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Combining Bevacizumab With Trifluridine/Thymidine Phosphorylase Inhibitor Improves the Survival Outcomes Regardless of the Usage History of Bevacizumab in Front-line Treatment of Patients With Metastatic Colorectal Cancer

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Abstract. *Background/Aim: The efficacy of trifluridine/thymidine phosphorylase inhibitor (FTD/TPI) plus bevacizumab as later-line treatment for metastatic colorectal cancer (mCRC) has been demonstrated. However, little is known about the impact of a usage history of bevacizumab in front-line treatment on the clinical benefit of combining bevacizumab with FTD/TPI. Patients and Methods: A total of 62 patients with mCRC treated with FTD/TPI±bevacizumab was enrolled and assessed for chemotherapeutic efficacy and adverse events. Results: Regardless of the usage history of bevacizumab in front-line treatment, the FTD/TPI plus bevacizumab group had a significantly better progression-free survival rate than the FTD/TPI monotherapy group, and no significant differences in the safety profile were observed between the two groups. Conclusion: Combining bevacizumab with FTD/TPI improves the survival outcomes with manageable toxicity, regardless of the usage history of bevacizumab in front-line treatment, in patients with mCRC.*

The phase III RECOURSE trial has demonstrated a survival benefit of trifluridine/thymidine phosphorylase inhibitor (FTD/TPI) compared with placebo in patients with chemorefractory metastatic colorectal cancer (mCRC) (1), and FTD/TPI is recommended as a later-line treatment in the NCCN and ESMO guidelines (2, 3). Furthermore, as the efficacy of bevacizumab in combination with FTD/TPI has been demonstrated in some previous studies, including the C-TASK FORCE (4-9), the application of FTD/TPI plus bevacizumab therapy is gradually spreading in clinical practice.

Bevacizumab is a recombinant, humanized monoclonal antibody that suppresses angiogenesis by inhibiting vascular endothelial growth factor (VEGF) (10). Combining bevacizumab with cytotoxic anti-cancer agents has been reported to improve the survival outcomes in the first-line and/or second-line treatment for mCRC (11, 12). In clinical practice, almost all patients are treated with the anti-angiogenic inhibitor in front-line treatment. In particular, patients treated with bevacizumab beyond progression (BBP) receive bevacizumab for a long period.

However, in some basic research using experimental animal models, it was reported that persistent suppression of VEGF may cause acquired resistance of cancer cells to the anti-angiogenic inhibitor (13). Therefore, the effect of combining bevacizumab with FTD/TPI in later-line treatment may be influenced by the usage history of bevacizumab in front-line treatment. However, there have been no reports focusing on the impact of the usage history of bevacizumab in front-line treatment on the clinical benefit of combining bevacizumab with FTD/TPI in later-line treatment.

The present study examined whether or not the clinical benefit and tolerance of the addition of bevacizumab to FTD/TPI in later-line treatment was influenced by the usage history of bevacizumab in front-line treatment.

Patients and Methods

Patients. We retrospectively reviewed the medical records of 62 patients with mCRC who were treated with FTD/TPI at Osaka City University Hospital between June 2014 and February 2020. All

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patients had received at least two previous chemotherapeutic regimens. Patients treated with an anti-angiogenic inhibitor other than bevacizumab, such as ramucirumab and aflibercept, in front-line treatment were excluded from this study.

This retrospective study was approved by the Ethics Committee of Osaka City University (approval number: 4182) and conducted in accordance with the Declaration of Helsinki. All patients provided their written informed consent.

Methods. Patients were treated with FTD/TPI (35 mg/m^2 of body surface area) orally twice a day on days 1-5 and 8-12 in a 28-day cycle with or without bevacizumab (5 mg/kg of body wight) administered by intravenous infusion every 2 weeks. Tumor measurements were taken within one month before the initiation of FTD/TPI. Response evaluations by computed tomography were performed every 8-10 weeks according to the Response Evaluation Criteria in Solid Tumors (14). If the treatment was discontinued due to adverse events before the first response evaluation, the response was judged as not evaluable. If the treatment was discontinued due to the deterioration of the general condition caused by tumor burden, the response was judged as progressive disease. The progression-free survival (PFS) was defined as the time from initiation of FTD/TPI to disease progression or death due to any cause. Disease control was defined as a complete or partial response or stable disease.

Adverse events were graded using Common Terminology Criteria for Adverse Events (Version 4.0) (15). FTD/TPI treatment was continued until progression or unacceptable toxicity.

Statistical analyses. All statistical analyses were performed using the SPSS software package for Windows (SPSS, Chicago, IL, USA). The significance of differences in the patients' characteristics, chemotherapeutic response and safety profile between treatment groups were analyzed using the chi-square test, Fisher's exact test and Mann-Whitney's *U*-test. Survival curves were estimated using the Kaplan–Meier method, and the differences in the survival curves were assessed with the log-rank test. Statistical significance was set at a value of $p<0.05$.

Results

Patient characteristics. There were no significant differences in patients' characteristics between the FTD/TPI plus bevacizumab group and the FTD/TPI monotherapy group (Table I).

Comparison of the chemotherapeutic effect and safety profile between FTD/TPI plus bevacizumab and FTD/TPI monotherapy in the overall patients enrolled in this study. The FTD/TPI plus bevacizumab group had a significantly better PFS rate and disease control rate (DCR) than the FTD/TPI monotherapy group (PFS: $p=0.0001$, DCR: $p=0.016$) (Figure 1) (Table II). Although the incidence of grade ≥3 neutropenia and thrombocytopenia was slightly higher in the FTD/TPI plus bevacizumab group than in the FTD/TPI monotherapy group, no significant differences in the safety profile were observed between the two groups (Table III).

Table I. *Patient characteristics*.

	FTD/TPI monotherapy group (n=26)	FTD/TPI+ bevacizumab group (n=36)	*p*-Value
Age (years)			
Median (range)	69 (24-89)	68 (44-88)	0.753
Gender, n			
Male	15	21	
Female	11	15	0.999
Performance status, n			
0, 1	21	35	
≥2	5	1	0.074
Location of primary tumor, n			
Right side	7	13	
Left side	19	23	0.584
RAS status, n			
Wild type	11	18	
Mutant type	10	16	0.999
Unknown	5	2	
Number of metastatic organs, n			
1	9	14	
≥2	17	22	0.794

FTD/TPI: Trifluridine/thymidine phosphorylase inhibitor; RAS: proto-oncogene.

Comparison of the chemotherapeutic effect between FTD/TPI plus bevacizumab and FTD/TPI monotherapy in an analysis limited to the patients treated with BBP in front-line treatment. The FTD/TPI plus bevacizumab group had a significantly better PFS rate and DCR than the FTD/TPI monotherapy group (PFS: $p=0.0001$, DCR: $p=0.026$) (Figure 2) (Table IV).

Comparison of the chemotherapeutic effect between FTD/TPI plus bevacizumab and FTD/TPI monotherapy in an analysis limited to the patients treated with bevacizumab-containing treatment for more than 12 months in front-line treatment. The FTD/TPI plus bevacizumab group had a significantly better PFS rate than the FTD/TPI monotherapy group ($p=0.0006$) (Figure 3), although significant differences in the DCR were observed between the two groups (Table V).

A sub-group analysis of the adverse events according to the usage history of bevacizumab in front-line treatment in patients treated with FTD/TPI plus bevacizumab. The incidence of adverse events was not associated with the number of bevacizumab-containing regimens in front-line treatment, although the incidence of neutropenia, anemia, nausea, vomiting and proteinuria was slightly higher in patients treated with BBP than in those treated with bevacizumab-containing treatment either in the first- or second-line treatment (Table VI). Similarly, the incidence of adverse events was not associated with the duration of

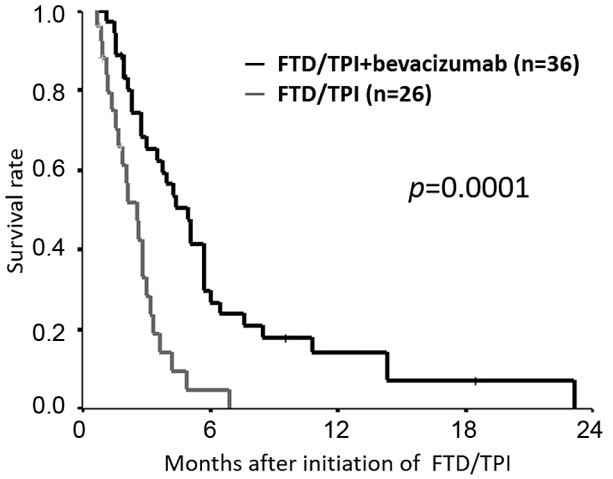

Figure 1. *Kaplan–Meier survival curves for the relapse-free survival in the overall population enrolled in this study.*

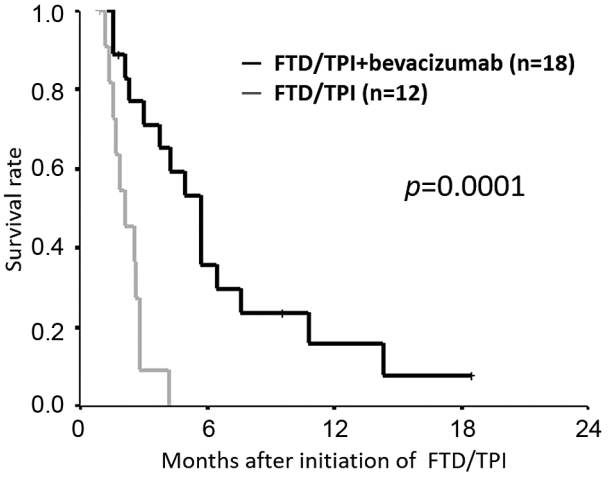

Figure 2. *Kaplan–Meier survival curves for the relapse-free survival in an analysis limited to the patients treated with bevacizumab beyond progression in front-line treatment.*

Table II. *Comparison of the disease control rate between the FTD/TPI monotherapy group and FTD/TPI+bevacizumab group.*

Response	FTD/TPI monotherapy group (n=26)	FTD/TPI+ bevacizumab group (n=36)	*p*-Value
Complete response	0	0	
Partial response	0	3	
Stable disease	6	18	
Progressive disease	17	14	
Not evaluable	3	1	
Disease control rate	23.1%	58.3%	0.016

FTD/TPI: Trifluridine/thymidine phosphorylase inhibitor.

bevacizumab-containing treatment in front-line treatment, although the incidence of nausea, vomiting and proteinuria was slightly higher in patients treated with bevacizumab-containing treatment for more than 12 months in front-line treatment than in those treated with bevacizumab-containing treatment for one year or less in front-line treatment (Table VII).

Discussion

In this study, FTD/TPI plus bevacizumab was revealed to be associated with better therapeutic outcomes than FTD/TPI monotherapy, as documented in previous reports (4-9). Furthermore, the efficacy of bevacizumab in combination with FTD/TPI was found to be unaffected by the number of bevacizumab-containing regimens and the duration of bevacizumab-containing treatment in front-line treatment. In contrast, there were no statistically significant differences in the incidence of adverse events between the FTP/TPI plus bevacizumab group and the FTD/TPI monotherapy group, although the addition of bevacizumab to FTD/TPI slightly increased the risk of adverse events. Furthermore, the incidence of adverse events was considered to be unaffected by the usage history of bevacizumab in front-line treatment.

The structural and functional abnormalities of newly formed tumor blood vessels, such as a lack of a basement membrane, large gaps between endothelial cells and defects in the pericyte coverage and function, contribute to the increased permeability of tumor vessels, leading to the insufficient distribution of drugs to cancer cells (16). However, the vascular normalization induced by an anti-angiogenic inhibitor increases the drug delivery and intracellular uptake of the drug, leading to the improvement of the chemotherapeutic efficacy (16). In clinical trials, the addition of bevacizumab to oxaliplatin-based first-line chemotherapy was proven to improve the survival outcomes (11). Furthermore, based on the evidence that the effect of bevacizumab is observed even in second-line treatment after progressive disease in first-line treatment with bevacizumab (12), bevacizumab is often used for a long period in both first- and second-line settings.

A mechanism underlying the effects of BBP has been suggested (17). In brief, resistance to treatment is caused by cancer cells becoming refractory to cytotoxic anticancer agents but not to bevacizumab. Therefore, the continuous administration of bevacizumab in subsequent treatment results in an improvement of the survival outcomes. Indeed, in previous clinical studies, there were no reports that the continuous use of bevacizumab diminishes its effect. However, in some basic research using experimental animal

Table III. *Comparison of adverse events between the FTD/TPI monotherapy group and FTD/TPI+bevacizumab group.*

	FTD/TPI monotherapy group (n=26)		FTD/TPI+ bevacizumab group (n=36)		*p*-Value (Any grade/Grade ≥3)
	Any grade	Grade ≥3	Any grade	Grade ≥3	
Hematological toxicity					
Neutropenia, n (%)	18 (69.2%)	7 (26.9%)	24 (66.7%)	14 (38.9%)	0.999/0.418
Anemia, n (%)	14 (53.8%)	7 (26.9%)	18 (50.0%)	4 (11.1%)	0.802/0.177
Thrombocytopenia, n (%)	6 (23.1%)	0 (0%)	8 (22.2%)	3 (8.3%)	0.999/0.258
Non-hematological toxicity					
Nausea, n (%)	11 (42.3%)	2 (7.7%)	10 (27.8%)	0 (0%)	0.283/0.172
Vomiting, n (%)	5 (19.2%)	0 (0%)	6 (16.7%)	0 (0%)	0.999/
Diarrhea, n (%)	6 (23.1%)	2 (7.7%)	2 (5.6%)	0 (0%)	0.059/0.172
Fatigue, n (%)	11 (42.3%)	3 (11.5%)	16 (44.4%)	1 (2.8%)	0.999/0.300
Febrile neutropenia, n (%)	2 (7.7%)	2 (7.7%)	0 (0%)	0 (0%)	0.172/0.172

FTD/TPI: Trifluridine/thymidine phosphorylase inhibitor.

Table IV. *Comparison of the disease control rate between the FTD/TPI monotherapy group and FTD/TPI+bevacizumab group in patients treated with bevacizumab beyond progression in front-line treatment.*

Response	FTD/TPI monotherapy group (n=12)	FTD/TPI+ bevacizumab group (n=18)	*p*-Value
Complete response	0	0	
Partial response	0	3	
Stable disease	2	8	
Progressive disease	10	7	
Not evaluable	0	0	
Disease control rate	16.7%	61.1%	0.026

FTD/TPI: Trifluridine/thymidine phosphorylase inhibitor.

Table V. *Comparison of the disease control rate between the FTD/TPI monotherapy group and FTD/TPI+bevacizumab group in patients treated with bevacizumab for more than 12 months in front-line treatment.*

Response	FTD/TPI monotherapy group (n=8)	FTD/TPI+ bevacizumab group (n=17)	*p*-Value
Complete response	0	0	
Partial response	0	3	
Stable disease	2	7	
Progressive disease	6	7	
Not evaluable	0	0	
Disease control rate	25.0%	58.8%	0.202

FTD/TPI: Trifluridine/thymidine phosphorylase inhibitor.

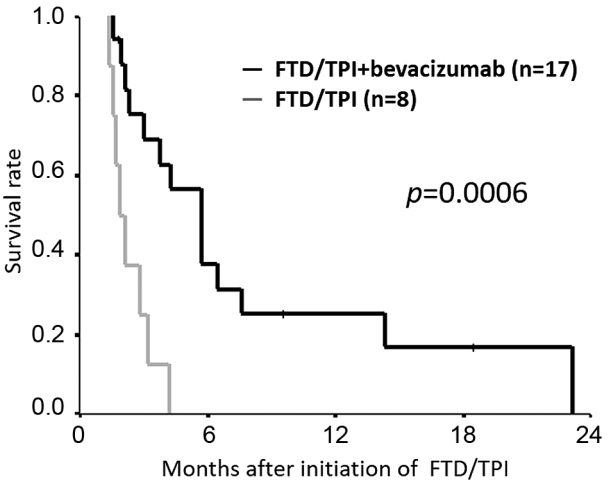

Figure 3. *Kaplan–Meier survival curves for the relapse-free survival in an analysis limited to the patients treated with treatment containing bevacizumab for more than 12 months in front-line treatment.*

models, it was reported that persistent suppression of VEGF may promote angiogenesis via pathways other than VEGF. For example, angiogenic factors such as fibroblast growth factor, host cells such as tumor-associated macrophages and myeloid-derived suppressor cells, stem cells and pericytes promote angiogenesis instead of VEGF (18-22). However, the current study revealed that the efficacy of continuous administration of bevacizumab in later-line treatments was maintained even in cases where bevacizumab had been used for a long period in the front-line treatment.

Table VI. *Comparison of adverse events according to the number of bevacizumab-containing regimens in front-line treatment in patients treated with FTD/TPI plus bevacizumab.*

	Number of bevacizumab-containing regimens in front-line treatment				*p*-Value (Any grade/Grade ≥3)
	1 (n=16)		2 (n=18)		
	Any grade	Grade ≥3	Any grade	Grade ≥3	
Hematological toxicity					
Neutropenia, n (%)	11 (68.8%)	5 (31.3%)	13 (72.2%)	9 (50.0%)	0.999/0.315
Anemia, n (%)	7 (43.8%)	1 (6.3%)	10 (55.6%)	3 (16.7%)	0.732/0.604
Thrombocytopenia, n (%)	4 (25.0%)	2 (12.5%)	4 (22.2%)	1 (5.6%)	0.999/0.591
Non-hematological toxicity					
Nausea, n (%)	3 (18.8%)	0 (0%)	6 (33.3%)	0 (0%)	0.448/
Vomiting, n (%)	1 (6.3%)	0 (0%)	5 (27.8%)	0 (0%)	0.180/
Diarrhea, n (%)	1 (6.3%)	0 (0%)	1 (5.6%)	0 (0%)	0.999/
Fatigue, n (%)	7 (43.8%)	0 (0%)	7(38.9%)	1 (5.6%)	0.999/0.999
Febrile neutropenia, n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Proteinuria, n (%)	9 (56.3%)	1 (6.3%)	12 (66.7%)	0 (0%)	0.725/0.999
Hypertension, n (%)	0 (0%)	0 (0%)	1 (5.6%)	1 (5.6%)	0.999/0/999

FTD/TPI: Trifluridine/thymidine phosphorylase inhibitor.

Table VII. *Comparison of adverse events according to the duration of bevacizumab-containing treatment in front-line treatment in patients treated with FTD/TPI plus bevacizumab.*

	Duration of bevacizumab-containing treatment in front-line treatment				*p*-Value (Any grade/Grade ≥3)
	<1 year (n=17)		≥1 year (n=17)		
	Any grade	Grade ≥3	Any grade	Grade ≥3	
Hematological toxicity					
Neutropenia, n (%)	13 (76.5%)	8 (47.1%)	11 (64.7%)	6 (35.3%)	0.708/0.728
Anemia, n (%)	9 (52.9%)	3 (17.6%)	8 (47.1%)	1 (5.9%)	0.999/0.601
Thrombocytopenia, n (%)	5 (29.4%)	3 (17.6%)	3 (17.6%)	0 (0%)	0.688/0.227
Non-hematological toxicity					
Nausea, n (%)	3 (17.6%)	0 (0%)	6 (35.3%)	0 (0%)	0.438/
Vomiting, n (%)	1 (5.9%)	0 (0%)	5 (29.4%)	0 (0%)	0.175/
Diarrhea, n (%)	2 (11.8%)	0 (0%)	0 (0%)	0 (0%)	0.485/
Fatigue, n (%)	7 (41.2%)	0 (0%)	7 (41.2%)	1 (5.9%)	0.999/0.999
Febrile neutropenia, n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Proteinuria, n (%)	9 (52.9%)	1 (5.9%)	12 (70.6%)	0 (0%)	0.481/0.999
Hypertension, n (%)	0 (0%)	0 (0%)	1 (5.6%)	1 (5.9%)	0.999/0.999

FTD/TPI: Trifluridine/thymidine phosphorylase inhibitor.

In the present study, the addition of bevacizumab to FTD/TPI was not associated with increased adverse events. Furthermore, the usage history of bevacizumab in front-line treatment was not associated with an increased risk of adverse events. In previous reports on FTD/TPI plus bevacizumab treatment, it was concluded that the addition of bevacizumab caused only a slight increase in adverse events and that adverse events were manageable. Previous studies regarding BBP concluded that, as there were no substantial differences in the safety profile of bevacizumab between first- and second-line treatment with BBP, the continuous administration of bevacizumab did not increase the risk of unacceptable toxicity (12). Furthermore, the safety of the continuous administration of bevacizumab has also been reported not only in colorectal cancer but also in non-small cell lung cancer and ovarian cancer (23, 24). Of course, the

frequency of adverse events, such as neutropenia and proteinuria, will increase in cases with a long-term administration of FTD/TPI plus bevacizumab, due to its effectiveness. Therefore, in cases where long-term administration is possible, it is necessary to be alert for the occurrence of adverse events and to perform appropriate dose reduction as needed.

Several limitations associated with the present study warrant mention. First, the current study was a retrospective study with a small cohort in a single center. Second, the impact of the usage history of anti-angiogenic inhibitors other than bevacizumab, such as ramucirumab and aflibercept, on the clinical benefit of combining bevacizumab with FTD/TPI in later-line treatment was not investigated in this study.

In conclusion, combining bevacizumab with FTD/TPI improves the survival outcomes with manageable toxicity, regardless of the usage history of bevacizumab in front-line treatment in patients with mCRC.

Conflicts of Interest

The Authors declare that they have no competing interests in regard to this study.

Authors' Contributions

MS designed the study, performed the statistical analysis and draft the manuscript. HN, TF, YI EW and YO collected the clinical data and revised the manuscript critically. SK, KM, KH and MO designed the study and critically reviewed the manuscript. All Authors read and approved the final manuscript.

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