Original Article

Real-world Efficacy and Safety of Modified Trifluridine/tipiracil (TAS-102) Administration in Patients with Refractory Metastatic Colorectal Cancer Progression after Regorafenib Treatment

Kuan-Ling Li
Hsiang-Lin Tsai
Wei-Chih Su
Ching-Wen Huang
Jaw-Yuan Wang
Division of Colorectal Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

Key Words
Trifluridine/tipiracil (TAS-102);
Modified administration;
Refractory metastatic colorectal cancer (mCRC);
Efficacy;
Safety

Purpose. The RECOURSE and TERRA studies revealed high percentages of severe neutropenia (grade ≥ 3) when the standard administration of trifluridine/tipiracil (TAS-102) was employed. We therefore aimed to explore the efficacy and safety of a modified administration of TAS-102 in patients with refractory metastatic colorectal cancer (mCRC) progression after regorafenib treatment.

Methods. We observationally analyzed the medical records of the 33 qualified patients with mCRC who started TAS-102 between December 2018 and November 2020. The demographic, clinical, tumor, and treatment variables were recorded. We analyzed the efficacy and safety of a modified method of administering TAS-102 and compared these data with those of the RECOURSE and TERRA studies.

Results. Severe neutropenia (grade ≥ 3) was the most common severe adverse event in the RECOURSE, TERRA, and our studies. Our study demonstrated a relatively low incidence of grade 3 or 4 neutropenia (9.1% versus 38.0% [RECOURSE] versus 33.2% [TERRA]) but similar median progression-free survival (PFS) and overall survival (OS) (median PFS: 2.0 months; median OS: 7.0 months).

Conclusions. In the observational study, we showed that this modified administration of TAS-102 has lower incidence of severe neutropenia for mCRC patients with progression after regorafenib treatment.

[*J Soc Colon Rectal Surgeon* (*Taiwan*) *2021;32:191-199]*

The incidence of colorectal cancer (CRC) is increasing in Asian countries and is currently the fourth most common cause of cancer-related deaths after cancers of the lung, liver, and stomach.[1] Moreover, between 20% to 30% of patients present with synchronous metastatic disease, and more than 50% of patients ultimately develop metastatic disease, most are unresectable metastases.[2] In the treatment of metastatic disease, substantial progress has been made through combining chemotherapeutics and biologics,[3] which has contributed to improvements in overall survival (OS) and quality of life.[4] Many patients with

Received: August 13, 2021. Accepted: September 27, 2021.
Correspondence to: Prof. Jaw-Yuan Wang, Division of Colorectal Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, No. 100, Tzyou 1st Road, Kaohsiung 807, Taiwan. Tel: 886-7-312-2805; Fax: 886-7-311-4679; E-mail: cy614112@ms14.hinet.net; jawyuanwang@gmail.com

metastatic disease refractory to standard chemotherapy maintain good performance status and would be candidates for further treatment.

Although the cytotoxic agents associated with new targeted molecules have improved the prognosis of patients with advanced disease, no treatments were available beyond third-line treatments until recently.[5] The American Society of Clinical Oncology and the National Comprehensive Cancer Network recommended regorafenib or TAS-102 as late-line treatments for patients with metastatic CRC (mCRC). TAS-102 is widely used as the third-line treatment for mCRC in Japan.[6] It is an oral cytotoxic agent that was initially approved in Japan, and its efficacy and safety were confirmed shortly afterward in Western and Asian patients, respectively, in the placebo-controlled phase III clinical trials RECOURSE[7] and TERRA.[1] The most commonly reported adverse events were hematologic, 30%-40% of which were severe neutropenia.[1,7]

TAS-102 was administered orally 1 hour after morning and evening meals on days 1-5 and days 8-12 of each 28-day cycle.[8] The treatment cycle was repeated every 4 weeks until progressive disease or unacceptable toxicity occurred. Nonetheless, the results of clinical trials do not always reflect the reality of clinical practice, despite the randomization procedures and selection criteria used. This study assessed the efficacy and safety of TAS-102 under a modified administration regimen in real-life practice in patients with progressive refractory mCRC after regorafenib treatment.

Methods

Study design and patient eligibility

This observational study investigated the safety and efficacy of TAS-102 in patients with mCRC that progressed after previous use of regorafenib as the 3rd line regimen. We reviewed medical charts and records to gather data on the clinical outcomes of treatment. Clinically, the physician decided the therapeutic plan including the chemotherapeutic agents and biologics according to the clinical status (e.g. EGOC), genomic profiling, and the rules of the Taiwan Health Insurance. TAS-102 was reimbursed by the National Health Insurance. All data were obtained with informed consent from each patient, and the Institutional Review Board of Kaohsiung Medical University Hospital [KMUHIRB-2012-03-03(II)] approved our study protocol.

Patients were considered eligible for this study if mCRC progression was confirmed according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines[9] and they had received prior treatment after regorafenib. Other inclusion criteria were an age of ≥ 20 years, life expectancy of > 3 months, and Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. The qualified patients were treated using a modified administration regimen of TAS-102.

Treatment and measures

We included demographic (age, sex), clinical (ECOG performance status), tumor (primary tumor site, *RAS* status, *BRAF* status, time since diagnosis of first metastasis, and number and sites of metastases) and treatment (number and type of previous treatments) variables.

TAS-102 was originally administered orally at 35 mg/m^2 twice daily in the following 28-day cycle: 2 weekly cycles of 5 consecutive days of treatment and 2 days of rest, followed by 14 days of rest[8] (Fig. 1A). The modified administration method was also in a 28-day cycle as follows: TAS-102 (each dose of 35 mg/m^2) was administered twice daily for 5 consecutive days of treatment followed by 9 days of rest. The protocol was repeated once (Fig. 1B).

Assessment

We evaluated progression-free survival (PFS), OS, best objective response rates (ORRs), disease control rates (DCRs), and toxicity of the modified administration of TAS-102 in patients with mCRC progression after regorafenib treatment failed according to RECIST criteria.[10] The Kaplan-Meier method was used to calculate PFS and OS. The day that TAS-102 was introduced was considered the starting point for the mea-

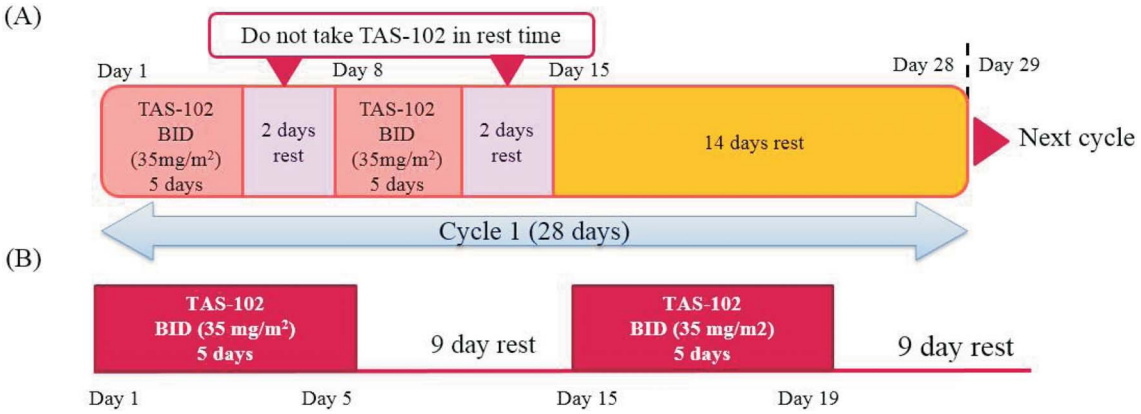

Fig. 1. The administration of trifluridine/tipiracil (TAS-102). (A) Original regimen: 2 weekly cycles of 5 consecutive days of treatment and 2 days of rest, followed by 14 days of rest in a 28-day cycle. (B) Modified regimen: trifluridine/tipiracil (each dose: 35 mg/m^2) was administered twice daily, with 5 consecutive days of treatment followed by 9 days of rest. This protocol was repeated once.

surement of PFS and OS.

Toxicities were monitored and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03 (http://ctep.cancer.gov/reporting/ctc.html). Radiographic assessments were performed at baseline (within 4 weeks prior to registration). Computed tomography or magnetic resonance imaging was used to assess target and non-target lesions and to confirm the presence or absence of new lesions for diagnostic assessment of efficacy; imaging was performed every 8 weeks. The best response was defined as the best of all responses during the period of TAS-102 therapy.

Statistical analysis

Baseline characteristics were summarized using descriptive statistics. Continuous variables are presented as medians with 25%-75% interquartile range (IQR) or means with standard deviation. Categorical variables are expressed as frequencies and percentages. Statistical Package for the Social Sciences, Version 19.0 (SPSS Inc., Chicago, IL, USA) was used to perform all analyses. The time elapsed between the initiation of the study therapy and date of disease progression, death, or last follow-up was defined as PFS. OS was defined as the time elapsed between the initiation of the study therapy and date of death from any cause or final follow-up. The Kaplan-Meier method was used to evaluate the PFS and OS, and the log-rank test was used to compare time-to-event distribution. Statistical significance was set at $p < 0.05$.

Results

Patient characteristics

Between December 2018 and November 2020, we initially enrolled 37 patients in the study; however, four were excluded because of disease progression or poorer ECOG (≥ 2) status before TAS-102 administration. Finally, 33 patients were enrolled for the efficacy and safety analysis. Table 1 shows the demographic and baseline characteristics of the enrolled patients. The median age was 60.0 years (IQR, 54.0-67.5 years). Overall, 25 patients (75.8%) were diagnosed with synchronous or metachronous mCRC for less than 18 months. All enrolled patients had received the third-line regimen of regorafenib before this treatment. In total, 19 patients (57.6%) had more than two metastatic sites. The liver and lungs were the two most common metastatic sites in these patients. Moreover, 18 patients (54.5%) exhibited the mutant-type *KRAS* gene, 17 patients (51.5%) did not undergo the *NRAS* test, and the wild-type *BRAF* gene was observed in all enrolled patients (100%).

Table 1. The 33 enrolled patient demographics and baseline characteristics

Variables	N (%)
Age, years, median (IQR)	60.0 (54.0-67.5)
PFS, months, median (IQR)	2.0 (2.0-3.0)
OS, months, median (IQR)	7.0 (4.0-12.0)
Gender	
Male	24 (72.7)
Female	9 (27.3)
Age (y/o)	
< 65	23 (69.7)
≥ 65	10 (30.3)
ECOG PS	
0	3 (9.1)
1	30 (90.9)
KRAS status	
Wild type	15 (45.5)
Mutant type	18 (54.5)
NRAS status	
Wild type	16 (48.5)
Mutant type	0 (0)
No done	17 (51.5)
BRAF status	
Wild type	33 (100)
Mutant type	0 (0)
Type of mCRC	
Synchronous	17 (51.5)
Metachronous	16 (48.5)
Time since diagnosis of first metastasis, months	
< 18	25 (75.8)
≥ 18	8 (24.2)
Primary tumor site	
Left-sided colon	25 (75.8)
Right-sided colon	8 (24.2)
Number of prior regimen	
3rd line	21 (63.6)
4th line	10 (30.3)
5th line	2 (6.1)
Number of metastatic sites	
Only 1 site	14 (42.4)
≥ 2 sites	19 (57.6)
Metastatic sites	
liver	19 (57.6)
Lung	17 (51.5)
Peritoneum	11 (33.3)
Ovary	3 (9.1)
Uterus	1 (3.0)
Bone	4 (12.1)
Brain	1 (3.0)
Left adrenal gland	3 (9.1)
Para-aortic lymph nodes	3 (9.1)
Retroperitoneal lymph nodes	1 (3.0)
All prior systemic cancer therapeutic agents	
Bevacizumab/Aflibercept/Ramucirumab	33 (100)
Cetuximab/Panitumumab	15 (45.5)
Fluoropyrimidine	33 (100)
Irinotecan	33 (100)
Oxaliplatin	33 (100)
Regorafenib	33 (100)
Best objective response	
PR	1 (3.0)
SD	6 (18.2)
PD	26 (78.8)

PFS: progression-free survival; OS: overall survival; IQR: interquartile range; PS: performance status; mCRC: metastatic colorectal cancer; Left-sided colon: descending colon + sigmoid colon + rectosigmoid colon + rectum; Right-sided colon: cecum + ascending colon + transverse colon; PR: partial response; SD: stable disease; PD: progression-free survival.

Safety

Table 2 presents the adverse events (AEs). They were divided into hematologic and non-hematologic events, with eight events of grade 1 (24.2%) and eight events of grade 2 (24.2%) for anemia; two events of grade 1 (6.1%) and one event of grade 3 (3.0%) for thrombocytopenia. Three events (9.1%) of grade 3 or

Table 2. Common toxicities of the enrolled 33 mCRC patients (NCI-CTACE Version 4.03)

	N (%)			
Grade	1	2	3	4
Hematologic AEs				
Anemia	8 (24.2)	8 (24.2)	0 (0)	0 (0)
Neutropenia	5 (15.2)	4 (12.1)	2 (6.1)	1 (3.0)
Thrombocytopenia	2 (6.1)	0 (0)	1 (3.0)	0 (0)
Non-hematologic AEs				
Fatigue	12 (36.4)	17 (51.5)	0 (0)	0 (0)
Nausea	4 (12.1)	2 (6.1)	0 (0)	0 (0)
Vomiting	3 (9.1)	1 (3.0)	0 (0)	0 (0)
Anorexia	9 (27.3)	0 (0)	0 (0)	0 (0)
Diarrhea	2 (6.1)	1 (3.0)	0 (0)	0 (0)
Oral mucositis	2 (6.1)	0 (0)	0 (0)	0 (0)
Skin rash	2 (6.1)	1 (3.0)	0 (0)	0 (0)
Liver function impairment	4 (12.1)	2 (4.8)	0 (0)	0 (0)
Renal function impairment	2 (6.1)	0 (0)	0 (0)	0 (0)
Paresthesia	1 (3.0)	0 (0)	0 (0)	0 (0)

AEs: adverse events.

4 neutropenia occurred in three patients. No severe AEs were observed in the non-hematologic events category, and fatigue was the most common event (grade 1: 36.4% and grade 2: 51.5%). We also observed other non-hematologic events including nausea (grade 1: 12.1% and grade 2: 6.1%), vomiting (grade 1: 9.1% and grade 2: 3.0%), anorexia (grade 1: 27.3%), diarrhea (grade 1: 6.1% and grade 2: 3.0%), oral mucositis (grade 1: 6.1%), skin rash (grade 1: 6.1% and grade 2: 3.0%), liver function impairment (grade 1: 12.1% and grade 2: 4.8%), renal function impairment (grade 1: 6.1%) and paresthesia (grade 1: 3.0%).

Efficacy

Regarding the best response, one patient was partial response (3.0%) and six patients (18.2%) had stable disease, 26 (78.8%) had progressive disease, and seven (21.2%) achieved disease control (Table 3). Median PFS was 2.0 months (IQR, 2.0-3.0 months; Table 1), and median OS was 7.0 months (IQR, 4.0-12.0 months; Table 1). Fig. 2A and 2B show the Kaplan-Meier analyses of PFS and OS, respectively.

Comparison of safety and efficacy between RECOURSE and TERRA trials and current study

Table 3 summarizes the safety and efficacy of the RECOURSE and TERRA trials and the current study. Although severe neutropenia was the most common severe AE in the RECOURSE and TERRA studies (38.0% and 33.2%, respectively), an incidence of only 9.1% for severe neutropenia was observed in the current study. The median OS of the RECOURSE, TERRA, and current studies were 7.1 months, 7.8 months, and 7.0 months, respectively. The median PFS was 2.0 months in all studies. The current study had the highest percentage of patients (75.8%) with time since diagnosis of first metastasis less than 18 months (RECOURSE: 21.0% and TERRA: 49.0%). The percentages of prior regimens below third-line treatments were 18.0%, 23.0%, and 0% for RECOURSE, TERRA, and current studies, respectively. All our enrolled patients received oral regorafenib as a prior anticancer agent; however, only 17.0% of patients underwent this treatment in the RECOURSE study. ORR was 3%

Table 3. Comparison of safety profile and efficacy between RECOURSE, TERRA, and current study

	RECOURSE		TERRA		Current study	
Safety	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Neutropenia	67.0%	38.0%	67.2%	33.2%	36.4%	9.1%
Anemia	77.0%	18.0%	77.1%	17.7%	48.5%	0%
Thrombocytopenia	42.0%	5.0%	35.4%	3.0%	9.1%	3.0%
Efficacy	RECOURSE		TERRA		Current study	
Median OS	7.1 months		7.8 months		7.0 months	
Median PFS	2.0 months		2.0 months		2.0 months	
Time since diagnosis of first metastasis, %						
< 18 months	21.0%		49.0%		75.8%	
Number of prior regimens						
< 3rd line	18.0%		23.0%		0%	
≥ 3rd line	82.0%		77.0%		100%	
Prior systemic anticancer agents, %						
Anti-VEGF	100%		19.0%		100%	
Anti-EGFR	52.0%		17.0%		45.5%	
Regorafenib	17.0%		Unknown		100%	
Best response, %						
ORR	1.6%		1.1%		3.0%	
DC	44.0%		44.1%		21.2%	

OS: overall survival; PFS: progression-free survival; VEGF: vascular endothelial growth factor; EGFR: epithelial growth factor receptor; ORR: objective response rates; DCR: disease-control rates.

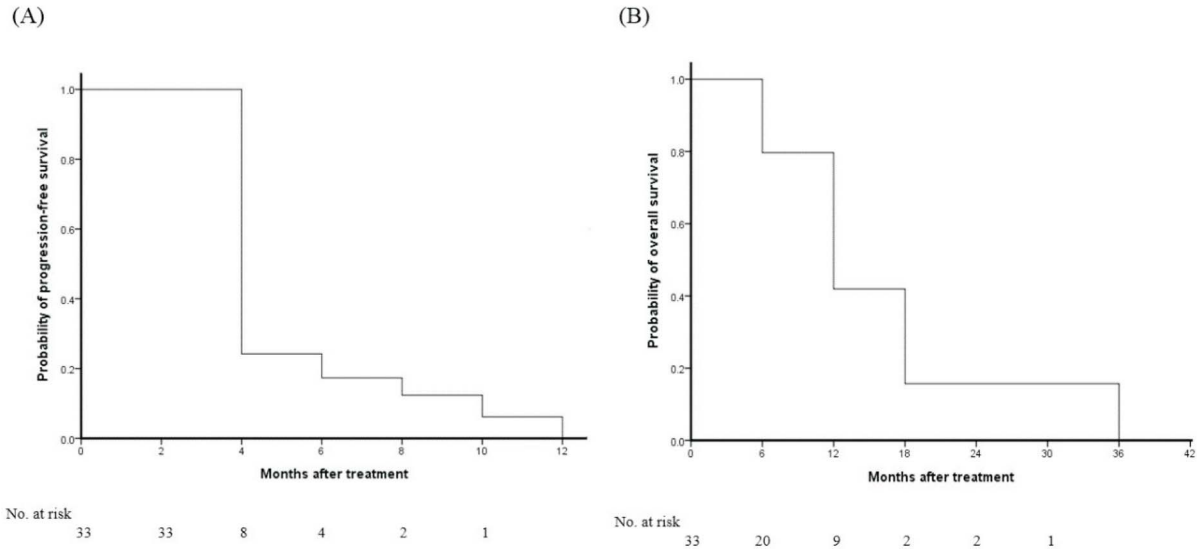

Fig. 2. Cumulative survival rates of the 33 enrolled patients with mCRC obtained using the Kaplan-Meier method. (A) Median progression-free survival was 2.0 months. (B) Median overall survival was 7.0 months.

in our study and 1.6% and 1.1% were found in the RECOURSE and TERRA studies, respectively. DCR was approximately 44.0% in the other two studies but only 21.2% in the current study.

Discussion

This observational study revealed real-world experience with a modified method of TAS-102 administration for patients with progressive refractory mCRC upon failure of previous regorafenib treatment. As we know, the most important and severe adverse event of TAS-102 is severe neutropenia clinically. So it is very important that how to reduce the severe AE clinically. We think whether this reason of severe neutropenia is caused by re-administration after the clearance time of TAS-102 is too short. Under this view, we maintain the same period of one cycle (28 days) and the same total dosage of TAS-102 but prolonged the interval of re-administration for 2 days to 9 days. We collected data on the feasibility, use, and toxicity of the drug. The result of our study demonstrated that the modified administration method clinically outperformed the original method of TAS-102 administration in terms of its effects on severe neutropenia. Moreover, our median PFS and median OS seemed not inferior to those of the RECOURSE and TERRA studies.

Taking into consideration the results of the previous studies and absence of patients with ECOG scores of > 1 in the pivotal study, we believe that ECOG performance status should be considered a variable that limits the appropriateness of TAS-102 administration. In 2018, Kwakman et al. demonstrated that TAS-102 showed poorer survival results for patients with an ECOG score of 2 than those with an ECOG score of 0-1.[11] Consistent with the performance status of patients with mCRC in the RECOURSE and TERRA trials, the performance status of the enrolled patients in the current study was also ECOG 0-1.

Although TAS-102 and regorafenib have not been compared directly in a clinical trial but only in observational series, their efficacy and effectiveness seem comparable in third-line therapy for patients with mCRC.[3,12,13] A Japanese phase II trial and two phase III trials (RECOURSE and TERRA) have demonstrated that TAS-102 prolonged OS.[14] All enrolled patients in our study had undergone both TAS-102 and regorafenib treatments, whereas only 17% of patients underwent both treatments in RECOURSE. In 2018, Cremolini et al. compared patients who had received both TAS-102 and regorafenib, TAS-102 after regorafenib, and regorafenib after TAS-102 and reported that all outcomes were independent of the sequence.[15]

Therefore, it likely had no impact on our overall estimates of effectiveness.

The efficacy of treatment is known to decrease with subsequent lines of therapy, and the proportion of patients receiving therapy decreases in subsequent lines.[16] In a purely palliative setting, strategic planning of treatment sequences following the continuum of care concept evaluates the toxicity of chemotherapy and tumor biology to individualize therapeutic approaches. The two main goals of patients with mCRC undergoing more than third-line regimens are to delay tumor progression and maintain quality of life.[16,17] PFS is a commonly used endpoint for third-line trials in mCRC[18] and the ORR was around 1-13% with PFS was 2 months.[16] Although TAS-102 was at least a fourth-line cytotoxic drug for our patients, the median PFS and median OS were quite similar to those of patients in the RECOURSE and TERRA studies. However, a greater proportion of our patients were < 18 months from having received a diagnosis of first metastasis compared with the proportions in the RECOURSE and TERRA studies (75.8%, 21.0%, and 49.0%, respectively), and all patients had previously undergone at least a third-line regimen before TAS-102 administration. This may have led to a worse DCR (current: 21.2% vs. RECOURSE: 44.0% vs. TERRA: 44.1%) but not inferior ORR in our study than those in the RECOURSE and TERRA studies (3.0%; 1.6%; and 1.1%, respectively).

Most of the toxicity associated with TAS-102 was hematologic abnormalities,[19] with grade 3 or 4 neutropenia occurring in 9.1% of patients in our study and 38.0% and 33.2% in the RECOURSE and TERRA trials, respectively. The modified administration of TAS-102 seemed to reduce this severe hematologic AE. Although the reason for this is not yet known, the extension of the interval between each administration in a cycle from 2 days to 9 days may have possibly reduced the accumulation of toxicity.

This current study has some limitations, including (1) Its observational design and a small sample size. (2) This study was a retrospective analysis based on data from electronic medical records, we were unable to accurately assess the patients' adherence to the TAS-102 regimen. This may have resulted in the low incidence of neutropenia and poor efficacy observed in our study. (3) All patients had used regorafenib, it cannot accurately compare with RECOURSE and TERRA studies. Prospective studies are needed to confirm our results and examine the potential effects of adherence. Nevertheless, this real-world study provides insights into the effects of TAS-102 using a modified administration method in patients with disease progression of refractory mCRC after regorafenib treatment.

Conclusions

Based on the same cycle duration and same dosage in one cycle. We designed the modified regimen. This current study might be demonstrated a safety benefit associated with the modified method of TAS-102 administration in patients with mCRC who received TAS-102 as a late-line therapy. So far, there is no study or experience using such regimen. To our knowledge, this observational, retrospective study is the first to analyze the tolerability of TAS-102 using the modified regimen. These findings might be important for adjustment of AEs and guidance for patients with mCRC receiving TAS-102. In the future, it is needed a prospective study to validate.

Acknowledgments

This work was supported by grants from the Ministry of Science and Technology (MOST 109-2314-B-037-035, MOST 109-2314-B-037-040, MOST 109-2314-B-037-046-MY3) and the Ministry of Health and Welfare (MOHW107-TDU-B-212-123006, MOHW 107-TDU-B-212-114026B, MOHW108-TDU-B-212-133006, MOHW109-TDU-B-212-134026, MOHW 109-TDU-B-212-114006). Additional funding was provided by the Health and Welfare Surcharge of Tobacco Products, Kaohsiung Medical University (KMU) Hospital (KMUH109-9R32, KMUH109-9R33, KMUH 109-9R34, KMUH109-9M30, KMUH109-9M31, KMUH109-9M32, KMUH109-9M33, KMUH-DK 109003, KMUH-DK(C)110010, KMUHS10903,

KMUHSA10903), the KMU Center for Cancer Research (KMU-TC109A04-1) as well as and a KMU Center for Liquid Biopsy and Cohort Research Center Grant (KMU-TC109B05), Kaohsiung Medical University. In addition, this study was supported by the Grant of Taiwan Precision Medicine Initiative, Academia Sinica, Taiwan, R.O.C.

Conflicts of Interests

The authors declare no conflict of interests.

References

1. Xu JM, Kim TW, Shen L, et al. Results of a randomized, double-blind, placebo-controlled, phase III trial of trifluridine/tipiracil (TAS-102) monotherapy in Asian patients with previously treated metastatic colorectal cancer: The TERRA study. *J Clin Oncol* 2018;36:350-8.
2. Van Cutsem E, Nordlinger B, Cervantes A, ESMO Guidelines Working Group. Advanced colorectal cancer: ESMO Clinical Practice Guidelines for treatment. *Ann Oncol* 2010; 21 Supple 5;v93-7.
3. Abrahao A BK, Ko YJ, Scott B, Chan K KW. A comparison of regorafenib and TAS-102 for metastatic colorectal cancer: a systematic review and network meta-analysis. *Clin Colorectal Cancer* 2018;17:113-20.
4. Sanz-Garcia E, Graselli J, Argiles G, Elez Elena M, Tabernero J. Current and advancing treatments for metastatic colorectal cancer. *Expert Opin Biol Ther* 2016;16:93-110.
5. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 2016;27:1386-422.
6. Toshiaki W, Michio I, Yasuhiro S, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2014 for treatment of colorectal cancer. *Int J Clin Oncol* 2015;20: 207-39.
7. Robert JM, Eric Van C, Alfredo F, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med* 2015;372:1909-19.
8. Agencia Espanola de Medicamentos y Productos Sanitarios. Ficha tecnica trifluridina/tiperacilo (Lonsurf). Consultada [2/2019]. Disponible en: https://cima.aemps.es/cima/pdfs/es/ft/1161096001/FT_1161096001.pdf.
9. Eisenhauer EA, Therase P, Bogaerts J, et al. New response evaluation criteria in solid tumors. Revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228-47.
10. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205-16.
11. Kwakman JJM, Vink G, Vestjens JH, et al. Feasibility and effectiveness of trifluridine/tipiracil in metastatic colorectal cancer: real-life data from The Netherlands. *Int J Clin Oncol* 2018;23:482-9.
12. Masuishi T, Taniguchi H, Hamauchi S, et al. Regorafenib versus trifluridine/tipiracil for refractory metastatic colorectal cancer: a retrospective comparison. *Clin Colorectal Cancer* 2017;16:e15-22.
13. Toshikazu M, Shota F, Hiroya T, et al. Propensity score analysis of regorafenib versus trifluridine/tipiracil in patients with metastatic colorectal cancer refractory to standard chemotherapy (REGOTAS): a Japanese society for cancer of the colon and rectum multicenter observational study. *Oncologist* 2018; 23:7-15.
14. Andersen SE, Andersen IB, Jensen BV, Pfeiffer P, Ota T, Larsen JS. A systematic review of observational studies of trifluridine/tipiracil (TAS-102) for metastatic colorectal cancer. *Acta Oncol* 2019;58:1149-57.
15. Cremolini C, Rossini D, Martinelli E, et al. Trifluridine/tipiracil (TAS-102) in refractory metastatic colorectal cancer: a multicenter register in the frame of the Italian compassionate use program. *Oncologist* 2018;23:1178-87.
16. Grothey A. Medical treatment of advanced colorectal cancer in 2009. *Ther Adv Med Oncol* 2009;1:55-68.
17. Ma CJ, Huang CW, Yeh YS, et al. Regorafenib plus FOLFIRI with irinotecan dose escalated according to uridine diphosphate glucurosyltransferse 1A1 genotyping in patients with metastatic colorectal cancer. *Oncol Res* 2017;25:673-9.
18. Cicero G, De Luca R, Dieli F. Progression-free survival as a surrogate endpoint of overall survival in patients with metastatic colorectal cancer. *Onco Targets Ther* 2018;11:3059-63.
19. Jonathan ML, Scott K. Recent developments in the treatment of metastatic colorectal cancer. *Ther Adv Med Oncol* 2017; 9:551-64.

原　著

針對 Regorafenib 治療無效的轉移性大腸直腸癌，調整後的 TAS-102 服藥方式可有效降低藥物副作用

李冠陵　蔡祥麟　蘇偉智　黃敬文　王照元

高雄醫學大學附設醫院　大腸直腸外科

目的　接受過 Regorafenib 治療反應不佳的轉移性大腸直腸癌患者，藉由調整後的 TAS102 服藥方式來降低藥物本身帶來的毒性跟副作用。

方法　藉回溯性觀察，於 2018 年 12 月到 2020 年 11 月間蒐集罹患轉移性大腸直腸癌並且以 Regorafenib 做為第三線但治療無效的患者，將 TAS-102 做為第四線以後的治療選擇，並記錄這些病患之疾病無惡化存活期、整體存活、最佳客觀反應率、疾病控制率、藥物毒性資料。

結果　共計 33 位患者被納入此觀察性研究，其中有 19 位 (57.6%) 患者有兩處以上的遠端轉移。有 18 位 (54.5%) 患者有突變型 KRAS 基因，所有患者的 BRAF 基因皆為野生型。此研究未觀察到 3 級以上的嚴重副作用，最常見的為 1 和 2 級的血紅素低下以及倦怠感。腫瘤治療成效方面，這群患者之平均疾病無惡化存活期為 2 個月，平均整體存活為 7 個月，與先前其他的大型觀察性研究無太大差異。

結論　嗜中性球低下是患者服用 TAS-102 最常見之三級以上嚴重副作用，使用調整過後的給藥方式可以有效降低此副作用，且不會降低藥物治療惡性腫瘤的效果。

關鍵詞　TAS-102、調整後服藥方式、副作用。