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Usefulness of TAS-102 as Third-line Chemotherapy for Metastatic Colorectal Cancer

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Abstract. *Background/Aim: The feasibility and oncological outcomes of treatment with TAS-102, that is recommended as third-line chemotherapy for patients with metastatic colorectal cancer (mCRC), remain unknown. Patients and Methods: Between 2013 and 2015, seven patients (five males, two females) with mCRC who were administered TAS-102 as third-line chemotherapy at our Institution were retrospectively studied. During the same period, seven patients with mCRC with Kirsten rat sarcoma viral oncogene homolog (KRAS) wild-type primary lesions who were administered irinotecan with panitumumab comprised the control group. Results: The duration of third-line chemotherapy in the TAS-102 group was 217.0 (range=136-337) days compared to 226.9 (range=122-335) days in the control group, with no significant difference in the duration of administration between the two groups. No significant difference in overall survival was identified between the two groups No serious adverse effects were encountered in either group. Conclusion: TAS-102 may be suitable as third-line chemotherapy for patients with mCRC.*

In Japan, first-, second-, third-, and fourth-line chemotherapy treatments for patients with metastatic colorectal cancer (mCRC) are administered according to the recommendations of the Japanese Society for Cancer of the Colon and Rectum Guidelines (1, 2). TAS-102 (Taiho Pharmaceutical Co. Ltd, Tokyo, Japan) is a novel oral antitumor agent recommended as third- or fourth-line chemotherapy in the 2016 guidelines (2). However, the feasibility and oncological outcomes of treatment with TAS-102 compared with those of other third-line regimens remain unknown. We retrospectively evaluated the usefulness of TAS-102 as third-line chemotherapy.

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Patients and Methods

Patients. The Ethics Committee for Biomedical Research of the Jikei Institutional Review Board approved the protocol [29-041 (8657)], and all patients or their family members provided their written informed consent to participation. Between 2013 and 2015, seven patients with mCRC who received TAS-102 as third-line chemotherapy were enrolled in the study. During the same period, seven patients with unresectable mCRC who were administered irinotecan with panitumumab comprised the control group. These 14 patients were given oxaliplatin with oral S-1 (tegafur, gimeracil, oteracil potassium) (SOX) as first-line chemotherapy, followed by the administration of irinotecan with oral S-1 (IRIS) as second-line chemotherapy. Patients were only included in this study if they demonstrated adequate organ function [leukocytes: 4, 000 to <12, 000/mm^3; thrombocytes, ≥100, 000/ mm^3; total serum bilirubin, ≤1.5 mg/dl; aspartate aminotransferase (AST) and alanine aminotransferase (ALT), <100 IU/l; and creatinine, ≤1.5 mg/dl]. Patients with a history of drug hypersensitivity or serious surgical and non-surgical complications were excluded.

Treatment schedule. Physical examinations, routine blood analyses, and serum carcinoembryonic antigen (CEA) measurements were performed every month before chemotherapy. Computed tomography (CT) was performed every 2 months or when a patient's serum CEA value on the treatment day was higher than it had been before the initial chemotherapy. The response of measurable and accessible disease sites was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) (3).

SOX (4) was employed as the first-line treatment. Oxaliplatin at 130 mg/m^2 was administered on the first day, followed by 14-day administration and 6-day withdrawal of oral S-1 (Taiho Pharmaceutical, Tokyo, Japan) at 80 mg or 100 mg per day according to the patient's body surface area (BSA), with 80 mg/day administered to those patients with BSA<1.5 m^2 and 100 mg/day administered to those patients with BSA>1.5 m^2. S-1 was administered orally twice daily after meals.

Irinotean with oral S-1 (IRIS) (5) was employed as the second-line treatment. Irinotecan at 120 mg/m^2 was administered on the first day, followed by 14-day administration and 6-day withdrawal of oral S-1

(Taiho Pharmaceutical, Tokyo, Japan) at 80 mg or 100 mg per day according to the patient's body surface area (BSA), with 80 mg/day administered to those patients with BSA<1.5 m^2 and 100 mg/day administered to those patients with BSA>1.5 m^2. S-1 was administered orally twice daily after meals.

Two regimens, TAS-102 or irinotecan with panitumumab therapy, were employed as the third-line treatment. TAS-102 at 35 mg/m^2 was administered twice daily, after morning and evening meals, 5 days a week for 2 weeks, followed by a 14-day rest period, thus completing one treatment cycle. The regimen was repeated every 4 weeks.

Irinotecan with panitumumab therapy was selected as the third-line treatment for those with Kirsten rat sarcoma viral oncogene homolog (KRAS) wild-type colorectal adenocarcinoma. Irinotecan at 120 mg/m^2 and panitumumab at 6 mg/kg were administered on the first day, followed by a 13-day rest period.

Adverse events were classified and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03 (6).

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. Postoperative relapse-free survival rates were examined by the Kaplan–Meier method and log-rank analysis. A *p*-value of less than 0.05 indicated significance. All data were analyzed with IBM SPSS Statistics, version 22.0 (IBM Japan, Ltd, Tokyo, Japan).

Table I. *Clinicopathological characteristics of patients treated with TAS-102 and the control group treated with the combination of irinotecan with panitumumab.*

Variable	TAS-102 (n=7)	Control (n=7)	*p*-Value
Mean age (range), years	69.0 (63-76)	67.0 (43-75)	0.592
Gender, n (%)			
Male	5 (71)	5 (71)	1.000
Female	2 (29)	2 (29)	
Primary site of disease, n (%)			
Colon	4 (58)	4 (58)	1.000
Rectum	3 (42)	3 (42)	
Recurrent site, n (%)			
Liver	2 (29)	1 (14)	0.766
Lung	2 (29)	3 (43)	
Peritoneum	3 (42)	3 (43)	
Median duration of therapy (range), days			
First line	224.0 (203-245)	220.4 (202-234)	0.684
Second line	282.1 (178-365)	278.6 (233-304)	0.565
Third line	217.9 (136-337)	226.9 (122-335)	0.995

Results

Patient characteristics. No significant differences in age, gender, primary site of disease, recurrent site of disease, or the duration of each chemotherapy treatment were identified between the two treatment groups (Table I).

Comparison of survival after second-line chemotherapy between the two groups. The survival time after second-line chemotherapy was 271.0 (136-337) days in the TAS-102 group and 226.9 (122-335) days in the combination group. No significant difference was identified between the two groups (Figure 1).

Comparison of overall survival between two groups. Overall survival was 852.3 (681-964) days in the TAS-102 group and 840.1 (722-954) days in the combination group. No significant difference was identified between the two groups (Figure 2).

Adverse effects after starting the two chemotherapy regimens. No serious adverse effects greater than grade 2 were encountered in either group.

Discussion

The infusion of fluorouracil and leucovorin combined with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI), as well as oral drugs combined with either oxaliplatin [SOX (4), XELOX (7)] or irinotecan [IRIS (5), XELIRI (8)], have been widely used as first-line or second-line chemotherapy for mCRC. There is no effective third-line chemotherapy regimen, although irinotecan with panitumumab (9) was recommended as third-line chemotherapy in the 2014 guidelines (1). TAS-102 is a novel oral antitumor agent recommended as third-line chemotherapy in the 2016 guidelines (2). TAS-102 is a combination of an antineoplastic thymidine-based nucleoside analog, trifluridine, and a thymidine phosphorylase inhibitor, tipiracil hydrochloride, at a molar ratio of 1:0.5 (weight ratio, 1:0.471) (10-12). Based on the results of a randomized phase II trial (13), TAS-102 was approved for the first time in Japan in March 2014 by the Pharmaceutical and Medical Devices Agency, with an initial indication being in patients with mCRC that is refractory to all standard therapies defined in the 2014 Japanese colorectal cancer treatment guidelines (1). A large-scale global phase III trial (RECOURSE trial) to evaluate the efficacy and safety of TAS-102 showed significant improvement in overall and progression-free survival in patients administered TAS-102 compared to those administered a placebo (14). Accordingly, the recommendation of TAS-102 as third- or fourth-line chemotherapy was revised to include treatment for patients with mCRC in the 2016 guidelines (2). However, the feasibility and oncological outcomes of using TAS-102 as third-line chemotherapy compared with the those using other third-line regimens are unknown. We retrospectively evaluated the usefulness of TAS-102 as third-line chemotherapy.

In this study, seven patients with mCRC with KRAS wild-type primary lesions who were administered irinotecan with

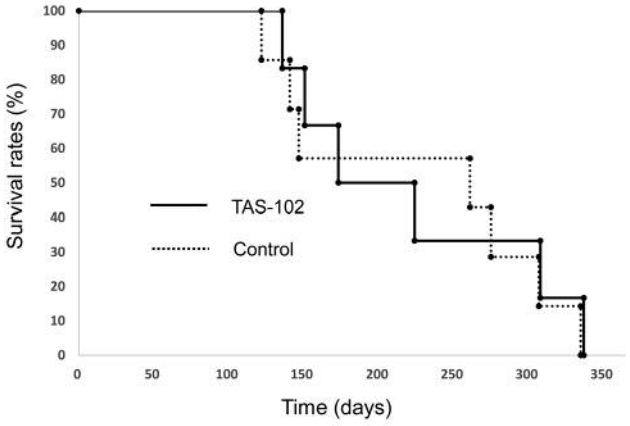

Figure 1. *Comparison of survival after second-line chemotherapy between patients subsequently treated with TAS-102 and the control group treated with the combination of irinotecan with panitumumab; no significant difference in survival was identified between groups.*

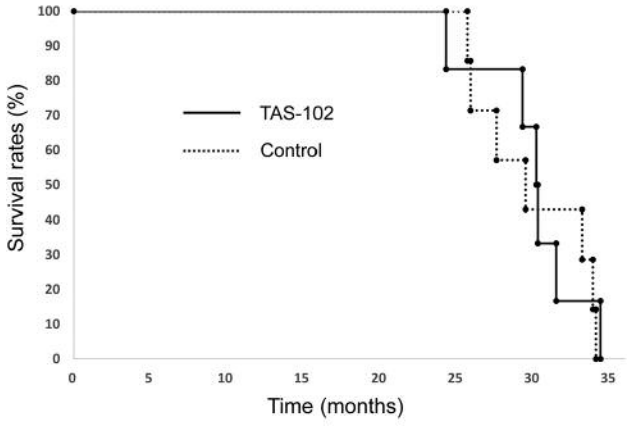

Figure 2. *Comparison of overall survival between patients treated with TAS-102 and the control group treated with the combination of irinotecan with panitumumab; no significant difference in survival was identified between groups.*

panitumumab comprised the control group. This combination has been recommended for more than 5 years as third-line chemotherapy for patients with mCRC whose primary lesions are *KRAS* wild-type (1). No significant difference was identified between the two groups in terms of survival after second-line chemotherapy. Therefore, the feasibility and oncological outcomes of TAS-102, an oral antitumor agent, seem to be equivalent to those of irinotecan with panitumumab, which is infused chemotherapy.

The toxic effects of TAS-102 were generally mild, and the agent was well tolerated (15). Myelosuppression was the main adverse event caused by TAS-102; however, it was manageable with dose reductions or temporary interruptions in treatment. Non-hematological adverse events, such as peripheral neuropathy, hand–foot syndrome, fatigue, and diarrhea, were uncommon (16). No serious adverse events greater than grade 2 were encountered in our study.

In conclusion, TAS-102 may be suitable as third-line chemotherapy that is comparable to irinotecan with panitumumab for patients with mCRC; however, a large-scale prospective study is needed.

Conflict of Interest

The Authors declare that they have no conflict of interest in regard to this study.

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