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Prospective Multicenter Phase II Study of Biweekly TAS-102 and Bevacizumab for Metastatic Colorectal Cancer

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Abstract. *Background: This study assessed the efficacy and safety of biweekly trifluridine and tipiracil hydrochloride (TAS-102) with bevacizumab combination therapy for patients with metastatic colorectal cancer (mCRC). Patients and Methods: We included 19 patients with mCRC who received TAS-102 and bevacizumab combination therapy biweekly as third-line chemotherapy. The primary endpoint was progression-free survival. Results: Patients had a median age of 73 years and most (73.4%) were men. The median progression-free and overall survival were 5.6 and 11.5 months, respectively. Five (26.3%) patients achieved a response and the disease control rate was 12/19 (63.1%). One patient (5.2%) experienced neutropenia grade 3 or more. The median time from baseline performance status 0/1 to worsening to 2 or more was 10.3 months. Conclusion: Biweekly TAS-102 plus bevacizumab facilitates tumor shrinkage by reducing the incidence of grade 3 or more neutropenia, improving survival, and maintaining performance status. This combination may represent a treatment option for patients with late-stage mCRC receiving third- or later-line therapy.*

Chemotherapy for metastatic colorectal cancer (mCRC) has radically advanced in recent years, and combination therapy with cytotoxic drugs (*e.g.* fluoropyrimidine, oxaliplatin, or irinotecan) and molecularly targeted agents (*e.g.* bevacizumab, aflibercept, ramucirumab, cetuximab, and panitumumab) have extended the median overall survival time to approximately 30 months (1, 2). While there is no established therapy for patients who are refractory to or intolerant of these anticancer agents, there are a few reports of chemotherapeutic drugs being efficacious for mCRC, particularly when used as third- or later-line therapy.

Under such circumstances, in 2014, Japan was the first country to approve the use of an oral anticancer agent containing a combination of trifluridine (FTD) and tipiracil hydrochloride, dubbed TAS-102 (3). In terms of its molecular mechanism, the FTD component of TAS-102 is incorporated into the DNA of CRC cells, where it exerts its antitumor effects (4). In addition, the other component, tipiracil hydrochloride, inhibits the FTD-degrading enzyme thymidine phosphorylase to maintain a high blood concentration of FTD. The phase III RECOURSE trial (5) conducted in 2015 demonstrated significant improvements in progression-free survival (PFS) [hazard ratio (HR)=0.48, $p<0.001$] and overall survival (OS) (HR=0.68, $p<0.001$) for patients with mCRC in the TAS-102-treated group compared with those in the placebo-treated with group. In contrast, bevacizumab suppresses angiogenesis and tumor vascularization to produce anticancer effects (6). Based on the differences in their toxicity profiles, a therapy combining TAS-102 and bevacizumab is valuable clinically, as the combination induces antitumor activity and prolongs survival by elevating the FTD concentration in the DNA of tumors without increasing systemic exposure (7). In 2017, the phase I/II C-TASK FORCE study demonstrated the efficacy of the combination therapy of TAS-102 plus bevacizumab (7). Subsequently, in 2020, a randomized phase II Danish trial (8), which compared TAS-102 alone with TAS-102 plus bevacizumab reported that the PFS (HR=0.45, $p=0.001$) and OS (HR=0.55, $p=0.028$) of those in the group treated with

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Key Words: Biweekly, TAS-102, neutropenia, bevacizumab, metastatic colorectal cancer.

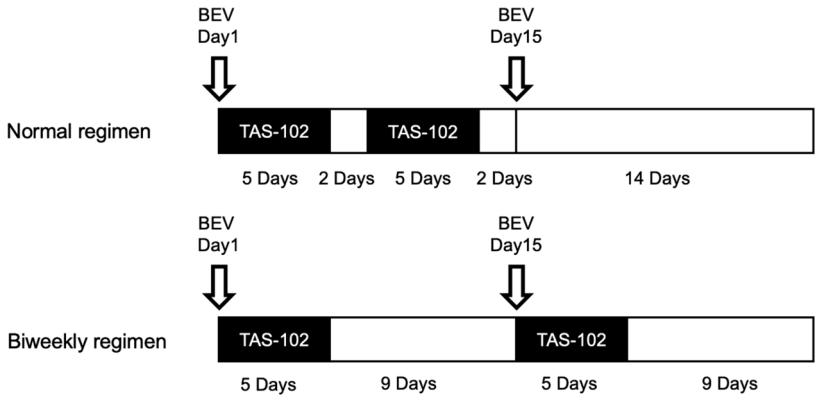

Figure 1. *Chemotherapy regimen. TAS-102: Trifluridine, tipiracil hydrochloride, BEV: bevacizumab.*

TAS-102 plus bevacizumab group were significantly extended compared with rates in the group receiving TAS-102 alone. These two studies suggested that TAS-102 plus bevacizumab may be efficacious in patients with refractory mCRC receiving later-line therapy.

However, these studies included patients who had potentially shown a treatment response to second-line therapy. In addition, TAS-102 administration on days 1-5 and 8-12 (normal regimen) and grade 3 or higher neutropenia are factors associated with a high incidence of treatment-related adverse events. Therefore, this study included patients with mCRC refractory to treatment and receiving third- or later-line therapy. The days of TAS-102 administration were also changed to days 1-5 and 15-19 (biweekly regimen) with the aim of reducing neutropenia and to examine the efficacy and safety of biweekly administration of TAS-102 plus bevacizumab in a prospective study.

Patients and Methods

Study design and patients. This non-randomized study was conducted as a prospective, investigator-initiated, open-label, single-arm, multi-centered phase II trial of TAS-102 plus bevacizumab in patients who were enrolled from four treatment centers in Japan. Written informed consent was obtained from all patients prior to any screening or inclusion procedure. All procedures were performed in accordance with the Declaration of Helsinki, and the Ethics Committee of Tokyo Medical University Hospital approved the study (no. SH3384). The trial was organized by the Department of Gastrointestinal and Pediatric Surgery, Tokyo Medical University, Japan (trial registration number: UMIN000026043).

Patient selection criteria. The inclusion criteria were defined as follows: Eligible patients were 20-80 years old, had no history of treatment with regorafenib, unresectable mCRC confirmed histologically, had previously received two or more standard chemotherapy treatment regimens, and were refractory or intolerant to fluoropyrimidine, irinotecan, oxaliplatin, anti-vascular endothelial growth factor therapy, and anti-epidermal growth factor receptor therapy (only for those with unmutated/wild-type *RAS*). For inclusion, patients needed to have target lesions that were evaluable using the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) (9), along with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1. We confirmed adequate bone marrow, hepatic, and renal functions in patients *via* examination of blood samples 7 days before enrollment in the study. Patients who had experienced thromboembolic events within the 6 months before enrollment were excluded, as were those with uncontrolled hypertension or diabetes, an unhealed wound or traumatic fracture, thromboembolism, or a history or complications associated with severe lung disease.

Chemotherapy. This study regimen was designed to assess biweekly administration of TAS-102 (orally administered at a dose of 35 mg/m^2 twice daily on days 1-5 and 15-19 of every 28-day cycle) plus bevacizumab (5.0 mg/kg on days 1 and 15) (Figure 1). The protocol recommended patients should continue to receive treatment until the occurrence of disease progression, unacceptable toxicity, or they wished to discontinue treatment. When neutropenia occurred during treatment (defined as a neutrophil count of <1,000 $cells/mm^3$), the dose of TAS-102 was reduced by 5 mg/day. Except in cases of febrile neutropenia or delayed treatment administration, the prophylactic use of granulocyte colony-stimulating factor treatment was not recommended. In principle, we also did not recommend a dose reduction of bevacizumab; however, if bevacizumab-related toxicities occurred that were unacceptable to a patient, the patient was treated with TAS-102 alone. During the study period, other treatment with chemotherapy, radiotherapy, immunotherapy, hormone therapy, or hyperthermia were not performed. Clinical evaluations using computed tomographic scans were performed 4 weeks after the initiation of treatment, after which they were re-assessed every 8 weeks until disease progression of the lesion occurred based on version 1.1 of the RECIST criteria. Toxicity was assessed every 4 weeks using version 4.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events (10).

Endpoints in this study. The primary endpoint was PFS. The secondary endpoints were OS, response rate (RR), disease control

Table I. *Baseline patient characteristics*.

Characteristic	Subgroup	Value
Age, years	Median (range)	73 (40-79)
Gender, n	Male	14
	Female	5
ECOG PS, n	0	14
	1	5
Primary site, n	Colon	10
	Rectum	9
Side, n	Right	3
	Left	16
KRAS, n	Wild-type	12
	Mutant	7
Treatment line, n	Third	13
	Fourth	5
	Fifth	1
Sites of metastasis, n	1	8
	2	10
Organs with metastasis, n	Liver	8
	Lung	11
	Lymph nodes	3
	Peritoneum	4
	Bone	4
Tumor	Recurrent	19
	Advanced	0

ECOG PS: Eastern Cooperative Oncology Group performance status.

rate (DCR), incidence of adverse events of grade 3 or higher, and time to an ECOG-PS of 2 or higher. PFS was defined as the time from study enrollment to the first instance of disease progression, or death, whichever occurred first. OS was defined as the time from study enrollment to the date of death from any cause. Tumor responses were classified as a complete response (CR), partial response (PR), stable disease, or progressive disease according to the RECIST criteria. The RR was defined as the sum of the CR and PR. DCR was defined as the sum of CR, PR, and stable disease.

Statistical analysis. In the phase III RECOURSE trial of TAS-102 (5), the median PFS was 2.0 months. The C-TASK FORCE study, in which a combination of TAS-102 plus bevacizumab was administered, observed a median PFS of 3.7 months. The present study aimed to evaluate a two-drug combination regimen similar to that used in the C-TASK FORCE study (7); therefore, assuming a threshold of 4.0 months for PFS, statistical power of 90%, a one-sided α=0.05, β=0.2, and a 10% rate of patient ineligibility or dropout, we calculated the required number of patients for sufficient statistical power; the target sample size was 19 patients.

IBM Statistical Package for the Social Sciences version 24.0 software (IBM Corp, Armonk, NY, USA) was used for all analyses. All patients receiving TAS-102 plus bevacizumab chemotherapy were subjected to the analysis. Dose intensity was assessed when all patients had completed the final treatment of two treatment cycles. RRs were calculated for all eligible patients. The Kaplan–Meier method was used to calculate the PFS, OS, incidence of adverse events of grade 3 or higher, and time to an ECOG-PS of 2 or more.

Table II. *Treatment results*.

	Value
Duration of therapy, months	
Median (range)	5.1 (1.4-27.8)
Overall relative dose intensity for TAS-102	
Median (range)	0.89 (0.79-0.98)
Relative dose intensity for bevacizumab	
Median (range)	0.93 (0.85-0.98)
Reason for treatment discontinuation, n (%)	
Progression	11 (89.6%)
Toxicity	1 (5.2%)
Patient's wish	1 (5.2%)
Overall response rates, n (%)	
CR	0 (0)
PR	5 (26.3%)
SD	7 (36.8%)
PD	7 (36.8%)
RR (CR+PR)	5 (26.3%)
DCR (CR+PR+SD)	12 (63.1%)

CR: Complete response; DCR: disease control rate; PD: progressive disease; PR: partial response; RR: response rate; SD: stable disease; TAS-102: Trifluridine, tipiracil hydrochloride.

Results

Between October 2015 and March 2019, 19 patients were enrolled. The median age was 73 years (range=40-79 years), and 14 patients (73.4%) were male. Fourteen (73.4%) and five (26.6%) patients had ECOG-PS scores of 0 and 1, respectively. Of the 19 patients, 13 (68.4%), five (26.3%), and one (5.3%) received chemotherapy as third-, fourth-, and fifth-line treatments, respectively. RAS mutations were confirmed in seven patients (36.8%) (Table I). All patients completed the follow-up period, and none were ineligible. The clinical cutoff date for analysis was June 30, 2020, and the median follow-up period was 11.5 months (range=2.4-38.9 months).

All patients received biweekly TAS-102 plus bevacizumab treatment. The median duration of therapy was 5.1 months (range=1.4-27.8 months, the median overall relative dose intensity for TAS102 was 0.89 (range=0.79-0.98), and the median relative dose intensity for bevacizumab was 0.93 (range=0.85-0.98). The RR was 5/19 (26.3%) and the DCR was 12/19 (63.1%) (Table II). The median PFS was 5.6 months (range=1.8-21.0 months) (Figure 2A), and the median OS was 11.5 months (range=2.4-34.9 months) (Figure 2B). Grade 3 adverse events were observed in three patients (15.8%), with one case each experiencing neutropenia, anemia, and malaise, respectively (Table III). There were no grade 4 or higher adverse events, nor were there any treatment-related deaths. The median time for worsening from a baseline ECOG-PS of 0 or 1 to 2 or more was 10.3 months (range=1.5-34.9 months) (Figure 3).

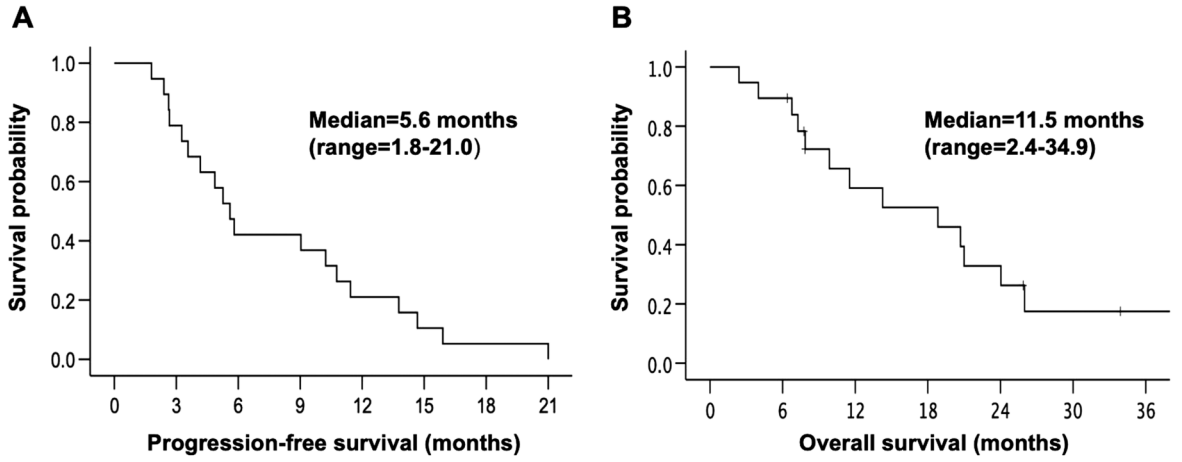

Figure 2. *Kaplan–Meier survival curve showing progression-free (A) and overall (B) survival.*

A summary of the previous studies using a combination of TAS-102 plus BEV is provided in Table IV.

Discussion

In our study, biweekly administration of a combination of TAS102 plus bevacizumab resulted in an increase in the primary endpoint, PFS, when used as third-line or later treatment for mCRC. Our results suggest that suppressing grade 3 or higher adverse events while maintaining the dose intensity of TAS102 improved the RR and DCR, and extended the time to a decline to ECOG-PS of 2 or more, possibly improving patients' quality of life.

Previous studies have shown that combination therapy with TAS102 plus bevacizumab is a promising therapy for mCRC (7, 8, 11); however, this combination therapy worsens neutropenia and toxicity. Normal TAS-102 plus bevacizumab therapy consists of a regimen of orally administered TAS-102 on days 1-5 and 8-12 in a 4-week cycle, as well as a regimen of intravenous administration of bevacizumab every 2 weeks. This normal regimen was determined through a phase I study (12, 13); studies that have used this regimen, however, have reported a high incidence rate (41-72%) of grade 3 or higher neutropenia (7, 8, 11). One study suggested that if neutropenia and adverse events of TAS-102 can be reduced, the dose intensity of TAS-102 can be kept relatively high thereby avoiding the need for dose reduction, which may improve patient prognosis (7). Therefore, with the aims of reducing toxicity, developing a simple drug administration regimen, and ensuring equivalent efficacy, the administration schedule of TAS-102 was changed to a biweekly regimen involving administration on days 1-5 and 15-19 in a 4-week cycle. Our non-randomized, prospective, investigator-initiated, open label, single-arm, multi-centered phase II trial

Table III. *The incidence of adverse events. Data are expressed as n (%).*

	Grade 2	Grade 3
Neutropenia	3 (15.7)	1 (5.2)
Anemia	0 (0)	1 (5.2)
Thrombocytopenia	0 (0)	0 (0)
Nausea	2 (10.5)	0 (0)
Vomiting	0 (0)	0 (0)
Diarrhea	0 (0)	0 (0)
Malaise	0 (0)	1 (5.2)
Proteinuria	1 (5.2)	0 (0)
Hypertension	0 (0)	0 (0)

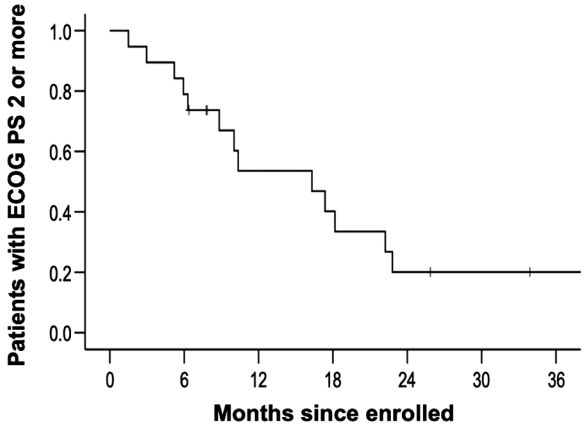

Figure 3. *Time to Eastern Cooperative Oncology Group performance status (ECOG PS) of 2 or more (from 0 or 1 to 2 or more during the course of the study). The median time to worsening of ECOG PS to 2 or higher was 10.3 months (range=1.5-34.9 months).*

Table IV. *Previous studies investigating TAS-102 plus bevacizumab.*

Study	Year	Design	N	TAS-102 regimen	Inclusion criteria chemotherapy line	PFS, months	OS, months	RR, %	DCR, %	Neutropenia, grade ≥3, %
C-TASK FORCE (7)	2017	Phase 1/2, single arm	25	Normal	2nd or more	3.7	11.4	0	64	72
DANISH (8)	2020	Randomized, phase 2, TAS-102 *vs*. TAS-102 plus BEV	47 *vs*. 46	Normal	2nd or more	4.6	9.4	2.2	67	41
TAS-CC3 (11)	2020	Phase 2, single arm	32	Normal	3rd or more	4.5	9.2	6.3	65.6	46.9
BiTS study (18)	2020	Phase 2, single arm	44	Biweekly	2nd or more	4.29	10.86	0	59.1	36.4
Our study	-	Phase 2, single arm	19	Biweekly	3rd or more	5.6	11.5	26.3	63.1	5.2

DCR: Disease control rate; PFS: progression-free survival; OS: overall survival, RR: response rate.

of biweekly TAS-102 plus bevacizumab demonstrated that the incidence of grade 3 or higher neutropenia was less frequent than that reported in the study using the normal TAS-102 dosing regimen. By suppressing the occurrence of neutropenia, TAS-102 dose reduction can be avoided, facilitating the maintenance of high levels of FTD in cancer cells, subsequently increasing its incorporation into DNA, which improves its antitumor effect (14). In our study, a high relative dose intensity of TAS102 was maintained, and a patient survival benefit was obtained.

According to the results of the two studies that used the normal regimen of TAS-102 plus bevacizumab (7, 8), the patients who received the combination treatment, including cases in which it was administered as second-line treatment, may have exhibited a relatively positive treatment response as the PFS was 3.7 and 4.6 months, and the OS was 9.4 and 11.4 months, respectively. In addition, a study of patients receiving the normal regimen of TAS-102 plus bevacizumab as third-line or later therapy exhibited a PFS of 4.5 months and an OS of 9.2 months (11). In the present study involving patients receiving third-line or later treatments after responding poorly to previous treatments, biweekly TAS-102 administration resulted in greater survival effects than those reported in previous studies; thus, the regimen was clinically beneficial.

In general, the effect of TAS-102 plus bevacizumab combination therapy on tumor shrinkage can be expected in patients receiving first-line treatment (15, 16), whereas in those receiving second-line or later-line therapy, little tumor shrinkage occurs. Studies including patients receiving second-line treatment using normal TAS-102 plus bevacizumab reported an RR of 0-6.3% and a DCR of 64-67% (7, 8, 11). Even though the patients were receiving third-line or later treatment in the present study, we obtained a better RR than has been previously reported, along with a similar DCR. Tanaka *et al*. reported a correlation between FTD incorporation into tumor-cell DNA and the number of drug administration days (4). Even though the drug dose used in the normal and biweekly regimens is unchanged, the incidence rate of neutropenia differs. In the biweekly regimen, the reduced neutropenia lowers the need for dose reduction, and higher TAS-102 doses lead to increased incorporation of FTD into the DNA of cancer cells, resulting in improved survival. A relatively high RR was observed in the present study, and our results suggest that tumor shrinkage may prolong the time to worsening of ECOG-PS of 2 or more by reducing local symptoms and minimizing functional impairment. The RECOURSE study reported a significant extension of the median time to an ECOG-PS of 2 or more in the TAS-102-treated group compared with the placebo group (5.7 *versus* 4.0 months, respectively; HR=0.66, $p<0.001$). For frail patients receiving third- or later-line chemotherapy, ensuring adequate treatment outcomes and improved quality of life are issues that should be considered simultaneously. In our study, we showed that the time to an ECOG-PS of 2 or more can be further extended by administering TAS-102 plus bevacizumab biweekly.

To the best of our knowledge, there has been no previous prospective study comparing normal TAS-102 plus bevacizumab and biweekly TAS-102 plus bevacizumab regimens. However, a retrospective comparison showed that biweekly TAS-102 plus bevacizumab significantly reduced the occurrence of grade 3 or higher neutropenia ($p=0.031$) and significantly extended PFS ($p<0.001$) (17). In the aforementioned study, Yoshida *et al*. used multiple Cox regression analysis and identified that administration regimen (normal or biweekly regimen; HR=0.22, $p<0.001$) significantly affected PFS (17). Furthermore, although it is difficult to draw a conclusion by comparing these results to those of previous studies with patients of different backgrounds, the biweekly regimen in our study suppressed grade 3 or higher neutropenia and resulted in a relatively high RR value.

This study had several limitations. Firstly, the sample size was small, this was a single-arm study, and it was non-randomized. Secondly, data were collected from only four institutions in Japan, and only Japanese patients were enrolled. Thirdly, only those receiving third-line or later therapy were enrolled.

In conclusion, this study demonstrated that biweekly TAS-102 plus BEV facilitates tumor shrinkage by reducing the occurrence of grade 3 or higher neutropenia and avoiding dose reduction to maintain the dose intensity of TAS102. This regimen is associated with survival benefits, while also maintaining the ECOG-PS. Thus, this appears to be a promising treatment option for mCRC patients undergoing third-line or later therapy, although the efficacy and safety of biweekly TAS-102 plus bevacizumab compared with normal TAS-102 plus bevacizumab need to be confirmed by a randomized controlled trial in the future.

Conflicts of Interest

The Authors declare that they have no conflicts of interest regarding this study.

Authors' Contributions

All Authors interpreted the data, wrote and approved the article and the decision to submit for publication. TI, JM and KK designed the study. TI, JM, ME, MS, TM, and HK recruited patients and curated data for the study. TI, JM, KK, YN and AT carried out interpretation of data and statistical analyses. KK, YN and AK provided administrative, technical and material support.

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