Long-term Outcome of Adjuvant Chemotherapy with S-1 Consisting of 3-week Administration Followed by 1-week Rest for Stage III Colorectal Cancer

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ABSTRACT

Background/Aims: The aim of this study is to evaluate long-term outcome of 3-week method (3-week administration followed by 1-week rest) for colorectal cancer as adjuvant chemotherapy with an oral anticancer drug, S-1.

Methods: Between 2008 and 2012, 142 patients with stage III colorectal cancer who underwent curative resection in our hospital and received oral adjuvant chemotherapy with S-1 for six months were enrolled in this study. They were divided into two groups, 3-week method or 4-week method (4-week administration followed 2-week rest).

Results: The six-month completion rate in the 3-week method group was 100% (49/49) which was significantly better than that in the 4-week method group, 85% (79/93) ($p=0.002$). In total patients, five-year relapse-free survival rates in the 3-week method group was 89.6% which was significantly better than that in the 4-week method group, 74.2% ($p=0.027$). There were no grade 3 or 4 adverse reactions in both laboratory and clinical findings in the 3-week method group.

Conclusions: The 3-week method of S-1 administration had good feasibility, high accumulated dose in six months and good relapse-free survival rates. The 3-week method with S-1 seems to be a standard adjuvant chemotherapy schedule for colorectal cancer.

Key words: S-1, administration schedule, adjuvant chemotherapy, colorectal cancer

INTRODUCTION

In Japan, adjuvant chemotherapy after curative resection of colorectal cancer was developed primarily using oral fluorinated pyrimidines such as UFT (combination of uracil and tegafur) (1,2). S-1 (Taiho Pharmaceuticals Co. Ltd., Tokyo, Japan) is an attractive oral fluorinated pyrimidine approved for clinical use since January 1999 in Japan. The agent contains tegafur, 5-chloro-2-dihydropyrimidine and potassium oxonate at a molar ratio of 1:0.4:1, based on a biochemical modulation of 5-FU (3). The response rate of S-1 alone exceeded 40% in two late phase 2 trials for patients with advanced or recurrence gastric cancer (4,5). In Japan, S-1 has been approved as a postoperative adjuvant

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chemotherapeutic agent for colorectal cancer since December 2003. The standard administration schedule of S-1 has been 4-week administration followed by 2-week rest (4-week method). However, the completion rate at one year did not reach 70% mainly due to adverse reactions (6,7). Compliance of the 4-week method was not satisfactory. Therefore, we tried to start a new administration schedule which was a 3-week administration followed by 1-week rest (3-week method) since 2005, and two study, a pilot study and a prospective randomized trial, were carried out to evaluate feasibility and safety of adjuvant chemotherapy by the 3-week method for colorectal cancer (8). We arrived at the conclusion that adjuvant chemotherapy with the 3-week method using S-1 after curative surgery for colorectal cancer had good feasibility, easily manageable toxicity, high accumulated dose in one year and good compliance (8).

The aim of this study is to evaluate long-term outcome of the 3-week method (3-week administration followed by 1-week rest) for colorectal cancer as adjuvant chemotherapy with an oral anticancer drug, S-1 as compared to that of the 4-week method.

PATIENTS AND METHODS

Between 2008 and 2012, 142 patients with stage III colorectal cancer who underwent curative resection in our hospital and received oral adjuvant chemotherapy with S-1 for six months were enrolled in this study. They were divided into two groups, 3-week method or 4-week method (4-week administration followed by 2-week rest). The 3-week method group underwent chemotherapy consisted of six courses of S-1 at 80mg or 100mg/body per day according to the body surface area (BSA): BSA < 1.5m², 80mg/day; > 1.5 m², 100 mg/day. S-1 was administered orally, twice daily after meals for 4 weeks after surgery. While, the 4-week method group underwent chemotherapy consisting of four courses of S-1 at 80 mg or 100 mg/body per day according to BSA: BSA < 1.5 m², 80 mg/day; > 1.5 m², 100 mg/day. S-1 was administered orally, twice daily after meals for 4 weeks after surgery. Choice of treatment schedule, 3-week method or 4-week method, was based on the preference of the patient's primary physicians.

Treatment schedule

Physical examinations, routine blood analyses, and serum carcinoembryonic antigen (CEA) measurements were performed every two months after surgery.

Colonoscopy was performed every year after surgery. Computed tomography (CT) was performed every six months or when a patient's serum CEA value was higher than the normal level, 5.0 ng/ml. Positron emission tomography (PET) or PET/CT was not routinely performed but was occasionally employed for patients who had equivocal conventional imaging studies to detect occult metastasis if indicated.

Statistical analysis

Continuous variables are expressed as the mean and range. The Wilcoxon rank-sum test was used for the comparison of continuous variables, and the chi-square test was used for the comparison of categorical data. Relapse-free survival rates after surgery were examined by the Kaplan–Meier method and log–rank test. A P-value of less than 0.05 indicated significance. All data were analyzed with SPSS version 24.0 (IBM Japan, Ltd, Tokyo, Japan).

RESULTS

Comparison of all patients' characteristic between the two groups.

No significant differences were identified in age, gender, tumor site, tumor diameter, pathological type of tumor, depth of tumor invasion, number of lymph node metastasis, or surgical procedure. While, significant difference was found in surgical procedure ($p < 0.001$). The six-month completion rate in the 3-week method group was 100% (49/49) which was significantly better than that in the 4-week method group, 85% (79/93) ($p = 0.002$) (table 1).

Comparison of relapse-free survival rates after surgery between the two groups

In total patients, five-year relapse-free survival rates in the 3-week method group was 89.6% which was significantly better than that in the 4-week method group, 74.2% ($p = 0.027$) (fig. 1).

Comparison of characteristic of patients with colon cancer between the two groups

No significant differences were identified in age, gender, tumor site, tumor diameter, pathological type of tumor, depth of tumor invasion, number of lymph node metastasis, or surgical procedure. While, the six-month completion rate in the 3-week method group

Table 1 - Comparison of characteristic between 3-week and 4-week method

Characteristic	3-week method (n=49)	4-week method (n=93)	p value
Mean age (range), years	64.1 (35-80)	65.5 (31-80)	0.518
Gender, n (%)			0.973
Male	32 (65)	61 (66)	
Female	17 (35)	32 (34)	
Tumor site, n (%)			0.994
Colon	30 (61)	57 (61)	
Rectum	19 (39)	36 (39)	
Mean tumor diameter (rang) mm	48.2 (10-140)	51.9 (12-210)	0.147
Pathology, n (%)			0.789
Well differentiated adenocarcinoma	10 (20)	23 (25)	
Moderately differentiated adenocarcinoma	33 (67)	61 (66)	
Others	6 (13)	9 (9)	
T number, n (%)			0.163
T1	2 (4)	5 (5)	
T2	6 (12)	2 (2)	
T3	25 (51)	56 (61)	
T4a	14 (29)	25 (27)	
T4b	2 (4)	5 (5)	
Number of lymph node metastasis			0.452
≤ 3	34 (69)	70 (75)	
> 3	15 (31)	23 (25)	
Surgical procedure			< 0.001
Laparoscopic surgery	30 (61)	19 (20)	
Open surgery	19 (39)	74 (80)	
Accomplishment of regimen			0.002
Complete	49 (100)	79 (85)	
Incomplete	0 (0)	14 (15)	

was 100% (30/30) which was significantly better than that in the 4-week method group, 84% (48/57) ($p=0.025$) (table 2).

Comparison of relapse-free survival rates after surgery between the two groups.

In patients with colon cancer, five-year relapse-free survival rates in the 3-week method group was 86.2% which was identified no significant difference compared with that in the 4-week method group, 73.7% ($p=0.253$) (fig. 2).

Figure 1 - Comparison of relapse-free survival rates after surgery between the two groups. In total patients, five-year relapse-free survival rates in the 3-week method group was 89.6% which was significantly better than that in the 4-week method group, 74.2% ($p=0.027$)

Figure 2 - Comparison of relapse-free survival rates after surgery between the two groups. In patients with colon cancer, five-year relapse-free survival rates in the 3-week method group was 86.2% which was identified no significant difference compared with that in the 4-week method group, 73.7%

Table 2 - Comparison of characteristic between 3-week and 4-week method in colon cancer

Characteristic	3-week method (n=30)	4-week method (n=57)	p value
Mean age (range), years	66.7 (36-80)	68.1 (44-80)	0.937
Gender, n (%)			0.338
Male	21 (70)	34 (60)	
Female	9 (30)	23 (40)	
Mean tumor diameter (rang) mm	48.6 (10-140)	50.6 (14-210)	0.430
Pathology, n (%)			0.873
Well differentiated adenocarcinoma	7 (23)	16 (28)	
Moderately differentiated adenocarcinoma	20 (67)	35 (61)	
Others	3 (10)	6 (11)	
T number, n (%)			0.479
T1	2 (7)	4 (7)	
T2	3 (10)	1 (2)	
T3	15 (50)	34 (60)	
T4a	9 (30)	15 (26)	
T4b	1 (3)	3 (5)	
Number of lymph node metastasis			0.757
≤ 3	22 (73)	40 (70)	
> 3	8 (27)	17 (30)	
Surgical procedure			0.004
Laparoscopic surgery	14 (47)	10 (18)	
Open surgery	16 (53)	47 (82)	
Accomplishment of regimen			0.025
Complete	30 (100)	48 (84)	
Incomplete	0 (0)	9 (16)	

Comparison of characteristic of patients with rectal cancer between the two groups

No significant differences were identified in age, gender, tumor site, tumor diameter, pathological type of tumor, depth of tumor invasion, number of lymph node metastasis, or completion rate. While, significant difference was found in surgical procedure ($p < 0.001$). (table 3).

Comparison of relapse-free survival rates after surgery between the two groups

In patients with rectal cancer, five-year relapse-free survival rates in the 3-week method group was 94.4% which was significantly better than that in the 4-week method group, 75.0% ($p = 0.043$) (fig. 3).

DISCUSSION

Ohtsu et al. (9) reported that S-1 achieves similar responses to the standard regimen of 5-FU plus LV for colorectal cancer and showed the potential of being an alternative to such a combination. The adjuvant chemotherapy after curative resection of colorectal

cancer was developed primarily using oral fluorinated pyrimidines in Japan. S-1 has already been a key drug of chemotherapy for colorectal cancer now (10). According to the 2016 guideline, the adjuvant chemotherapy indicates for patients with stage III colorectal cancer for which R0 resection has been

Figure 3 - Comparison of relapse-free survival rates after surgery between the two groups. In patients with rectal cancer, five-year relapse-free survival rates in the 3-week method group was 94.4% which was significantly better than that in the 4-week method group, 75.0% ($p = 0.043$)

Table 3 - Comparison of characteristic between 3-week and 4-week method for rectal cancer

Characteristic	3-week method (n=19)	4-week method (n=36)	p value
Mean age (range), years	59.8 (35-80)	61.3 (31-80)	0.714
Gender, n (%)			0.192
Male	11 (58)	27 (75)	
Female	8 (42)	9 (25)	
Mean tumor diameter (rang) mm	47.5 (15-100)	54.1 (12-108)	0.140
Pathology, n (%)			0.687
Well differentiated adenocarcinoma	3 (16)	7 (20)	
Moderately differentiated adenocarcinoma	13 (68)	26 (72)	
Others	3 (16)	3 (8)	
T number, n (%)			0.465
T1	0 (0)	1 (3)	
T2	3 (16)	1 (3)	
T3	10 (53)	22 (61)	
T4a	5 (26)	10 (27)	
T4b	1 (5)	2 (6)	
Number of lymph node metastasis			0.094
≤ 3	12 (63)	30 (83)	
> 3	7 (37)	6 (17)	
Surgical procedure			< 0.001
Laparoscopic surgery	16 (84)	9 (25)	
Open surgery	3 (16)	27 (75)	
Accomplishment of regimen			0.226
Complete	19 (100)	31 (86)	
Incomplete	0 (0)	5 (14)	

performed. And the recommend administration period is 6 months (10).

The 4 week administration of S 1 followed by a 2 week rest regimen has been established as the standard regimen for S 1 therapy. Results from a post marketing survey on 4,177 patients with advanced recurrent gastric cancer demonstrated that the rate of toxicity for the 4 week / 2 week regimen was 74.3% and the rate of ≥ grade 3 adverse events was 25%. In addition, in 3,801 patients assessed for the efficacy analysis, benefits with the 4 week / 2 week regimen were observed, with a median survival time of 8.3 months and a 1 year survival rate of 33.3% (95% confidence interval: 31.8 34.9) (11). The completion rate of the one-year schedule in the standard treatment schedule, 4-week method, did not reach 70% due to adverse reactions (6,7). Compliance of the 4-week method was not satisfactory and an improvement in compliance remains an issue that must be addressed.

In our previous prospective randomized trial, the completion rate of the one-year schedule in the 3-week method (3-week administration followed by 1-week rest) was 98% which was significantly greater than that in the 4-week method group. The 3-week method seemed to have excellent feasibility as adjuvant

chemotherapy. In this study, we tried to evaluate anti-tumor effect of 3-week method for colorectal cancer as adjuvant chemotherapy with an oral anticancer drug, S-1. Five-year relapse-free survival rates in the 3-week method group was 89.6% which was significantly better than that in the 4-week method group, 74.2%. The six-month completion rate in the 3-week method group was 100% which was significantly better than that in the 4-week method group, 85%. The six-month completion rate in the 4-week method for gastric cancer was reported to be 83% which was not satisfactory. From the view of compliance, the 4-week method may not be an ideal treatment schedule.

According to the 2016 guideline, the recommend administration period is 6 months for the adjuvant chemotherapy after curative resection of colorectal cancer (10). As for the total accumulated dose of S-1 in six months schedule, that of the 3-week method is 12,600 mg (100 mg × 21 days × 6 courses) as compared to 11,200 mg (100 mg × 28 days × 4 courses) for the 4-week method, if BSA is over 1.5 m². The total accumulated dose of the 3-week method must be greater than that of the 4-week method if the dose per day is the same. Furthermore, there were no grade 3 or 4 adverse reactions in both laboratory and clinical findings in the

3-week method group in this study.

2-week administration followed by 1-week rest (2-week method) was reported to be a more feasible oral administration regimen for S-1 as adjuvant chemotherapy in gastric cancer as compared to the 4-week method (12). However, total accumulated dose of S-1 in the 2-week method is as many as that in the 4-week method in the same period of treatment.

S-1 with oxaliplatin (SOX), or Capecitabine with oxaliplatin (CapeOX) were not the standard treatment regimens during the term of this study (2008 -2012) in Japan because of medical cost and adverse reactions. Fluoropyrimidines with oxaliplatin is the standard treatment for patients with stage IIIc (TNM classification) colorectal cancer after curative resection in Japan now. S-1 alone is indicated for patients with stage IIIa colorectal cancer as adjuvant chemotherapy.

CONCLUSION

In conclusion, the 3-week method of S-1 administration had good feasibility, high accumulated dose in six months and good relapse-free survival rates. The 3-week method with S-1 seems to be a standard adjuvant chemotherapy schedule for colorectal cancer. however, a large-scale prospective study is needed to clarify this issue.

Limitations

Some limitations of this study must be addressed. The study is a small cohort study which is based on the evaluation of retrospective data in a single institution, thus lacking randomization of patients.

Conflict of Interest and Source of Funding

All author has no conflict of interest. No financial support was obtained for this study.

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