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Clinical Outcomes Following Trifluridine/Tipiracil Treatment for Patients With Metastatic Colorectal Cancer Ineligible for Regorafenib Treatment

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Abstract. *Background/Aim: In later-line treatment of metastatic colorectal cancer (mCRC), trifluridine/tipiracil is often selected because regorafenib is difficult to use in patients with comorbidities such as thrombosis, hemorrhage, or cardiac events. However, the safety and efficacy of trifluridine/tipiracil in these patients is not clear. Patients and Methods: The clinical outcomes of trifluridine/tipiracil were retrospectively investigated in patients who were ineligible for regorafenib because of comorbidities. Results: Among the 27 patients who received trifluridine/tipiracil, many had comorbidities of deep venous thrombosis or hemorrhage. The median overall survival was 12.4 months, and the median progression-free survival was 2.8 months. The median overall survival was 7.7 months in 19 patients without subsequent regorafenib. Grade 3 or higher toxicities were found in 51% of patients. No treatment discontinuation because of comorbidities was observed. Conclusion: Trifluridine/tipiracil can be safely administered while maintaining efficacy in patients who were ineligible for regorafenib.*

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Colorectal cancer (CRC) is one of the most common types of cancer in the world, with an estimated age-standardized incidence and mortality rate of 19.7 and 8.9 per 100,000, respectively, in 2018 (1). The development of novel drugs for treating metastatic CRC (mCRC) has progressed, and the median overall survival (OS) from first-line chemotherapy is over 30 months (2-4). Later-line chemotherapeutic treatments, such as regorafenib or trifluridine/tipiracil (FTD/TPI), have also contributed to improved OS (5-8). Regorafenib is a multimolecular-targeting drug that inhibits angiogenesis and induces apoptosis (5), and FTD/TPI is an orally administered combination of the thymidine-based nucleic acid analogue trifluridine and the thymidine phosphorylase inhibitor tipiracil hydrochloride (7). In a randomized phase III trial, both drugs led to improved OS compared with placebo in patients with

mCRC refractory to standard chemotherapy (6, 8). The median OS was 6.4 months in the regorafenib group and 5.0 months in the placebo group [hazard ratio (HR)=0.77; 95% confidence interval (CI)=0.64-0.94; p=0.0052] (6). The median OS was 7.1 months in the FTD/TPI group and 5.3 months in the placebo group (HR=0.68; 95%CI=0.58-0.81; p<0.001) (7). Although head-to-head randomized trials of regorafenib *versus* FTD/TPI have not been conducted, several retrospective studies found no significant differences in OS between the two treatments (9-11).

Regorafenib-related toxicities include hypertension, thrombosis, and hemorrhage due to its angiogenesis-inhibitory effect, whereas FTD/TPI-related toxicities are rare (<1%) (6, 8). In clinical practice, we occasionally experience patients with mCRC who cannot receive regorafenib because of a comorbidity and/or a medical history such as thrombosis or hemorrhage. For these patients, FTD/TPI treatment might often be selected. However, a study analyzing the safety and efficacy of FTD/TPI in these patients has not been conducted.

In this study, we aimed to evaluate the safety and efficacy of FTD/TPI in patients with mCRC who could not receive regorafenib because of a comorbidity and/or a medical history.

Patients and Methods

Patient population. Among the excluded patients in the REGOTAS study (11), those who received FTD/TPI treatment because of an unfavorable comorbidity and/or a medical history associated with regorafenib treatment were analyzed in this study. Briefly, the REGOTAS study was a retrospective, observational study that compared the efficacy of regorafenib and FTD/TPI in patients with mCRC refractory to standard chemotherapy who had access to both drugs. The REGOTAS study was conducted between June 2014 and September 2015 and was approved by the ethics committee of each participating institution. Data were collected from 24 institutions in the Japanese Society for Cancer of the Colon and Rectum (JSCCR). After clinical data collection and blinded assessment, patients who could receive only a specific drug treatment, either regorafenib or FTD/TPI, because of a comorbidity and/or medical history adversely affecting those drug-related toxicities, were excluded from the REGOTAS study. No difference in OS was found between the two drugs using propensity score-adjusted analysis. The present study was approved by the Ethics Committee of JSCCR, and the requirement for informed consent was waived because of the retrospective design of this study.

Endpoints and statistical analysis. The primary endpoint was OS, defined as the time from the start of study treatment to death from any cause. Secondary endpoints included the best response rate and disease control rate (DCR) according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; progression-free survival (PFS), defined as the time from the start of study treatment to disease progression or death from any cause; time to Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2, defined as the time from the start of study treatment to decision of an ECOG PS ≥2; and safety according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The clinical outcomes, including OS, PFS, and time to ECOG PS ≥2, were evaluated using the Kaplan–Meier method. All analyses were performed using SPSS software version 21 (IBM, Armonk, NY, USA).

Results

Patients. Among 589 patients enrolled in the REGOTAS study, 39 patients were excluded. Of these patients, 27 were excluded because of comorbidities and/or a medical history unfavorable for regorafenib treatment and received FTD/TPI treatment. Patient characteristics are listed in Table I. The main reasons patients were not selected for treatment with regorafenib were deep venous thrombosis (n=8), hemorrhage (n=6), intestinal fistula (n=3), and cardiac event (n=3). All patients discontinued FTD/TPI because of disease progression. Fourteen patients (52%) received subsequent chemotherapies. These subsequent therapies included regorafenib (n=7), oxaliplatin-containing chemotherapy (n=3), irinotecan-containing chemotherapy (n=3), and panitumumab (n=1). One patient received regorafenib after oxaliplatin-containing chemotherapy. The reason for selecting FTD/TPI before regorafenib treatment in 8 patients was thrombosis (n=4), proteinuria (n=2), bleeding (n=1), and surgical site infection (n=1).

Efficacy outcomes. The median follow-up time was 10.5 months (range=2.2-26.2 months). Death occurred in 66% of patients. The median OS was 12.4 months (95%CI=5.9-18.8) (Figure 1A). The median PFS was 2.8 months (95%CI=1.4-4.1) (Figure 1B). ECOG PS ≥2 during FTD/TPI treatment was observed in 67% of patients. The median time to ECOG PS ≥2 was 7.8 months (95%CI=2.4-13.1) (Figure 1C). Among 26 patients with target lesions, no complete or partial responses were observed and DCR was 50%. The median PFS and the median OS in 8 patients with subsequent regorafenib treatment were 2.1 months (95%CI=0.8-3.3) and 15.7 months (95%CI=9.1-22.2), respectively. Finally, the median OS in 19 patients without subsequent regorafenib treatment was 7.7 months (95%CI=3.0-12.3) (Figure 1D).

Safety outcomes. No treatment discontinuation of FTD/TPU was observed related to comorbidities and/or medical history. The incidence of FTD/TPI-related grade 3 or higher toxicities was 51%. Documented toxicities were neutropenia (40%), anemia (22%), and skin disorders (4%). There were no febrile neutropenia and treatment-related deaths.

Discussion

Our study demonstrated the efficacy and safety of FTD/TPI for patients with mCRC who were not eligible to receive regorafenib because of an unfavorable comorbidity and/or a medical history. This result suggests that FTD/TPI treatment may produce a promising effect with tolerable toxicities in these patients.

Table I. *Patient characteristics*.

Characteristics	n (%)
Age, years	
Median (IQR)	64 (36-75)
≥65 years	12 (44)
Gender	
Male	18 (67)
Female	9 (33)
ECOG PS	
0	10 (37)
1	16 (59)
2	1 (4)
Primary tumor site	
Right[a]	7 (26)
Left[b]	20 (74)
Surgery on primary site	
Yes	18 (67)
Histological grade	
Well	11 (40)
Moderate	16 (59)
RAS status	
Wild	14 (52)
Mutant	13 (48)
Metastatic organ site	
Lung	18 (67)
Liver	12 (32)
Lymph node	16 (59)
Other	10 (37)
Number of metastatic organ site(s)	
1	5 (19)
2	15 (56)
≥3	7 (26)
Intolerable drug	
Any drugs	17 (50)
Fluoropyrimidine	2 (7)
Oxaliplatin	4 (15)
Irinotecan	3 (11)
Bevacizumab	4 (15)
Anti-EGFR antibody	2 (7)
Prior regimens	
2	17 (63)
≥3	10 (37)
Initial dose reduction	
Yes	2 (7)
Comorbidity and/or medical history	
Thrombosis	8 (30)
Hemorrhage	6 (22)
Cardiac event	3 (11)
Intestinal fistula	3 (11)
Gastro-duodenal ulcer	2 (7)
Proteinuria	2 (7)
Acute aortic dissection	1 (4)
Wound infection	1 (4)
Thrombosis and aneurysm	1 (4)

ECOG PS: Eastern Cooperative Oncology Group performance status; EGFR: epidermal growth factor receptor; IQR: interquartile range. [a]Including the cecum, ascending colon, and transverse colon. [b]Including the descending colon, sigmoid colon, and rectum.

In our study, although the median PFS, median time to ECOG PS ≥2, and DCR were similar to those in previous reports, the median OS for all patients examined was numerically higher than those in the REGOTAS and RECOURSE trials (8, 11). Similar to previous reports, wherein patients who received regorafenib were excluded from the study, the median OS was 7.7 months. The OS in 8 patients with subsequent regorafenib treatment tended to be longer than in patients without, although the PFS was comparable. Since 7 of the 8 patients had an ECOG PS of 0, this result may have been due to this population having a more favorable prognosis. Regorafenib might also be more beneficial than risk to patients with comorbidities affecting regorafenib-related toxicities. In *post-hoc* analyses of randomized control trials that evaluated chemotherapy plus bevacizumab, anti-vascular endothelial growth factor antibody *versus* chemotherapy alone and bevacizumab combination therapy in patients with a history of arterial thromboembolic events also showed improvement in OS, similar to that in the full population, although an increased risk for arterial thromboembolic events was observed in those patients (12). Further studies for evaluating the risks and benefits of regorafenib treatment in these patients are needed.

In our study, as in previous reports, toxicities of grade 3 or higher included neutropenia and anemia, and no comorbidity-related severe toxicities were observed. In addition, no treatment-related death was observed. A meta-analysis evaluating adjuvant chemotherapy using cytotoxic agents for patients with early breast cancer and comorbidities, reported that patients with comorbidities received less quality adjuvant chemotherapy and experienced greater toxicity than patients without comorbidities (13). There are no reports on whether a cytotoxic agent is tolerable in patients with risk factors associated with the targeted agent. To the best of our knowledge, our study is the first to suggest the tolerability of a cytotoxic agent in these patients.

Our study has some limitations. First, as this is a retrospective observational study with a small sample size, there may be sample bias. In fact, 8 patients who received regorafenib as subsequent chemotherapy were included in our study despite our exclusion of patients who could not receive regorafenib as a primary treatment because of a comorbidity and/or a medical history. However, even with this caveat, the efficacy outcomes were maintained when those patients were excluded. Second, detailed information on the severity of comorbidities and grades 1 or 2 toxicities were not collected because that was not a primary objective of the REGOTAS study (11). The comorbidity burden assessed by the Charlson comorbidity index is associated with a shorter OS in patients with colorectal cancer (13). Additional studies using this index will be needed. Finally, all patients in our study were Japanese. However, no ethnic differences between Japanese and Western patients were observed in the pivotal trial (8).

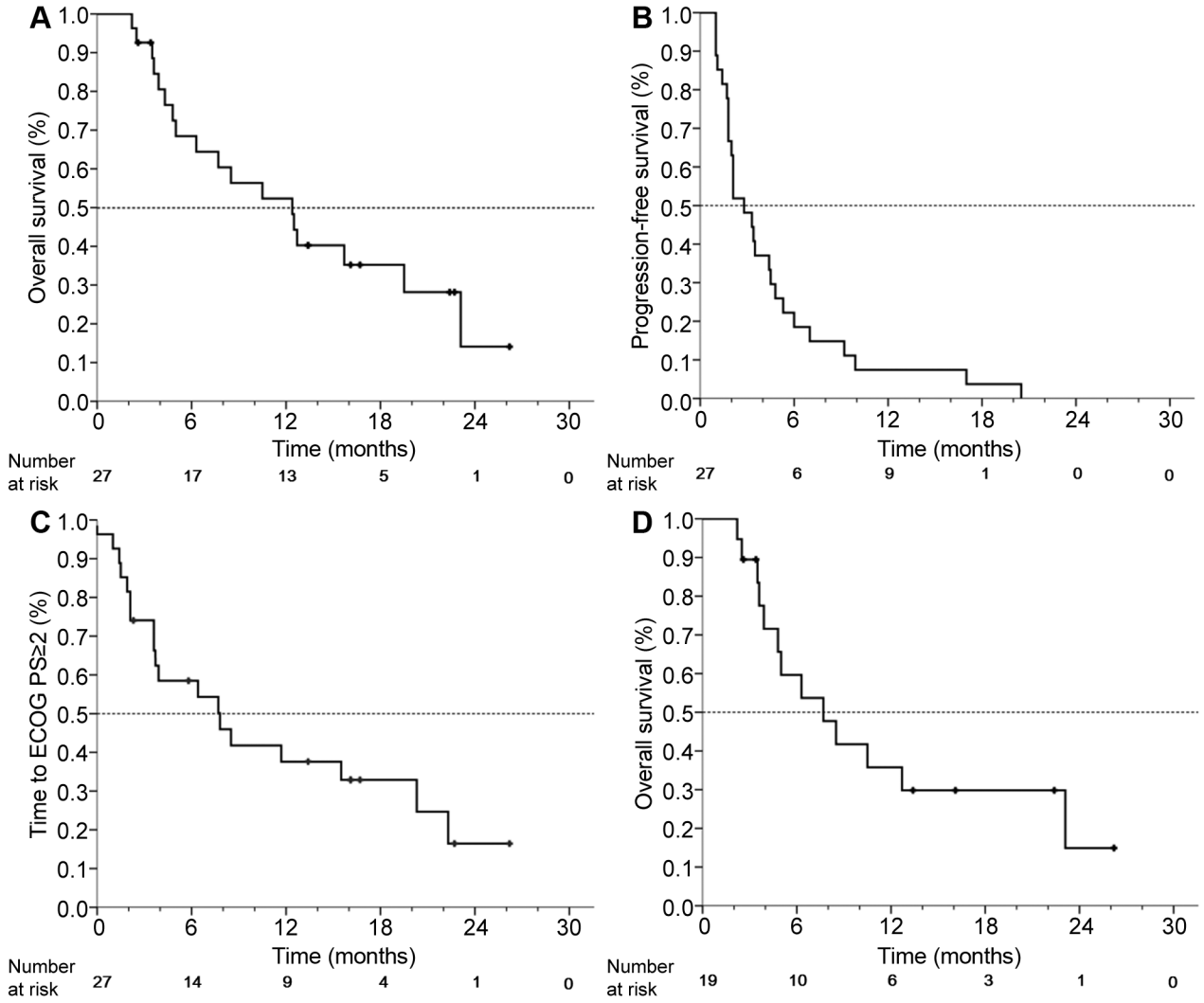

Figure 1. *Kaplan–Meier curves of overall survival (A), progression-free survival (B), time to Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≥2 (C), and overall survival in patients without subsequent regorafenib treatment (D).*

In conclusion, this study suggests that FTD/TPI can be safely administered while maintaining efficacy in patients who were denied regorafenib treatment because of a comorbidity and/or a medical history.

Conflicts of Interest

Toshikazu Moriwaki received honoraria from Taiho and Bayer, and a research grant from Taiho. Shota Fukuoka received research grant from MSD, Bayer and Ono. Toshiki Masuishi received honoraria from Takeda, Chugai, Merck Serono, Taiho, Bayer, Lilly, Yakult, Bristol-Myers Squibb, and Sanofi and research grant from MSD, Daiichi Sankyo, Novartis, and Ono. Atsuo Takashima received honoraria from Taiho. Takeshi Kajiwara received honoraria from Chugai, Taiho, Bristol, Merck Serono and Kyowa Kirin. Kentaro Yamazaki received honoraria from Chugai and Bayer. Taito Esaki received honoraria from Taiho, Chugai, Ono, Takeda, Bayer, Merck Serono, Sanofi, Bristol, Eli Lilly, Eisai, Daiichi Sankyo and Kyowa Kirin, and research grant from Astellas, MSD, Daiichi-Sankyo, Nihon Kayaku, Ono, Eli Lilly, Merck Serono, Dainippon Sumitomo, Bayer, Novartis, Pfizer, Bristol and Taiho. Akitaka Makiyama received honoraria from Takeda, Lilly and Chugai. Yukimasa Hatachi received honoraria from Taiho, Chugai, Bristol and Astrazeneca. Naotoshi Sugimoto received research grant from Taiho, MSD, Ono and Daiichi-Sankyo. All the other Authors declare no potential conflict of interest.

Authors' Contributions

Concept/design: Yusuke Niisato, Toshikazu Moriwaki. Provision of study material or patients: Toshikazu Moriwaki, Shota Fukuoka, Toshiki Masuishi, Atsuo Takashima, Yusuke Kumekawa, Takeshi Kajiwara, Kentaro Yamazaki, Taito Esaki, Akitaka Makiyama, Tadamichi Denda, Yukimasa Hatachi, Takeshi Suto, Naotoshi

Sugimoto, Yasuhiro Shimada. Collection and/or assembly of data: Yusuke Niisato, Toshikazu Moriwaki. Data analysis and interpretation: Yusuke Niisato, Toshikazu Moriwaki. Manuscript writing: Yusuke Niisato, Toshikazu Moriwaki. Final approval of manuscript: Yusuke Niisato, Toshikazu Moriwaki, Shota Fukuoka, Toshiki Masuishi, Atsuo Takashima, Yusuke Kumekawa, Takeshi Kajiwara, Kentaro Yamazaki, Taito Esaki, Akitaka Makiyama, Tadamichi Denda, Yukimasa Hatachi, Takeshi Suto, Naotoshi Sugimoto, Yasuhiro Shimada.

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