Original Article

Impact of TAS-102 and Regorafenib Sequencing on Overall Survival in Refractory Metastatic Colorectal Cancer: A Retrospective Cohort Study

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Key Words
TAS-102;
Regorafenib;
Metastatic colorectal cancer;
Overall survival

Background. Regorafenib and TAS-102 are recommended as third-line therapies for refractory metastatic colorectal cancer (mCRC); however, the optimal sequencing strategy remains unclear.
Methods. This retrospective study analyzed 38 patients with mCRC treated sequentially with both agents (between 2013 and 2024). Patients were stratified into TAS-102-first (TAS-f, n = 19) and regorafenib-first (Rego-f, n = 19) groups. Progression-free survival (PFS), overall survival (OS), and treatment duration were compared.
Results. Baseline characteristics were comparable between groups. The TAS-f group had significantly better OS (65.47 vs. 38.7 months; $p = 0.012$), with longer median survival after initiating third-line therapy (19.7 vs. 10.07 months; $p = 0.023$). Multivariate analysis identified TAS-102-first sequencing as the only independent predictor of improved OS (HR = 0.210, 95% confidence interval [CI], 0.064-0.682; $p = 0.009$).
Conclusion. Initiating TAS-102 before regorafenib treatment significantly improved the OS of patients with refractory mCRC, highlighting the clinical importance of therapeutic sequencing. Further prospective studies are required to confirm these findings.

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Colorectal cancer (CRC), which ranks third globally in both incidence and mortality,[1] has been the most frequently diagnosed cancer in Taiwan for many years. Approximately 17,000-18,000 new CRC are reported annually, accounting for 14-15% of all cancer cases in Taiwan.[2] Additionally, it causes approximately 5,800 deaths per year, ranking second to lung cancer. Current first-line treatments for CRC include surgery, chemotherapy, radiation therapy, and targeted therapy, with the latter being particularly effective for metastatic CRC (mCRC).

Patients with mCRC receiving conventional chemotherapy exhibit a median survival of 12-18 months, which can be extended to approximately 24-30 months with the targeted therapies.[3] However, this prolonged survival frequently leads to drug resistance and disease progression, necessitating a change in treatment.

Regorafenib, an oral multi-kinase inhibitor, was approved by the United States (US) Food and Drug Administration (FDA) in 2012 as a third to fourth-line treatment for mCRC. Clinical trials, including the CORRECT study, have demonstrated improved over-

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all survival (OS) compared to placebo (6.4 vs. 5.0 months) in patients with mCRC who had previously failed standard therapies, including chemotherapy and other targeted treatments.[4] Regorafenib is currently recommended for patients with disease progression after FOLFOX or FOLFIRI chemotherapy and targeted therapies against epidermal growth factor receptor (EGFR) orvascular endothelial growth factor (VEGF), such as Cetuximab or Bevacizumab.

TAS-102, an oral chemotherapeutic agent combining trifluridine (TFT) and tipiracil (thymidine phosphorylase inhibitor [TPI]), was approved in Japan in 2014 and by the U.S. FDA in September 2015 for treatment refractory mCRC. In the RECOURSE study, TAS-102 demonstrated longer OS compared to placebo (7.1 vs. 5.3 months) in heavily pretreated patients with mCRC,[5] additionally, the disease stabilization rate was significantly improved, establishing TAS-102 as a third-line alternative to regorafenib.

Per NCCN guidelines, regorafenib and TAS-102 are currently recommended as third-line therapies for mCRC. Despite increasing research on these agents, their optimal sequencing remains unclear. Therefore, this study aimed to investigate whether the sequencing of regorafenib and TAS-102 affects OS in patients receiving both therapies.

Materials and Methods

Study design and patient selection

This was a single-center retrospective study. We enrolled patients diagnosed with mCRC who received sequential treatment with regorafenib and TAS-102 between January 1, 2013, and December 31, 2024. The diagnosis of mCRC was confirmed by computed tomography (CT) imaging or histopathological examination. Key exclusion criteria included patients who received only one of the two drugs (regorafenib or TAS-102), and patients undergoing treatment with either drug at data collection. Subsequently, patients were stratified into two cohorts based on treatment sequence: the TAS-102-first group (TAS-f) and the regorafenib-first group (Rego-f). Demographic data, overall survival (OS), and clinical outcomes were retrospectively collected from medical records.

Management protocol in mCRC patients

All enrolled patients with mCRC had previously received 5-fluorouracil (5-FU)-based chemotherapy combined with targeted therapies and subsequently experienced disease progression. Either regorafenib

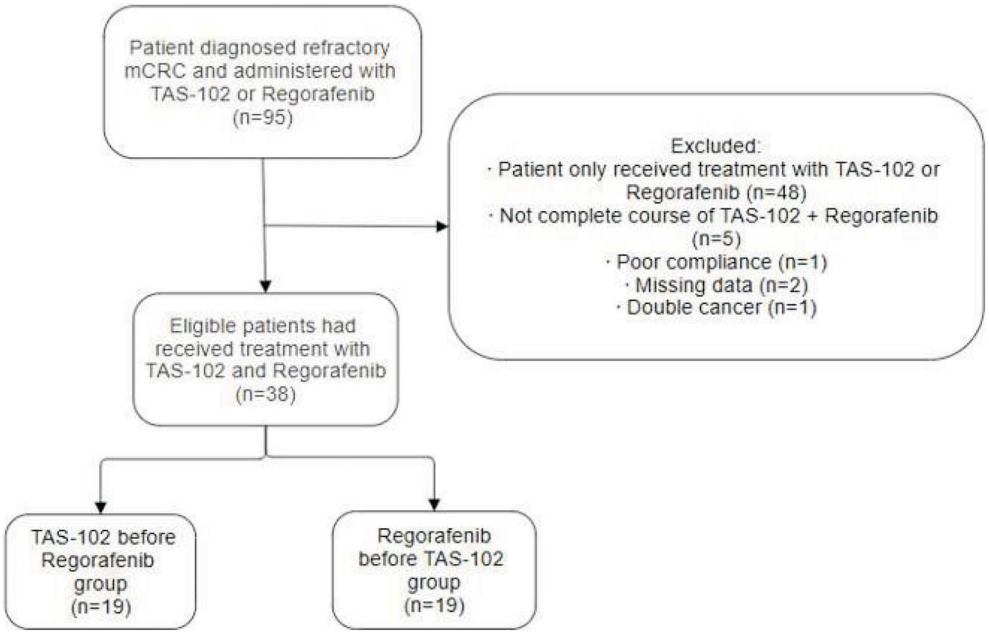

Fig. 1. Patients inclusion and group by the sequence of drug administration.

or TAS-102 was administered. Regorafenib was orally administered at 160 mg daily on days 1-21 of each 28-day cycle. TAS-102 was administered at 35 mg/m^2 (maximum 80 mg/dose based on the trifluridine component), twice daily on days 1-5 and 8-12 every 28 days. If severe adverse effects (Grade III or IV) occurred, the treatment was discontinued.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics software version 25. Baseline patient demographics and disease characteristics were compared between the TAS-f and Rego-f groups using independent t-tests for continuous variables and chi-squared tests for categorical variables. OS was analyzed using the Kaplan-Meier method, with statistical significance defined as $p < 0.05$.

Results

A total of 38 patients treated sequentially with TAS-102 and regorafenib were included in this analysis, with 19 patients in the TAS-f group and 19 in the Rego-f group. The baseline characteristics of the enrolled patients were summarized in Table 1. Age, sex, primary tumor location, and initial cancer stage were balanced between the two groups. However, the TAS-f group showed a slightly higher rate of distant lymph node metastasis and a lower rate of peritoneal metastasis.

Table 1. Descriptive statistics of demographic data

	TAS-f group (N = 19)		Rego-f group (N = 19)		*p*
	N	%	N	%	
Age (Y)	61.11 ± 11.03		66.53 ± 10.26		0.125
Sex					
M	12	63.2	14	73.7	0.485
F	7	36.8	5	26.3	
ECOG					0.080
0	2	10.5	7	36.8	
1	17	89.5	11	57.9	
2	0	0	1	5.3	
RAS					0.319
Mutant	10	52.6	13	68.4	
Non-mutant	9	47.8	6	31.6	
Metastatic sites					
Liver	9	47.4	9	47.4	1.000
Lung	9	47.4	9	47.4	1.000
Peritoneum	6	31.6	13	68.4	0.023
Distant L.N.s	10	52.6	4	21.1	0.044
Others (bone, brain, etc)	4	21.1	2	10.5	0.374
Primary tumor location					
Right	3	15.8	6	31.6	0.252
Left	16	84.2	13	68.4	
Origin stage					0.218
II	0	0	2	10.5	
III	12	63.2	8	42.1	
IV	7	36.8	9	46.4	
Treatment from metastatic lesion (other than C/T)	12	63.2	10	52.6	0.511
Median No. of line of TAS-102	4 (2-5)		4 (3-7)		
Duration of TAS-102 (months)	3.05 ± 2.21		2.27 ± 2.87		0.353
Duration of Stivarga (months)	2.65 ± 2.48		2.58 ± 1.73		0.910

In the first-line treatment of mCRC, 36 patients received mFOLFIRI with Avastin, one received mFOLFIRI with panitumumab, and one received mFOLFIRI with cetuximab. The median progression-free survival (PFS) after first-line treatment was significantly longer in the TAS-f group than in the Rego-f group (16.23 vs. 10.59 months; $p = 0.009$). Following disease progression, mFOLFOX combined with either bevacizumab or cetuximab was administered as second-line treatment. The median PFS during second-line therapy showed no significant difference between the groups (7.54 vs. 7.83 months, in TAS-f and Rego-f groups, respectively; $p = 0.887$).

Typically, TAS-102 is used as the fourth-line treatment for refractory mCRC (range: 2nd-5th lines in the TAS-f group vs. 3rd-7th lines in the Rego-f group). The duration of TAS-102 administration was slightly longer in the TAS-f group (3.05 ± 2.21 months) compared to the Rego-f group (2.27 ± 1.87 months). The duration of regorafenib administration was similar between groups (TAS-f group: 2.65 ± 2.48 months; Rego-f group: 2.58 ± 1.73 months).

OS was significantly longer in the TAS-f group than in the Rego-f group (65.47 vs. 38.7 months; $p = 0.012$) (Fig. 2). Additionally, survival duration following initiation of either TAS-102 (for the TAS-f group) or regorafenib (for the Rego-f group) also differed significantly, with median survival durations of 19.7 months and 10.07 months, respectively ($p = 0.023$) (Fig. 3). Considering the significant difference in the number of peritoneal metastasis cases between the two groups, and given that previous studies have identified peritoneal metastasis as an important prognostic factor,[6,7] a subgroup analysis was performed after excluding patients with peritoneal metastasis. The results showed that the TAS-f group still exhibited a longer median overall survival (54.37 vs. 52.27 months; $p = 0.379$) (Fig. 4) and better survival duration following initiation of either TAS-102 (for the TAS-f group) or regorafenib (for the Rego-f group) (Fig. 5); however, the difference was not statistically significant.

Multivariate Cox regression analysis revealed that initiating treatment with TAS-102 was the factor significantly associated with improved overall survival

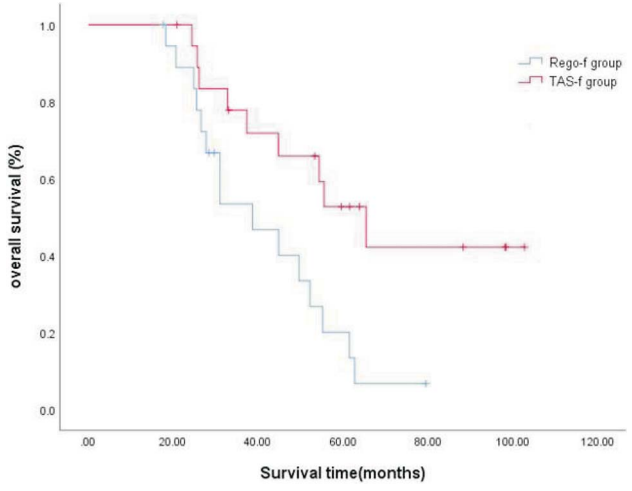

Fig. 2. OS from beginning Tx for stage IV disease.

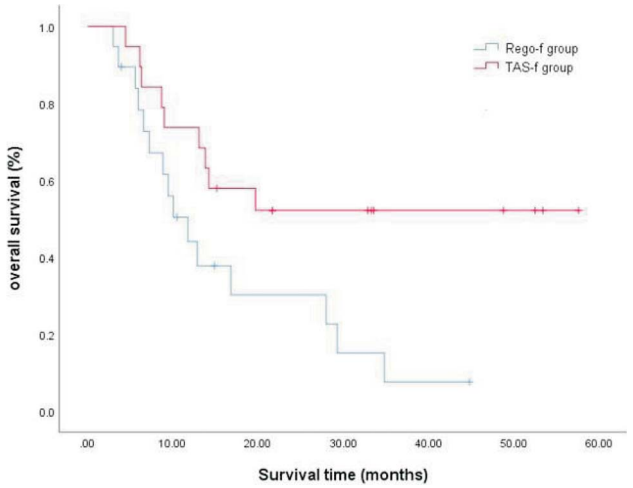

Fig. 3. OS from beginning Tx with TAS-102 (in TAS-f group) or regorafenib (in Rego-f group).

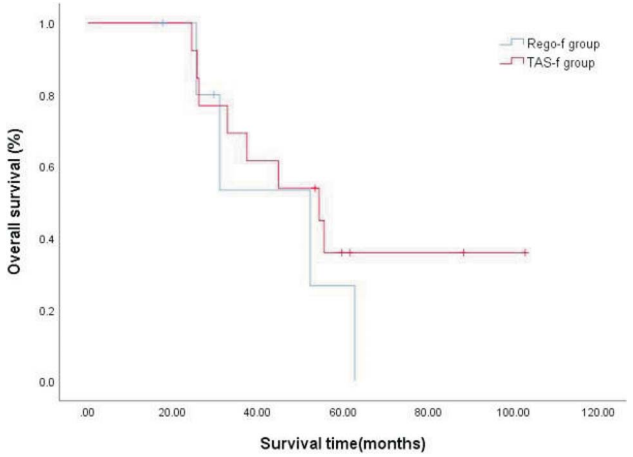

Fig. 4. OS from beginning Tx for stage IV disease excluded peritoneal seeding cases.

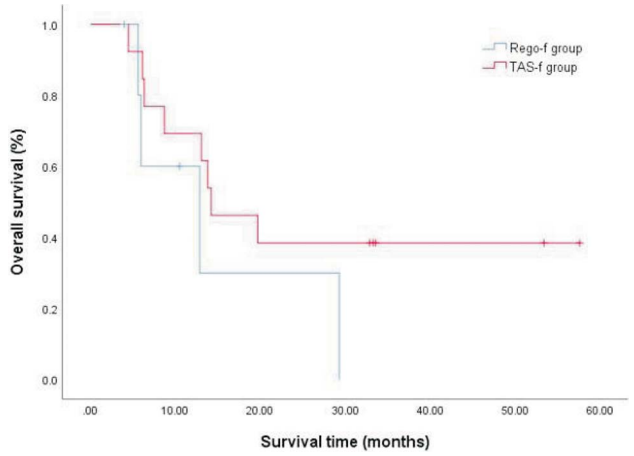

Fig. 5. OS from beginning Tx with TAS-102 (in TAS-f group) or regorafenib (in Rego-f group) excluded peritoneal seeding cases.

(hazard ratio [HR] = 0.292, 95% confidence interval [CI], 0.089-0.957; $p = 0.042$). In addition, RAS mutation was identified as a significant negative prognostic factor for overall survival (hazard ratio [HR] = 5.719, 95% confidence interval [CI], 1.905-17.168; $p = 0.002$). Other variables, including tumor location (sidedness), liver metastasis, lung metastasis, peritoneal metastasis, and distant lymph node metastasis, did not reach statistical significance (Table 2).

Discussion

In this retrospective analysis of 38 patients treated with TAS-102 and regorafenib for refractory mCRC, we observed significantly improved OS in patients who received TAS-102 before regorafenib. This finding is particularly noteworthy, given the current uncertainty regarding the optimal sequencing of these agents.

Recently, several studies have evaluated TAS-102 and regorafenib efficacy. As previously mentioned, the CORRECT trial demonstrated a median OS benefit 6.4-month with regorafenib compared with placebo in patients with refractory mCRC, whereas the RECOURSE trial reported a 7.1-month OS benefit with TAS-102 compared to placebo. Nevertheless, clinical decision-making regarding the sequencing of these drugs remains challenging. The current literature generally indicates no significant differences in OS or PFS between TAS-102 and regorafenib in a third-line setting.[8-10] However, several studies have highlighted that regorafenib is associated with higher overall toxicity rates than TAS-102.

The most frequently reported adverse effects of regorafenib include hand-foot skin reactions (HFSR), hypertension, and hepatotoxicity.[11] Although certain toxicities can accumulate over time, most regorafenib-associated adverse effects remain reversible. In contrast, TAS-102 was predominantly associated with reversible myelosuppression (neutropenia, anemia, and thrombocytopenia) and gastrointestinal symptoms, which resolved over time. In our study, patients who discontinued therapy prematurely due to grade III or higher toxicities were excluded prior to statistical analysis; therefore, the OS differences observed between the TAS-f and Rego-f groups may not be primarily attributable to differential toxicities.

The median treatment duration in both groups was approximately 8-12 weeks, which is slightly longer than typically reported in the literature. Despite this similarity, the TAS-first group exhibited superior OS. This result aligns with an actively debated issue in recent mCRC treatment research. Although large-scale randomized controlled trials (RCTs) directly comparing TAS-102-first and regorafenib-first sequencing strategies are currently unavailable, several systematic reviews, network meta-analyses, and real-world studies have provided indirect comparisons and clinical insights.

A multicenter retrospective analysis indicated a modest, albeit non-significant, trend toward improved

Table 2. Cox proportional hazards regression analysis for overall survival

Variable	HR (95% CI)	*p*-value
Sidedness (right vs. left)	0.655 (0.180-2.380)	0.520
ECOG	0.870 (0.383-1.974)	0.739
RAS mutation	5.719 (1.905-17.168)	0.002
Liver mets.	0.677 (0.274-1.671)	0.398
Lung mets.	1.153 (0.451-2.949)	0.766
Peritoneal seeding	0.793 (0.312-2.015)	0.626
Distal L.N.s mets.	1.865 (0.603-5.766)	0.279
TAS-102 before Regorafenib use	0.292 (0.089-0.957)	0.042

OS when TAS-102 preceded regorafenib treatment.[12] Furthermore, a 2020 Japanese cohort study demonstrated improved tolerability and prolonged treatment duration with TAS-102 administered before regorafenib, consistent with our findings. This Japanese study recommended prioritizing TAS-102 for older-adult patients, frail patients and those with hepatic impairment.[13] It is worth noting that the findings from Japanese studies may be more applicable to our retrospective analysis than those from Western cohorts, given the closer ethnic background shared between our patient population and the Japanese population.

In conclusion, while our retrospective study did not indicate a definitive preference for either treatment sequence in third-line mCRC therapy, multivariate analysis demonstrated that initiating treatment with TAS-102 was independently associated with significantly improved OS. These findings provide clinically relevant insights for therapeutic strategies. However, this study has several limitations, including its single-center retrospective design and small sample size (n = 38). Additionally, a subgroup analysis excluding patients with peritoneal metastasis showed a trend toward improved survival while use TAS-102 first; however, the difference did not reach statistical significance, possibly due to insufficient statistical power. Larger prospective cohorts are required to validate these results and investigate the underlying mechanisms.

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原　著

TAS-102 與 Regorafenib 使用順序對難治型轉移性大腸直腸癌總存活期之影響：回溯性世代研究

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背景　Regorafenib 與 TAS-102 均被建議作為難治型轉移性大腸直腸癌 (mCRC) 之第三線治療藥物，但其最佳使用順序仍未明確。

方法　本回溯性研究分析了 2013 年至 2024 年間接受 Regorafenib 與 TAS-102 治療的 38 位 mCRC 患者。依據用藥順序分為先使用 TAS-102 (TAS-f, n = 19) 與先使用 Regorafenib (Rego-f, n = 19) 兩組，並比較其無惡化存活期 (PFS)、總存活期 (OS) 與治療期間。

結果　兩組基礎特徵相似。TAS-f 組的總存活期顯著較佳 (65.47 個月 vs. 38.7 個月，p = 0.012)，且自第三線治療開始後的中位存活期亦較長 (19.7 個月 vs. 10.07 個月，p = 0.023)。多變項分析顯示，先使用 TAS-102 為唯一與較佳總存活期具獨立相關性的預測因子 (風險比 HR = 0.210，95% 信賴區間 CI = 0.064-0.682，p = 0.009)。

結論　在難治型 mCRC 中，先使用 TAS-102 再使用 Regorafenib 可顯著改善總存活期，凸顯治療順序在臨床上的重要性。建議進一步進行前瞻性研究以驗證本研究結果。

關鍵詞　TAS-102、Regorafenib、轉移性大腸直腸癌、總存活期。