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Salvage Therapy After Regorafenib or Trifluridine/Tipiracil Treatment of Metastatic Colorectal Cancer: A Conditional Landmark Analysis

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Abstract. *Background/aim: This study aimed to describe the chemotherapy effects after trifluridine/tipiracil (TFTD) and/or regorafenib treatment in colorectal cancer (CRC) patients. Patients and Methods: Patients receiving regorafenib or TFTD for metastatic CRC during 2013-2018 were selected and divided into two groups: one with additional chemotherapy after regorafenib or TFTD (CTX group) and one without additional chemotherapy (Non-CTX group). Patients were followed up from a landmark point (90 days from the last day of administration of regorafenib or TFTD). We compared overall survival (OS) between the groups. Results: The median OS was 7.7 months in the CTX group and 4.1 months in the non-CTX groups. Several sensitivity analyses did not negate the survival advantage detected in the CTX group. Conclusion: The chemotherapy after regorafenib or TFTD was associated with prolonged OS in advanced CRC patients. Further study is required to determine appropriate treatment choice.*

Colorectal cancer (CRC) is one of the most diagnosed cancers in Western countries and the second most common cause of cancer-related deaths in the United States (1, 2). Half of the patients diagnosed with CRC will develop metastases (3, 4). With advances in the prevention, diagnosis, and treatment (surgery, radiation, and chemotherapy), the mortality rate of CRC patients decreased by 53% from 1970 to 2016 in the United States (2). Furthermore, over the past two decades, the overall survival (OS) of metastatic CRC (mCRC) patients has been gradually prolonged due to improvements in treatment protocols, including the discovery of targeted therapies (2, 5). The current management of mCRC involves various active drugs, either in combination or as monotherapy. Many phase III trials have been conducted, and there are options for standard treatment depending on both clinical factors and molecular markers (1, 6-9). Trifluridine/tipiracil (TFTD) or regorafenib is the last line of treatment after standard cytotoxic and targeted agents, as described in the guidelines (1, 8, 9). Beyond TFTD, the available choices include clinical trial enrolment, best supportive care (BSC), and other chemotherapies. Because direct comparisons of these options have rarely been examined, deciding on how to proceed to the next care plan is challenging in mCRC patients who might benefit from further treatment. Therefore, the number of prospective trials evaluating re-challenge, re-introduction, sequence, and investigational compounds has continued to increase (10-12). However, the interpretation of these studies remains difficult because of the combination of multiple anticancer agents and differences in clinical factors involved.

This study aimed to describe the current status of administration of anticancer agents after TFTD and/or regorafenib treatment and examine the effect of those treatments on clinical outcomes in CRC patients.

Patients and Methods

This retrospective cohort study was conducted using data available at the administrative claims database provided by Medical Data Vision Co, Ltd., (MDV; Tokyo, Japan). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (13). The Ethics Committee of the Graduate School and Faculty of Medicine, Kyoto University approved the study protocol (approval number: R2007, May 27, 2019). The requirement for informed consent was waived due to the anonymous nature of the data.

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Key Words: Salvage therapy, chemotherapy, colorectal cancer, cohort study.

Data sources. The database contained data of inpatient and outpatient medical care from 269 acute care hospitals throughout Japan and covered approximately 17% of acute care hospitals as of September 2018. Information of the following variables were available from the database: age; sex; body weight; height; medical department; diagnoses coded according to the International Classification of Diseases, 10th revision (ICD-10); prescription information, including prescription dates, doses, number of days of supply, and quantity; medical procedures; prognosis; and death dates. When patients changed hospitals or decided to move to end-of-life care at home, no further data could be collected. The distribution of the population based on sex and age in the database was similar to that reported in the Japanese census (14).

Study cohort and clinical outcomes. The inclusion criteria were as follows: patients receiving TFTD (drug reimbursement codes: 622336101, 622336001) and/or regorafenib (drug reimbursement code: 622225801) treatment for CRC; aged over 19 years; and prescribed therapy at least once from June 2013 through September 2018. The patients were followed up until September 2018. The exclusion criteria were as follows: patients who were prescribed regorafenib or TFTD for diseases other than CRC (gastrointestinal stromal tumour, small intestine cancer, liver cancer, etc.), and those who did not undergo follow-up after regorafenib or TFTD discontinuation. We set the landmark point at 90 days from the last day on which regorafenib or TFTD was administered. We divided the patients into two groups: the CTX group (received any chemotherapy within 90 days after the administration of regorafenib and/or TFTD) and the Non-CTX group (no chemotherapy within 90 days after the administration of regorafenib and/or TFTD).

The primary outcome was OS. We used conditional landmark analysis to reduce the immortal time bias, and OS was defined as the time between the landmark point and death from any cause (15, 16). Secondary outcome measures included the proportions of the adverse events. The administration of each anticancer agent after regorafenib and/or TFTD was described. We collected information on patient's age, body weight, body mass index (BMI), comorbidity, primary site of disease, metastatic sites, previous anticancer agents, and treatment department. We also collected information on adverse events and comorbidity using ICD-10 codes.

Sensitivity and subgroup analyses. For the first sensitivity analysis, we conducted propensity score matching to control for confounding factors between the two groups. For the second sensitivity analysis, we performed survival analysis for different landmark points, set at 0, 30, 60, and 120 days. For subgroup analysis, survival analysis was performed for each drug in patients who were prescribed one anticancer agent.

Statistical analyses. Data of continuous variables are presented as the mean [standard deviation (SD)] or the median [interquartile range (IQR)] according to the distribution of values. Data of categorical variables are presented as counts and proportions (%). Continuous variables were compared using the Mann–Whitney *U*-test. Categorical variables were compared using Pearson's chi-square test. OS curves were estimated with the Kaplan–Meier method. We used the log-rank test to assess difference in OS and the Cox regression model to estimate the hazard ratio (HR) for OS. We calculated propensity score to perform sensitivity analysis for OS between the CTX and Non-CTX groups (17, 18). Propensity score-matched analysis was performed using a 1:1 ratio, and the calliper width was set to 0.1. The factors considered as potential confounders were age, sex, body weight, BMI, primary site of disease, comorbidity, previous systemic anticancer agents, duration of the last chemotherapy, number of computed tomography scans taken during the previous year, and doctor's department. If the confounding factors were missing, then we excluded these patients from matching. For each analysis, we set $p<0.05$ for a two-sided significance level. All analyses were performed with SAS 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

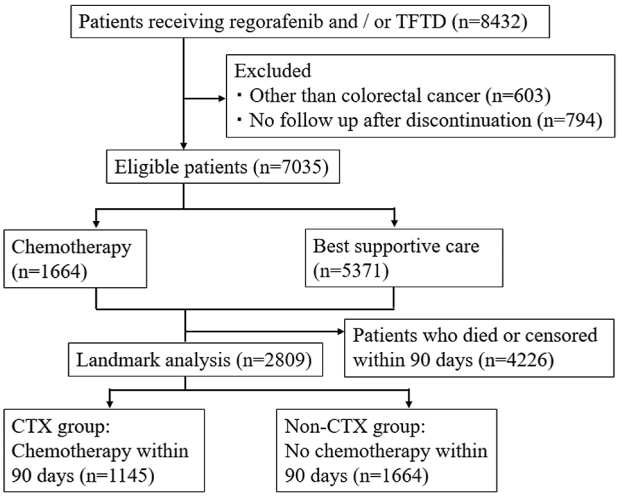

Figure 1. *Flowchart of the patient selection process.*

Results

Patients. The number of patients receiving regorafenib and/or TFTD between June 2013 and September 2018 was 8432. We excluded 603 patients receiving drugs for diseases other than CRC (gastrointestinal stromal tumour, intestinal cancer, and liver cancer). We also excluded 794 patients for insufficient follow-up. Chemotherapy was administered to 1664 patients after discontinuing regorafenib and/or TFTD. BSC was administered to 5367 patients. Before the landmark point, 4226 patients died or were censored. Finally, 1145 patients received chemotherapy (CTX group) and 1664 patients did not receive chemotherapy (Non-CTX group). The flow diagram of the patient selection process is shown in Figure 1. Patient characteristics are summarized in Table I. Patients in the Non-CTX group were, on an average, older than those in the CTX group (68.5 *vs*. 65.8 years old, $p<0.001$). The Non-CTX group had lower average BMI than the CTX group (21.7 *vs*. 22.2, $p<0.001$). Regarding comorbidities, a difference of 0-3% was observed between the two groups. Fifty-seven and 113 patients in the CTX and Non-CTX groups, respectively, had no diagnosis of metastasis.

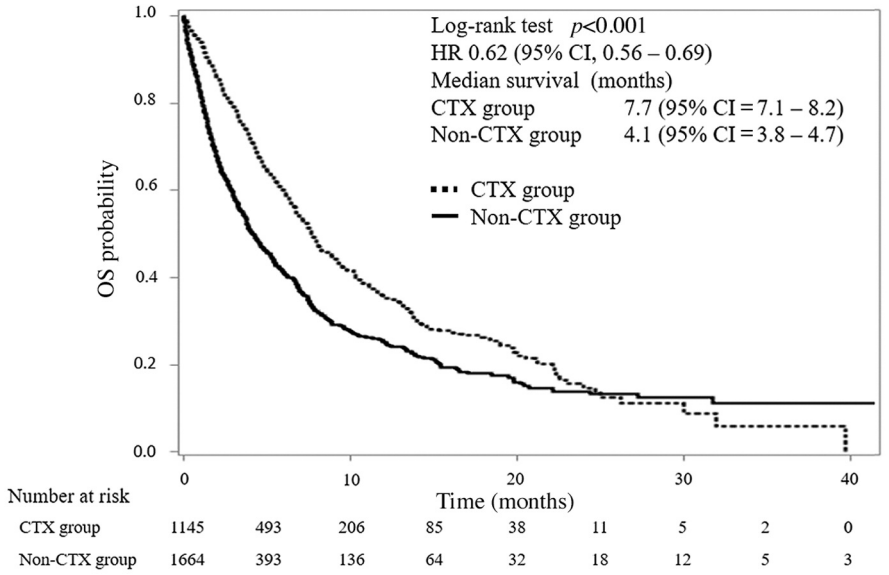

Figure 2. *Kaplan–Meier curves for overall survival (OS). The median OS was 7.7 months in the CTX group and 4.1 months in the Non-CTX group.*

Regarding the number of administrations and re-administrations in each anticancer agent, bevacizumab (n=820) was the most frequently used agent. The proportion of re-administration varied from 0% (aflibercept) to 87% (bevacizumab) depending on each anticancer agent. The total re-administration proportion was 58%.

Effectiveness. The median OS was significantly longer in the CTX group than in the Non-CTX group: 7.7 months [95% confidence interval (CI)=7.1-8.2] *vs*. 4.1 months (95%CI=3.8-4.7) (HR 0.62, 95%CI=0.56-0.69, log-rank $p<0.001$) (Figure 2). The median follow-up durations were 4.2 months (IQR=1.8-7.9) and 2.0 months (IQR=0.8-4.7) in the CTX and Non-CTX groups, respectively (Table II). The adverse events were more common in the CTX group (Table II).

Subgroup analysis and sensitivity analyses. We conducted two sensitivity analyses. First, propensity score-matched analysis was performed, with 1044 patients in each group. The characteristics of patients in the two groups were well balanced as shown in Table I. The median OS in the CTX group and Non-CTX group were 7.6 months (95%CI=6.9-8.0) and 3.8 months (95%CI=3.4-4.5), respectively (HR=0.61, 95%CI=0.54-0.69, $p<0.001$) (Figure 3). Second, we changed the landmark points to 0, 30, 60, and 120 days. At all points, OS was significantly higher in the CTX group. For instance, at the landmark point of 0 days, median OS was 10.2 months (95%CI=9.7-10.8) for the CTX group *vs*. 3.3 months (95%CI=3.2-3.5) for the Non-CTX group (HR=0.34, 95%CI=0.31-0.37, log-rank $p<0.001$).

For the subgroup analysis, we focused on the patients who were prescribed a single anticancer agent, and the survival analysis was performed for each drug (Figure 4). We show the analysis for drugs administered to more than nine patients. Fluorouracil (injection), UFT (a combination of tegafur and uracil), S-1, and capecitabine were collectively analysed as fluorouracil. Bevacizumab was the most frequently used agent (n=218); however, it showed a significantly shorter OS than fluorouracil: 3.3 months (95%CI=3.0-3.7) in bevacizumab *vs*. 7.5 months (95%CI=6.5-8.5) in fluorouracil (HR=0.30, 95%CI=0.20-0.43). In contrast with fluorouracil, the OS was not significantly prolonged for either cetuximab (n=58, HR=0.78, 95%CI=0.52-1.16) or panitumumab (n=83, HR=0.93, 95%CI=0.65-1.31) (Figure 4).

Discussion

This study showed that chemotherapy, when administered after standard therapy, prolonged OS. To the best of our knowledge, this is the first study to investigate the effectiveness of anticancer drug treatment administered after discontinuing regorafenib and TFTD. The guidelines recommended appropriate treatments based on the best currently available evidence. For mCRC, the last recommended lines of treatments are TFTD or regorafenib (1, 8, 9). There are no randomized controlled trials addressing therapies beyond these treatments. The choice of optimal therapy beyond the recommended lines remains unclear. Therefore, further research is required to help

Table I. *Patient characteristics of the CTX group and the Non-CTX group before and after propensity score matching.*

	CTX group before match (n=1145)	Non-CTX group before match (n=1664)	*p*-Value before match	CTX group after match (n=1044)	Non-CTX group after match (n=1044)	*p*-Value after match
Gender (male), n (%)	694 (61)	1011 (61)	0.94	622 (60)	627 (60)	0.82
Mean age (SD)	65.8 (10.2)	68.5 (10.1)	<0.001	66.2 (10.2)	66.7 (10.6)	0.14
>65, n (%)	633 (55)	1119 (67)	<0.001	592 (57)	631 (60)	0.083
Mean body weight (SD), kg	57.5 (12.6)	55.7 (12.0)	<0.001	57.2 (11.8)	56.7 (12.1)	0.28
Missing data, n (%)	29 (3)	39 (2)		-	-	
Mean body mass index (SD), kg/m^2	22.2 (3.8)	21.7 (3.7)	<0.001	22.0 (3.7)	21.9 (3.7)	0.30
<18.5, n (%)	184 (17)	337 (21)	0.006	177 (17)	184 (18)	0.69
Missing data, n (%)	34 (3)	44 (3)		-	-	
Comorbidity, n (%)						
Hypertension	724 (63)	1076 (65)	0.44	662 (63)	673 (64)	0.62
Diabetes mellitus	365 (32)	524 (31)	0.83	331 (32)	340 (33)	0.67
Hyperlipidemia	230 (20)	322 (19)	0.63	210 (20)	217 (21)	0.70
Hepatitis B	101 (9)	183 (11)	0.060	92 (9)	99 (9)	0.60
Hepatitis C	39 (3)	46 (3)	0.33	30 (3)	32 (3)	0.80
Peripheral neuropathy	483 (42)	654 (39)	0.13	441 (42)	447 (43)	0.79
Hand-foot syndrome	221 (19)	278 (17)	0.077	196 (19)	190 (18)	0.74
Anemia	27 (2)	49 (3)	0.35	27 (3)	28 (3)	0.89
Leukopenia	41 (4)	72 (4)	0.32	41 (4)	40 (4)	0.91
Interstitial pneumonitis	38 (3)	60 (4)	0.68	36 (3)	42 (4)	0.49
Primary site of disease, n (%)			0.32			0.89
Colon	637 (56)	878 (53)		573 (55)	583 (56)	
Rectum	619 (28)	490 (29)		294 (28)	285 (27)	
Colon and rectum	189 (17)	296 (18)		177 (17)	176 (17)	
Metastatic sites, n (%)						
Liver	768 (67)	972 (58)	<0.001	691 (66)	674 (65)	0.43
Lung	621 (54)	911 (55)	0.79	567 (54)	572 (55)	0.83
Lymph node	304 (27)	419 (25)	0.41	278 (27)	270 (26)	0.69
Peritoneum	324 (28)	477 (29)	0.83	304 (29)	306 (29)	0.92
Bone	179 (16)	279 (17)	0.42	170 (16)	155 (15)	0.37
Brain	75 (7)	155 (9)	0.009	71 (7)	76 (7)	0.67
Other metastases	141 (12)	204 (12)	0.97	127 (12)	138 (13)	0.47
Number of metastatic sites (≥3), n (%)	392 (34)	544 (33)	0.39	361 (35)	351 (34)	0.64
No metastatic diagnosis, n (%)	57 (5)	113 (7)				
Time since first diagnosis of metastasis, months						
Median (IQR)	20.4 (5.5-34.6)	18.9 (4.5-34.1)	0.43	20.1 (4.8-33.6)	20.3 (5.4-34.7)	0.42
≥18 months, n (%)	609 (53)	821 (49)	0.045	546 (52)	543 (52)	0.90
Previous anticancer agents, n (%)						
Fluorouracil (injection)	729 (64)	972 (58)	0.005	655 (63)	676 (65)	0.34
Capecitabine	408 (36)	676 (41)	0.008	395 (38)	376 (36)	0.39
S-1	379 (33)	567 (34)	0.59	344 (33)	335 (32)	0.67
UFT (tegafur and uracil combination)	111 (10)	171 (10)	0.61	109 (10)	92 (9)	0.21
Oxaliplatin	789 (69)	1129 (68)	0.55	728 (70)	723 (69)	0.81
Irinotecan	857 (75)	1246 (75)	0.98	783 (75)	784 (75)	0.96
Bevacizumab (anti-VEGF antibody)	902 (79)	1192 (72)	<0.001	818 (78)	801 (77)	0.37
Cetuximab (anti-EGFR antibody)	219 (19)	200 (12)	<0.001	170 (16)	167 (16)	0.86
Panitumumab (anti-EGFR antibody)	337 (29)	453 (27)	0.20	311 (30)	308 (30)	0.89
Aflibercept (anti-VEGF antibody)	9 (1)	8 (0)	0.31	8 (1)	8 (1)	1.0
Ranibizumab (anti-VEGF antibody)	71 (6)	74 (4)	0.039	61 (6)	58 (6)	0.78
Regofarenib	542 (47)	718 (43)	0.028	480 (46)	476 (46)	0.86
Trifluridine/tipiracil	1001 (87)	1364 (82)	<0.001	906 (87)	896 (86)	0.52
Mean number of previous anticancer agents (SD)	5.5 (2.0)	5.3 (2.0)	<0.001	5.5 (2.0)	5.5 (2.0)	0.37
Any previous targeted therapy, n (%)	993 (87)	1357 (82)	<0.001	905 (87)	891 (85)	0.38

Table I. *Continued*

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	CTX group before match (n=1145)	Non-CTX group before match (n=1664)	*p*-Value before match	CTX group after match (n=1044)	Non-CTX group after match (n=1044)	*p*-Value after match
Duration of last chemotherapy						
≥90 days, n (%)	471 (41)	645 (39)	0.21	424 (41)	431 (41)	0.76
Number of CT scans (previous year)						
≥4 times, n (%)	583 (51)	886 (53)	0.22	541 (52)	546 (52)	0.83
Department, n (%)			0.29			0.60
Medical oncology	89 (8)	119 (7)		82 (8)	72 (7)	
Internal medicine	251 (22)	406 (24)		229 (22)	242 (23)	
Surgery	805 (70)	1139 (68)		733 (70)	730 (70)	

SD: Standard deviation; EGFR: epidermal growth factor receptor; VEGF: vascular endothelial growth factor receptor.

Table II. *Comparison of drug exposure and adverse events.*

	CTX group (n=1145)	Non-CTX group (n=1664)	*p*-Value
Median follow-up duration (IQR), months	4.2 (1.8-7.9)	2.0 (0.8-4.7)	<0.001
Any chemotherapy after landmark point (90 days), n (%)	821 (72)	87 (5)	<0.001
Adverse events, n (%)			
Any adverse events	879 (77)	1022 (61)	<0.001
Hand-foot skin reaction	204 (18)	127 (8)	<0.001
Peripheral neuropathy	236 (21)	264 (16)	0.001
Hypertension	404 (35)	480 (29)	<0.001
Nausea	428 (37)	298 (18)	<0.001
Diarrhea	211 (18)	153 (9)	<0.001
Oral mucositis	228 (20)	94 (6)	<0.001
Rash/desquamation	115 (10)	58 (3)	<0.001
Hepatotoxicity	13 (1)	10 (1)	0.12
Fatigue	24 (2)	39 (2)	0.66
Anemia	198 (17)	327 (20)	0.12
Leukopenia	176 (15)	107 (6)	<0.001

IQR: Interquartile range; EGFR: epidermal growth factor receptor; VEGF: vascular endothelial growth factor receptor.

patients and doctors choose the appropriate treatment for post-standard chemotherapy.

This study showed that approximately one-fourth of patients received post-standard chemotherapy in Japan. Post chemotherapy showed significantly higher OS than non-chemotherapy even without conditional landmark analysis (HR=0.34; 95%CI=0.31-0.37). Naturally, it is conceivable that patients in the chemotherapy group had good performance status (PS) or slower disease progression. However, we could not acquire information on PS from the database used in this study. Furthermore, patients who died or were censored shortly after the last prescription date of regorafenib or TFTD would have an immortal time bias of concern because they were classified into the Non-CTX group. To overcome these problems, we performed the landmark analysis for the main outcome. To confirm the robustness of the result, we adjusted for values related to the patient's condition, including age, previous anticancer agents, time since the first diagnosis of metastasis, and metastatic disease. Propensity score-matched analysis showed almost the same survival time as that shown by the primary analysis. For the second sensitivity analysis, we changed the landmark points, but it did not change the survival advantage observed in the CTX group. Future studies in patients with well-balanced PS and expected prognosis are necessary to confirm the results.

Tolerability, life expectancy, and quality of life of the patients should be considered when selecting a treatment beyond the recommended standard line. Many patients could be exhausted, and experience adverse events caused by the

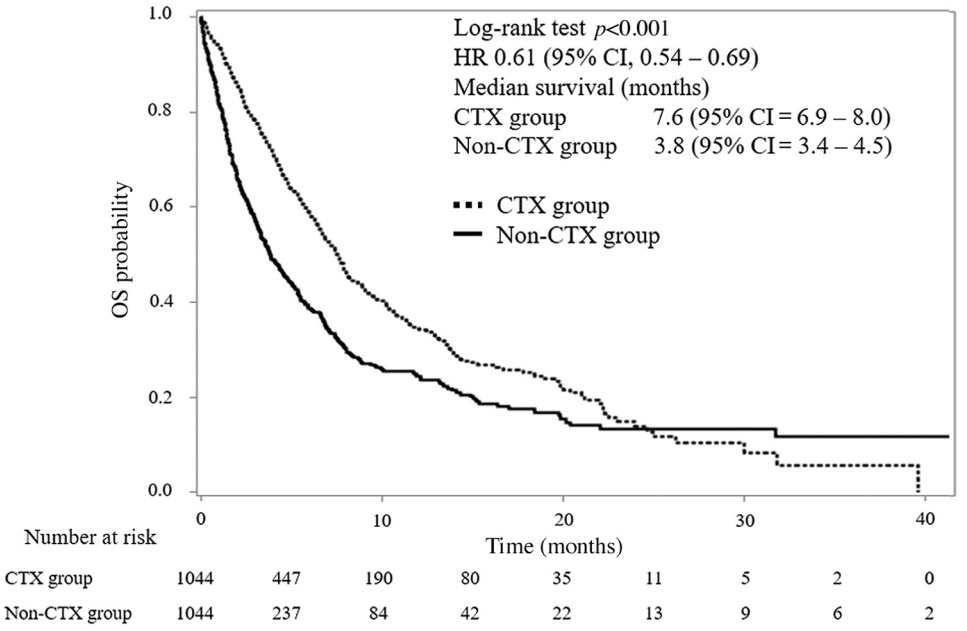

Figure 3. *Kaplan–Meier curves for overall survival (OS) after propensity score-matched analysis. The median OS was 7.6 months in the CTX group and 3.8 months in the Non-CTX group.*

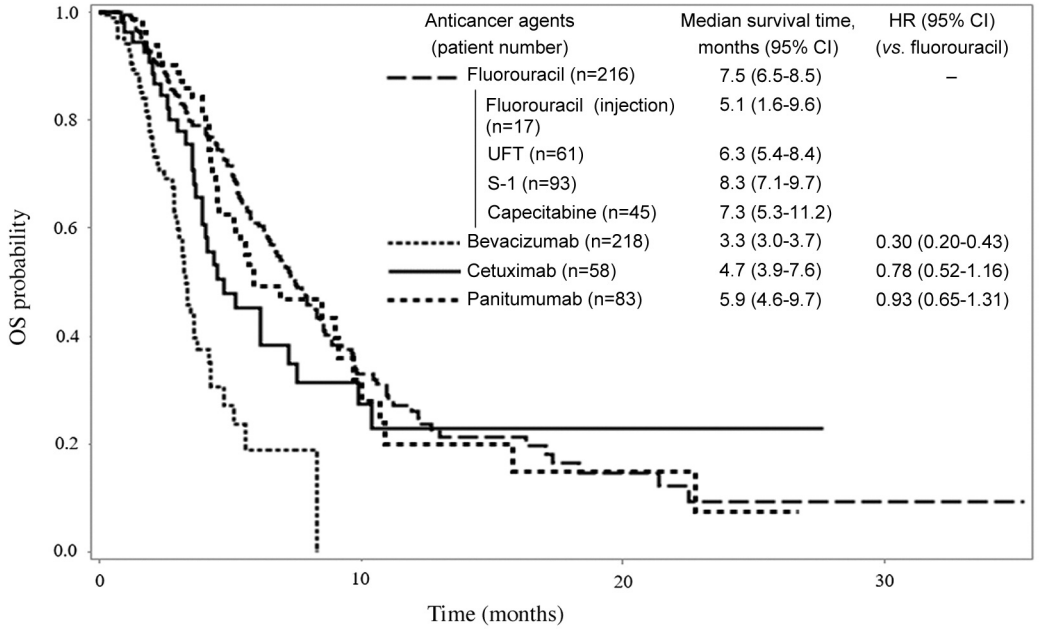

Figure 4. *Kaplan–Meier curves for overall survival (OS) (for patients who were prescribed a single anticancer agent).*

previous treatment. Treatments with fewer adverse events, including oral monotherapy, may be considered in some cases. Small retrospective studies have shown the efficacy of capecitabine and S-1 monotherapy (19, 20). Furthermore, several studies have addressed re-challenge, re-introduction, sequence, and dose intensification of epidermal growth factor receptor (EGFR) targeting agents in heavily pre-treated mCRC patients (10). Many of these studies focused

on single agents (10). Therefore, in the subgroup analysis, we focused on patients treated with a single anticancer agent after standard therapy. Although bevacizumab was the most frequently administered therapy, OS in patients receiving this drug was significantly shorter than that in patients who were treated with fluorouracil. Moreover, a large phase II trial has shown that bevacizumab was not effective as a third-line treatment (21). We also did not observe the effectiveness of bevacizumab monotherapy and suggest that other treatments should be selected for the monotherapy. However, oral monotherapies, including capecitabine and S-1, showed longer median survival time. Treatment strategies vary depending on the patient's condition, including RAS status, the order of prescribed anticancer agents, and the state of adverse events. Thus, the results of a single anticancer agent should be interpreted as exploratory, requiring future investigation.

Due to the nature of the database, the present study has several limitations. Importantly, data of several important variables were missing (*e.g.*, PS, grade of adverse events, time of diagnosis of metastatic disease, RAS mutational status, reasons for discontinuation, and therapeutic evaluation by imaging tests). We could not examine disease control rates and progression-free survival due to the inability to obtain imaging results. Some patients had no diagnosis of metastases (5% and 7% in the CTX and Non-CTX groups, respectively). In these patients, the primary site might be unresectable or metastatic diagnosis might have been omitted. For sensitivity analysis, we excluded these patients, and the results did not change. The second limitation is that most patients in this study were Japanese, especially those receiving S-1, which is rarely used outside East Asia (22, 23); therefore, a future study is necessary for the generalization of these results to other races.

In conclusion, we described salvage treatment following regorafenib or TFTD therapy and compared survival time between the CTX and Non-CTX groups. The introduction of anticancer agents after discontinuing regorafenib or TFTD was associated with prolonged OS. In the absence of clear evidence, further research (including randomized trials, quality of life studies, or cost-effectiveness analysis) is required to define the treatment choice after regorafenib or TFTD in mCRC patients.

Conflicts of Interest

K.K. received advisory fee from Shin Nippon Biomedical Laboratories, Ltd, Japan, JMDC Inc., Japan, AGREE Inc., Japan; research funds from Sumitomo Dainippon Pharma Co, Ltd, Japan, Pfizer Inc., Japan, Stella Pharma Corporation, Japan, CMIC Co, Ltd, Japan, Suntory Beverage & Food Ltd, Japan, Medical Platform Co, Ltd, Japan, and Real World Data, Co, Ltd., Japan; and holds stocks of Real World Data, Co, Ltd., Japan. There are no patent products under development or marketed products to declare, relevant to these companies. The remaining Authors have stated that they have no conflicts of interest.

Authors' Contributions

Conception/design: Masayuki Nakashima, Masato Takeuchi, Koji Kawakami. Collection and/or assembly of data: Masayuki Nakashima. Data analysis and interpretation: Masayuki Nakashima, Masato Takeuchi, Shiro Tanaka, Koji Kawakami. Manuscript writing: Masayuki Nakashima, Masato Takeuchi. Final approval of manuscript: Masayuki Nakashima, Masato Takeuchi, Shiro Tanaka, Koji Kawakami.

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