in the 5-year survival rate was found among the three groups, with the rate being 75.4% in group A, 81.9% in group B, and 76.9% in group C (log-rank test, $P = 0.203$; g-Wilcoxon test, $P = 0.220$; Fig. 2). The 5-year

Table 1. Distribution of patients among treatment groups

	Study 1 (colon cancer)			Study 2 (rectal cancer)		
	Group A	Group B	Group C	Group D	Group E	Group F
Entered cases	254	259	247	222	218	229
Eligible cases	251 (98.8)	255 (98.5)	242 (98.0)	218 (98.2)	216 (99.1)	223 (97.4)
Ineligible cases	3 (1.2)	4 (1.5)	5 (2.0)	4 (1.8)	2 (0.9)	6 (2.6)
Treated case before surgery	–	–	–	1	–	–
Benign tumor	–	–	1	–	–	–
Nonepithelial tumor	–	–	–	1	1	–
Double cancer	1	1	1	–	–	2
Multicentric cancer	1	–	1	–	–	–
Location violation	–	1	1	1	–	1
Stage violation	–	1	–	–	–	1
Macroscopic noncurative resection	1	2	1	1	1	2

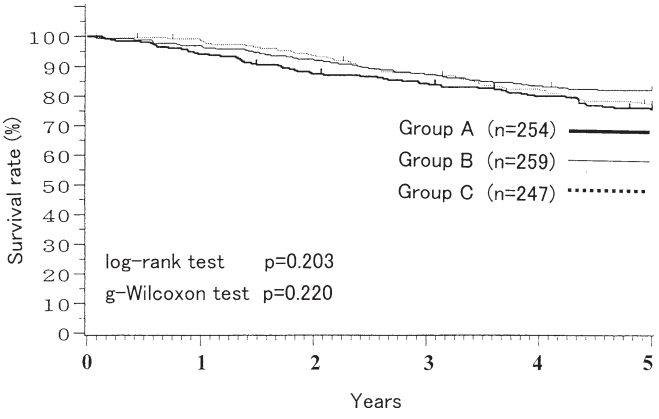

Fig. 2. 5-Year survival curves in study 1 (colon cancer). *g-Wilcoxon*, generalized Wilcoxon

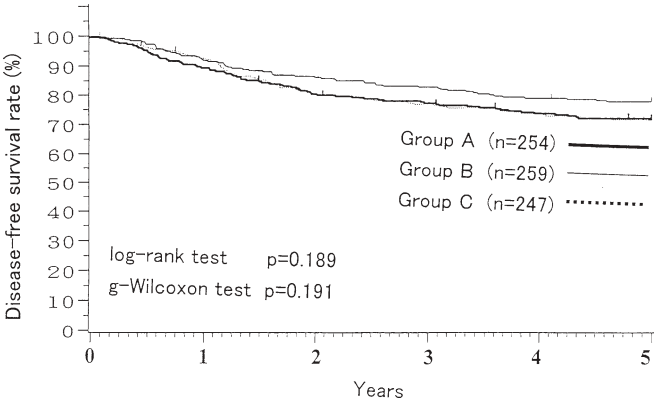

Fig. 3. 5-Year disease-free survival curves in study 1 (colon cancer)

disease-free survival rate was 71.5% in group A, 77.6% in group B, and 71.3% in group C. There were no significant differences between the groups (log-rank test, $P = 0.189$; g-Wilcoxon test, $P = 0.191$; Fig. 3). When compared by staging, the results for Dukes' B were poor in group A compared with groups B and C (log-rank test, $P = 0.038$; g-Wilcoxon test, $P = 0.039$). The 5-year disease-free rate for Dukes' B was 78.8% in group A, 81.8% in group B, and 74.3% in group C. However, no significant difference was found (log-rank test, $P = 0.129$; g-Wilcoxon test, $P = 0.132$).

Study 2 (rectal cancer)

A total of 669 registered patients with rectal cancer were randomly assigned to treatment in group D (5-FU + MMC + UFT + OK-432; 222 patients); group E (5-FU + MMC + UFT; 218 patients); or group F (control; 229 patients). In this study, 12 cases were ineligible (Table 1). No significant differences in the main clinicopathological background factors were found among the three groups (Table 2).

The compliance rate, based on the prescribed administration of 100 ± 20%, was 50.5% for MMC (group D, 49.1%; group E, 51.8%); 91.4% for 5-FU (group D, 91.0%; group E, 91.7%); 52.5% for UFT (group D, 49.5%; group E, 55.5%); and 45.0% for OK-432 (Table 3). As regards MMC, 5-FU, and UFT, no difference in compliance was found between the groups.

The toxicity profiles of these treatments are presented in Table 4. The incidence of toxicities was in the following order: group D > group E > group F. The most common toxicity was skin disorders. Parameters showing significant differences in groups D and E compared with group F were hematologic disorders, anorexia, nausea, vomiting, diarrhea, and respiratory disorders. The parameter showing a significantly high incidence in group D compared with groups E and F was fever. There was no severe toxicity such as death related to the adjuvant therapy.

The 5-year follow-up rate was 98.4%. No statistically significant difference in the 5-year survival rate was found among the three groups, with the rate being 73.5% in group D, 71.8% in group E, and 72.6% in group F (log-rank test, $P = 0.933$; g-Wilcoxon test, $P = 0.934$; Fig. 4). The 5-year disease-free survival rate was 67.8% in group D, 65.4% in group E, and 64.8% in group F, but no significant difference was found (log-rank test, $P = 0.785$; g-Wilcoxon test, $P = 0.745$; Fig. 5).

Table 2. Clinicopathological background factors

	Study 1 (colon cancer)				Study 2 (rectal cancer)			
	Group A	Group B	Group C	*P* value	Group D	Group E	Group F	*P* value
	254	259	247		222	218	229	
Age (years)								
≦49	34	40	45		26	38	38	
50–59	79	65	75	$P = 0.277$ (K–W test)	62	71	67	$P = 0.128$ (K–W test)
60–69	91	120	90	$P = 0.063$ (χ^2 test)	109	86	86	$P = 0.074$ (χ^2 test)
70–74	50	34	37		25	23	38	
Sex								
Male	136	129	125	$P = 0.674$ (χ^2 test)	143	127	133	$P = 0.298$ (χ^2 test)
Female	118	130	122		79	91	96	
Location of tumor								
I	0	0	0		0	0	0	
V	0	0	0		0	0	0	
C	24	22	26		0	0	0	
A	54	60	41		0	0	0	
T	34	42	34		0	0	0	
D	16	22	22	$P = 0.532$ (χ^2 test)	0	0	0	$P = 0.796$ (χ^2 test)
S	126	112	123		0	0	0	
Rs	0	0	1		61	50	62	
Ra	0	1	0		71	69	67	
Rb	0	0	0		89	99	99	
P	0	0	0		1	0	1	
E	0	0	0		0	0	0	
Depth of tumor invasion								
m	0	0	0		0	1	1	
sm	1	2	2		6	3	6	
pm	24	24	23	$P = 0.623$ (K–W test)	34	47	41	$P = 0.522$ (K–W test)
ss,a1	145	151	132	$P = 0.886$ (χ^2 test)	89	83	81	$P = 0.682$ (χ^2 test)
s,a2	77	72	77		87	78	91	
si,ai	6	10	12		4	6	9	
Unknown	1	0	1		2	0	0	
Lymph node metastasis								
n0	147	157	138		119	122	121	
n1	62	62	60		65	63	58	
n2	34	31	35	$P = 0.470$ (K–W test)	33	32	44	$P = 0.479$ (K–W test)
n3	9	9	12	$P = 0.872$ (χ^2 test)	3	1	5	$P = 0.517$ (χ^2 test)
n4	0	0	1		0	0	1	
Unknown	2	0	1		2	0	0	
Histological stage								
Stage I	18	21	19		29	31	36	
Stage II	124	130	113		88	89	79	
Stage III	66	68	65	$P = 0.490$ (K–W test)	66	65	61	$P = 0.456$ (K–W test)
Stage IV	43	38	46	$P = 0.972$ (χ^2 test)	36	33	49	$P = 0.252$ (χ^2 test)
Stage V	2	2	3		1	0	4	
Unknown	1	0	1		2	0	0	

Duke's classification								
A	18	21	19		29	31	36	
B	128	136	119	$P = 0.595$ (K–W test)	89	91	84	$P = 0.804$ (K–W test)
C	105	100	105	$P = 0.960$ (χ^2 test)	101	96	105	$P = 0.387$ (χ^2 test)
D	2	2	3		1	0	4	
Unknown	1	0	1		2	0	0	
Lymphatic invasion								
ly0	74	73	73		65	55	70	
ly1	107	113	87		82	100	92	
ly2	51	55	57	$P = 0.753$ (K–W test)	53	43	55	$P = 0.819$ (K–W test)
ly3	15	12	19	$P = 0.521$ (χ^2 test)	13	13	9	$P = 0.465$ (χ^2 test)
ly(+)	0	0	1		0	1	0	
Unknown	7	6	10		9	6	3	
Venous invasion								
v0	143	151	136		113	114	110	
v1	73	71	70		64	64	77	
v2	24	21	22	$P = 0.872$ (K–W test)	27	25	26	$P = 0.819$ (K–W test)
v3	5	6	3	$P = 0.903$ (χ^2 test)	8	9	8	$P = 0.952$ (χ^2 test)
v(+)	0	0	1		0	0	0	
Unknown	9	10	15		10	6	8	
Histological type								
Benign tumor	0	0	1		0	0	0	
Well-differentiated adenocarcinoma	134	140	119		115	112	116	
Moderately differentiated adenocarcinoma	98	100	107		97	92	101	
Poorly differentiated adenocarcinoma	13	10	11		1	7	3	
Mucinous adenocarcinoma	7	8	8		7	5	7	
Signet-ring cell carcinoma	0	0	1	$P = 0.822$ (χ^2 test)	0	0	0	$P = 0.554$ (χ^2 test)
Squamous cell carcinoma	0	0	0		0	1	2	
Adenosquamous carcinoma	0	0	0		0	0	0	
Undifferentiated carcinoma	1	1	0		0	0	0	
Unclassified carcinoma	0	0	0		0	0	0	
Others	0	0	0		1	1	0	
Unknown	1	0	0		1	0	0	
Lymph node dissection								
D0	0	0	0		0	0	0	
D1	11	8	2	$P = 0.217$ (K–W test)	9	7	11	$P = 0.413$ (K–W test)
D2	79	98	109	$P = 0.010$ (χ^2 test)	104	103	91	$P = 0.446$ (χ^2 test)
D3	163	153	136		108	108	127	
Unknown	1	0	0		1	0	0	
Microscopic curability								
Absolute curative resection	229	239	215		196	193	192	
Relative curative resection	22	16	24	$P = 0.171$ (K–W test)	21	20	27	$P = 0.171$ (K–W test)
Relative noncurative resection	1	3	4	$P = 0.423$ (χ^2 test)	0	0	6	$P = 0.038$ (χ^2 test)
Absolute noncurative resection	1	1	3		3	5	4	
Unknown	1	0	1		2	0	0	

K–W, Kruskal–Wallis

Table 3. Compliance with prescribed doses

Percentage compliant	Study 1 (colon cancer)		Study 2 (rectal cancer)	
	Group A	Group B	Group D	Group E
	254	259	222	218
MMC (i.v.)				
0%	3 (1.2)	1 (0.4)	4 (1.8)	4 (1.8)
<80%	97 (38.2)	99 (38.2)	101 (45.5)	96 (44.0)
80%–120%	143 (56.3)	150 (57.9)	109 (49.1)	113 (51.8)
>120%	10 (3.9)	7 (2.7)	6 (2.7)	5 (2.3)
Unknown	1 (0.4)	2 (0.8)	2 (0.9)	0 (0.0)
5-FU (i.v.)				
0%	9 (3.5)	8 (3.1)	9 (4.1)	8 (3.7)
<80%	8 (3.1)	8 (3.1)	8 (3.6)	9 (4.1)
80%–120%	236 (92.9)	240 (92.7)	202 (91.0)	200 (91.7)
>120%	0 (0.0)	1 (0.4)	1 (0.5)	1 (0.5)
Unknown	1 (0.4)	2 (0.8)	2 (0.9)	0 (0.0)
HCFU (p.o.)				
0%	15 (5.9)	8 (3.1)		
<80%	68 (26.8)	74 (28.6)		
80%–120%	151 (59.4)	155 (59.8)		
>120%	19 (7.5)	20 (7.7)		
Unknown	1 (0.4)	2 (0.8)		
UFT (p.o.)				
0%			20 (9.0)	6 (2.8)
<80%			73 (32.9)	76 (34.9)
80%–120%			110 (49.5)	121 (55.5)
>120%			17 (7.7)	15 (6.9)
Unknown			2 (0.9)	0 (0.0)
OK-432 (i.c.)				
0%	14 (5.5)		11 (5.0)	
<80%	104 (40.9)		104 (46.8)	
80%–120%	121 (47.6)		100 (45.0)	
>120%	14 (5.5)		5 (2.3)	
Unknown	1 (0.4)		2 (0.9)	

Figures in parentheses are percentages
MMC, mitomycin C; 5-FU, 5-fluorouracil; HCFU, 1-hexylcarmaboyl-5-fluorouracil; UFT, uracil/tegafur

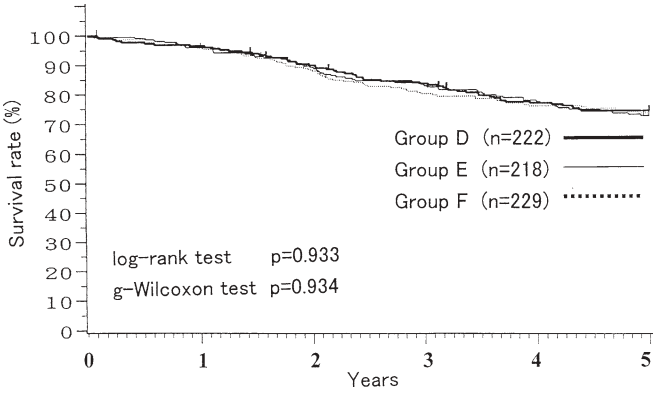

Fig. 4. 5-Year survival curves in study 2 (rectal cancer)

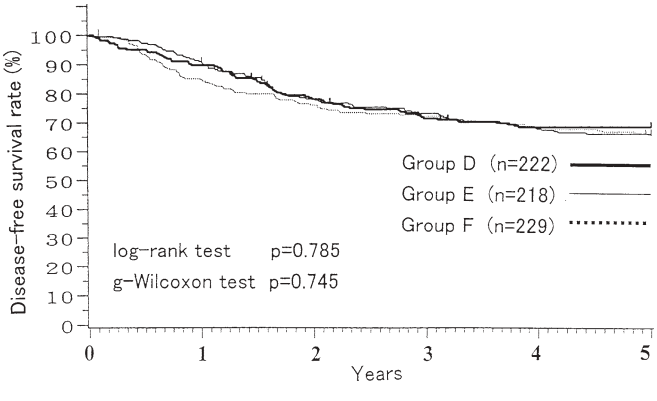

Fig. 5. 5-Year disease-free survival curves in study 2 (rectal cancer)

Discussion

The rates of ineligible cases and of those lost to follow-up were low, with the former being 12/760 cases (1.6%) of colon cancer and 12/669 cases (1.8%) of rectal cancer and the latter being 1.4% overall. Therefore, the present study is considered to be a multi-institutional joint control study in which the accuracy is very high. The compliance rate, based on the prescribed administration of 100 ± 20%, was high for 5-FU, at about 90%, versus about 50% for MMC, HCFU, UFT, and OK-432. Presumably, this was due mainly to the relatively simple administration method for 5-FU versus the intermittent administration method for MMC

Table 4. Incidence of toxic effects (%)

	Study 1 (colon cancer)				Study 2 (rectal cancer)			
	Group A	Group B	Group C	*P* Value	Group D	Group E	Group F	*P* Value
Anorexia	15.0 (2.0)	13.5 (1.5)	1.6 (0.4)	$P < 0.001$	18.0 (0.5)	21.1 (2.8)	3.9 (0)	$P < 0.001$
Nausea, vomiting	13.0 (2.4)	10.0 (0.8)	2.4 (0.4)	$P < 0.001$	11.3 (0.9)	17.4 (2.8)	2.2 (0)	$P < 0.001$
Diarrhea	7.1 (1.2)	5.4 (1.2)	2.8 (0)	$P = 0.089$	9.0 (2.7)	11.0 (2.8)	3.9 (0)	$P = 0.013$
Stomatitis	3.1 (0)	1.9 (0)	0 (0)	$P = 0.022$	2.3 (0)	2.3 (0)	0 (0)	$P = 0.066$
Respiratory system disorders	3.9 (2.0)	1.9 (0.8)	0 (0)	$P = 0.006$	5.4 (0.5)	5.0 (1.4)	1.3 (0)	$P = 0.042$
Fever	10.6 (0.4)	3.4 (0)	1.6 (0)	$P < 0.001$	9.5 (0)	3.7 (0)	2.2 (0)	$P < 0.001$
Sensory abnormality	3.5 (1.6)	0.4 (0)	0 (0)	$P < 0.001$	2.7 (1.4)	0.9 (0.5)	0 (0)	$P = 0.026$
Skin disorders	6.3 (0.8)	6.6 (0.8)	0 (0)	$P < 0.001$	7.2 (1.4)	3.2 (0)	0.4 (0)	$P < 0.001$
Alopecia	1.6 (0)	1.2 (0)	0 (0)	$P = 0.165$	3.2 (0)	1.4 (0)	0.4 (0)	$P = 0.063$
Consciousness disturbance	1.2 (0.4)	0.4 (0)	0 (0)	$P = 0.165$	1.4 (0)	0 (0)	0 (0)	$P = 0.045$
Depression	0.8 (0.4)	0.4 (0)	0 (0)	$P = 0.369$	1.8 (0)	0.5 (0)	0 (0)	$P = 0.066$
Phlebitis	1.2 (–)	1.9 (–)	0 (–)	$P = 0.107$	1.4 (–)	0 (–)	0 (–)	$P = 0.046$
Dizziness	5.1 (–)	5.8 (–)	0.4 (–)	$P = 0.004$	3.6 (–)	4.1 (–)	1.7 (–)	$P = 0.265$
Frequent urination	2.0 (–)	2.7 (–)	0.4 (–)	$P = 0.153$	5.9 (–)	2.8 (–)	3.9 (–)	$P = 0.266$
Feeling hot	5.9 (–)	4.2 (–)	0 (–)	$P = 0.001$	3.6 (–)	2.3 (–)	0.9 (–)	$P = 0.127$
Hemoglobin decreased	29.5 (3.5)	22.0 (1.2)	13.4 (0.8)	$P < 0.001$	25.7 (4.1)	24.3 (2.8)	12.2 (0)	$P < 0.001$
Leucopenia	39.4 (3.9)	28.6 (1.9)	7.7 (0)	$P < 0.001$	33.8 (2.7)	33.9 (4.1)	8.7 (0)	$P < 0.001$
Neutropenia	21.7 (3.5)	12.7 (2.3)	3.6 (0.8)	$P < 0.001$	15.8 (2.3)	16.5 (5.5)	5.7 (0)	$P < 0.001$
Thrombopenia	12.6 (4.3)	7.3 (1.9)	1.6 (1.2)	$P < 0.001$	18.9 (5.4)	16.5 (2.3)	2.6 (0.9)	$P < 0.001$
T. Bilirubin increased	2.0 (0)	2.7 (0)	1.2 (0)	$P = 0.507$	3.2 (0)	5.5 (0.5)	1.3 (0)	$P = 0.048$
BUN increased	7.9 (0.8)	5.8 (1.2)	0 (0)	$P < 0.001$	3.2 (0)	3.2 (0)	0.9 (0)	$P = 0.181$
Creatinine increased	5.1 (0.4)	2.7 (1.2)	0 (0)	$P = 0.002$	2.7 (0)	1.8 (0)	0 (0)	$P = 0.054$
Hematuria	5.9 (0)	5.8 (0.4)	2.4 (0)	$P = 0.109$	7.2 (0)	6.4 (0)	3.5 (0)	$P = 0.191$
Hypotension	1.6 (0.4)	0 (0)	0 (0)	$P = 0.018$	0 (0)	1.4 (0)	0 (0)	$P = 0.046$

Figures in parentheses are percentages of toxic effects of grade 3 or more

and OK-432. The long administration period of HCFU and UFT, 1 year after surgery, may be a factor in the reduced compliance rate. However, no difference in the total dose was found among the groups.

With all the registered groups, the incidence of side-effects was significantly higher in the chemotherapy group than in the surgery-alone group. Furthermore, the incidence of side-effects was higher in the immunochemotherapy groups (groups A and D) than in the chemotherapy groups (groups B and E) for both colon cancer and rectal cancer. The addition of OK-432 tended to cause the incidence of side-effects to increase. Whether this was due to the side-effects of OK-432 alone or whether it was the result of the side-effects of chemotherapy being amplified by OK-432 remains to be seen. In both study 1 and study 2, the proportion of side-effects accounting for the discontinuation of medication was lower in the immunochemotherapy group than in the chemotherapy group, and the side-effects themselves in the immunochemotherapy group were considered to be mild. In both study 1 and study 2, the incidence of toxicity was higher in the chemotherapy group and the immunochemotherapy group than in the control group, but there was no severe toxicity such as death related to treatment. The adjuvant therapy was considered to be highly tolerable and safe.

It is well known that there is a limit to the improvement in prognosis that can be gained by surgical treatment alone for advanced colorectal cancer. There is no objection to the necessity for some adjuvant therapies. The present study, following JFMC07-8601, is of significance as the basis of argument for the propriety of adjuvant therapy centered around 5-FU. However, MMC + 5-FU + OK-432 + oral fluoropyrimidine could not prolong the survival of patients with surgically resected colorectal cancer, and it led to no conclusion on the significance of the combined use of MMC and the optimal administration method of 5-FU. In both study 1 and study 2, the compliance rate for MMC, HCFU, UFT, and OK-432 in the treatment groups was only about 50%. Whether the low compliance rate for the drug has an influence on the lack of effectiveness found in the chemotherapy and immunochemotherapy groups remains unknown. In this study, registration of the immunotherapy groups had to be stopped in the middle of the study because the insurance coverage on OK-432 for colorectal cancer was no longer available. Therefore, the number of cases fell short of the required sample size, resulting in a decline of the statistical power. This may be mentioned as one of the reasons that no significant difference in survival rate or disease-free survival rate was found between the chemotherapy group and immunotherapy group, on the one hand, and the drug-treatment groups and the control group on the other.

As adjuvant therapy for Dukes' C colon cancer, 5-FU/LEV therapy was recommended by the American NIH in 1990, based on various clinical trials.[9] Subsequently, 5-FU/leucovorin (LV) therapy following 5-FU/LEV therapy started to draw attention, and a large-scale clinical trial of 5-FU/LV therapy was conducted.[11,12] As a result, 5-FU/LV therapy was found to be the most effective adjuvant therapy for Dukes' C colon cancer, in terms of the duration of administration, side-effects, recurrence rate, and survival rate, compared with 5-FU/LEV therapy.[13] At present,

therefore, 5-FU/LV therapy is regarded as the standard adjuvant therapy. On the other hand, group comparison studies of 5-FU/LV and UFT/LV have been conducted in Europe and the United States, and preliminary analysis of the toxicity findings has indicated that both regimens were well tolerated and had similar toxicity profiles.[14] This shows that the safety and convenience of oral fluoropyrimidine as adjuvant chemotherapy are being recognized in Europe and the United States. The current study is significant in that it demonstrated the safety of oral fluoropyrimidine as adjuvant therapy prior to those studies.

The combined use of irinotecan (CPT-11)[15] or oxaliplatin[16] has been reported to exert an effect on metastatic colorectal cancer that is superior to that of 5-FU/LV alone. Studies may focus on determining which treatments are valid as adjuvant chemotherapy for colorectal cancer – combined therapy with CPT-11 or oxaliplatin or combined therapy with an oral fluoropyrimidine. In the future, clinical trials similar to JFMC 15-8901, including the question of how to select subjects responsive to adjuvant therapy, should be conducted as soon as possible.

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