

Impact of TAS-102 dose reduction on severe neutropenia and survival outcomes in patients with metastatic colorectal cancer and prior chemotherapy-induced neutropenia

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Abstract. The present study aimed to evaluate the impact of initial dose reduction of trifluridine/tipiracil (TAS-102) monotherapy on the incidence of severe neutropenia and overall survival (OS) in individuals with metastatic colorectal cancer, considering prior chemotherapy-induced severe neutropenia. Participants were classified into the following three groups: A group, individuals who did not experience severe neutropenia during previous chemotherapy and did not undergo dose reduction (n=61); B1 group, those who experienced severe neutropenia during previous chemotherapy and received an initial dose reduction of TAS-102 (n=28); and B2 group, those who experienced severe neutropenia but did not receive a dose reduction (n=88). Neutropenia severity, progression-free survival (PFS) and OS were compared among the groups. Notably, there was no significant difference in the incidence of grade 3 or higher neutropenia among the three groups during TAS-102 administration (P=0.958). The median OS times in the A group (n=61), B1 group (n=28) and B2 group (n=88) were 273 days (95% CI, 199-299), 285 days (95% CI, 202-NA) and 233 days (95% CI, 182-272), respectively (log-rank test, P=0.165). The median PFS times among the three groups were 133.0 days (95% CI, 98-153), 94.5 days (95% CI, 77-133) and 93.5 days (95% CI, 83-100), respectively (log-rank test, P=0.053). In conclusion, a proactive dose reduction at TAS-102 treatment initiation based on pre-existing severe neutropenia should be carefully considered, as it may not be necessary.

Introduction

Trifluridine/tipiracil (TAS-102) is an oral antitumour agent comprising a thymidine-based nucleic acid analogue, trifluridine, and the thymidine phosphorylase inhibitor, tipiracil hydrochloride, at a molar ratio of 1:0.5. In a phase 3 clinical trial, TAS-102 demonstrated a significant survival benefit over placebo in terms of overall survival (OS) in individuals with metastatic colorectal cancer (mCRC) who were unresponsive to standard therapies, including fluoropyrimidines, irinotecan, and oxaliplatin (1,2). Additionally, a randomised phase 2 trial revealed that TAS-102 in combination with bevacizumab (Bmab) extended progression-free survival (PFS) compared to that of TAS-102 monotherapy (3).

Neutropenia is the most frequently observed adverse event (AE) associated with TAS-102 monotherapy. In the RECURSE trial, 37.9% of individuals receiving TAS-102 monotherapy developed grade 3 or higher neutropenia (1). Furthermore, the incidence of grade 3 or higher neutropenia was higher in individuals receiving TAS-102 plus Bmab than in those receiving TAS-102 monotherapy (67% vs. 38%) (3). Several retrospective cohort studies have suggested that the development of neutropenia during TAS-102 monotherapy or TAS-102 plus Bmab therapy is associated with improved long-term survival (4-7).

In cases where TAS-102 cannot be combined with Bmab, TAS-102 monotherapy is administered, often as a late-line treatment following regimens known to cause bone marrow suppression such as FOLFOX (fluorouracil/leucovorin and oxaliplatin) therapy. To mitigate severe neutropenia, dose reduction of TAS-102 may be considered from the initial administration, particularly in individuals with a history of severe neutropenia from prior chemotherapy. However, given that severe neutropenia is a prognostic factor, there is concern that reducing the dose could not only lower the risk of neutropenia but also potentially compromise OS.

Understanding the impact of dose reduction at the initiation of TAS-102 monotherapy in mCRC management is crucial for optimising treatment strategies. Therefore, this study aimed to investigate the effect of dose reduction during the initial administration of TAS-102 monotherapy on the occurrence of severe neutropenia and OS.

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Patients and methods

Patients and evaluations. A total of 203 patients treated with TAS-102 among patients with advanced or recurrent colorectal cancer (CRC) at Ogaki Municipal Hospital (Ogaki, Japan) between January 2015 and December 2024 were retrospectively evaluated. Patients who were unable to complete one course of TAS-102 and who received TAS-102 in combination with Bmab were excluded from the study, as this regimen had not yet been routinely adopted at our institution during the study period. Furthermore, patients who underwent an initial dose reduction of TAS-102 for reasons other than neutropenia were excluded from the study. Thus, 177 patients were considered eligible for this study. Participants were categorised into those who did not experience severe neutropenia during previous chemotherapy and did not undergo dose reduction (A group, n=61), those who experienced severe neutropenia during previous chemotherapy and received an initial dose reduction of TAS-102 (B1 group, n=28), and those who had severe neutropenia but did not receive a dose reduction (B2 group, n=88). The flow diagram is presented in Fig. 1. We analysed the patients' characteristics, OS, PFS, and neutropenia grade with TAS-102 treatment in patients with CRC using data collected from electronic charts and pharmacy service records. AEs were evaluated according to the Common Terminology Criteria for Adverse Events, version 5.0 (8), and the most severe grades during chemotherapy were reported. Personal information was protected in aggregated data. The study protocol was approved by the Institutional Review Board of Ogaki Municipal Hospital, Ogaki, Japan (approval no. 202520227-22). The requirement for informed consent was waived owing to the retrospective study design. Consent to participate was waived by the Institutional Review Board of Ogaki Municipal Hospital owing to the retrospective study design. Consent to publish was also waived by the Institutional Review Board for the same reason.

Treatment protocol. Trifluridine/tipiracil combination tablet: TAS-102 (at a dose of 35 mg per square metre) was administered twice daily after morning and evening meals for 5 days, followed by a 2-day rest period. This regimen was repeated for 2 weeks, followed by a 14-day rest period, constituting one treatment cycle. The cycle was repeated every 4 weeks.

The dose of TAS-102 was generally reduced by one level in individuals with severe neutropenia due to prior chemotherapy.

Statistical analysis. Kruskal-Wallis tests or Fisher's exact probability tests were used for comparisons of patient characteristics, AEs, and reasons for treatment discontinuation. Steel-Dwass test was used for multiple comparisons of creatinine clearance among the 3 groups. The Kaplan-Meier method and log-rank tests were used to compare treatment duration. $P < 0.05$ was considered to indicate a statistically significant difference. All statistical analyses were performed using EZR software (v1.30; Saitama Medical Centre, Jichi Medical University, Saitama, Japan) (9).

Results

Patient characteristics. The patient characteristics are summarised in Table I. Differences in creatinine clearance

were observed among the 3 groups. Moreover, differences were observed in certain metastatic sites. No significant differences were observed in other variables.

A significant difference in creatinine clearance was observed between groups A and B2 ($P=0.006$). No difference was observed between groups A and B1 or between groups B1 and B2 ($P=0.059, 0.892$, respectively).

No significant differences were observed in prior treatment regimens among the three groups (Table I).

Overall survival according to the highest neutropenia grade. Kaplan-Meier survival curves stratified by neutropenia severity are presented in Fig. 2. The median OS in the absent (n=40), mild (n=49), and severe (n=88) neutropenia groups was 147 days (95% CI, 126-176), 234 days (95% CI, 183-281), and 300 days (95% CI, 269-393), respectively (log-rank test, $P < 0.001$).

Neutropenia grade during TAS-102 administration. Neutropenia grades among the 3 groups during TAS-102 administration are presented in Table II. There was no significant difference in the incidence of grade 3 or higher neutropenia among the 3 groups during TAS-102 administration ($P=0.958$). Differences in the incidence of grade 0 neutropenia were observed among the 3 groups ($P=0.033$). The dose reductions of TAS-102 based on severe neutropenia due to prior chemotherapy were as follows: 10 cases of a one-step dose reduction; 16 cases of a two-step dose reduction; 2 cases of a three-step dose reduction.

OS and PFS. OS and PFS among the 3 groups are presented in Fig. 3. The median OS in the A group (n=61), B1 group (n=28), and B2 group (n=88) were 273 days (95% CI, 199-299), 285 days (95% CI, 202-NA), and 233 days (95% CI, 182-272), respectively (log-rank test, $P=0.165$). The median PFS among the 3 groups were 133.0 days (95% CI, 98-153), 94.5 days (95% CI, 77-133) and 93.5 days (95% CI, 83-100), respectively (log-rank test, $P=0.053$).

Renal function and treatment outcomes. OS and PFS between the high and low Ccr groups are presented in Fig. 4. To evaluate whether renal function affected the incidence of severe neutropenia or survival outcomes, a subgroup analysis was performed by stratifying patients according to creatinine clearance (Ccr), using the median value of 70.6 ml/min as the cutoff. Of the 177 patients, 89 were in the high Ccr group (≥ 70.6 ml/min), and 88 were in the low Ccr group (< 70.6 ml/min).

The incidence of grade ≥ 3 neutropenia was similar between the two groups: 49/89 (55.1%) in the high Ccr group and 49/88 (55.7%) in the low Ccr group. There was no statistically significant difference in the rate of neutropenia.

Median progression-free survival (PFS) was 104 days (95% CI: 92-119) in the high Ccr group and 92.5 days (95% CI: 84-112) in the low Ccr group ($P=0.789$). Median overall survival (OS) was 262 days (95% CI: 199-285) in the high Ccr group and 253 days (95% CI: 201-299) in the low Ccr group ($P=0.411$).

Discussion

This study is the first to clarify the impact of initial dose reduction of TAS-102 monotherapy for colorectal cancer (CRC) on

Table I. Patient characteristics.

Variable	A group (n=61)	B1 group (n=28)	B2 group (n=88)	P-value
Age, years	67 (41-83)	72 (49-79)	70 (36-83)	0.299
Sex, Male/Female	37/24	16/12	49/39	0.838
Height, cm	164.0 (139.0-184.0)	161.0 (145.0-178.7)	159.3 (141.0-181.7)	0.240
Body weight, kg	59.8 (35.9-95.0)	54 (36.4-85.0)	52 (30.9-85.0)	0.133
Body surface area, m ²	1.62 (1.15-2.07)	1.60 (1.23-2.03)	1.54 (1.14-1.96)	0.151
Ccr, ml/min ^a	83.4 (19.0-142.0)	58.4 (37.6-150.1)	67.0 (32.9-171.1)	0.007 ^b
Number of prior chemotherapy regimens	2 (1-4)	2 (1-4)	2 (1-5)	0.961
Pre-chemotherapy regimens				
FOLFOX ± BV	37	15	58	0.546
FOLFOX + Pan	1	3	8	0.096
FOLFOX + Cet/ AFL/Ram	7	2	7	0.785
XELOX ± BV	13	7	9	0.122
SOX ± BV	1	2	2	0.311
FOLFIRI ± BV	32	20	58	0.253
FOLFIRI + Cet/ Pan/Ram/AFL	23	12	28	0.690
CPT-11 ± Cet	4	1	2	0.467
Xeloda ± BV	4	1	4	0.902
S-1	6	1	5	0.621
Others	24	5	26	0.216
Performance status	0 (0-2)	0 (0-1)	0 (0-2)	0.936
RAS mutation	32	19	56	0.282
Adjuvant chemotherapy, yes	21	6	27	0.491
Progression/recurrence	33/28	15/13	49/39	0.979
Metastatic sites				
Liver	30	20	60	0.470
Lung	29	13	49	0.879
Lymph nodes	18	10	40	0.477
Peritoneal dissemination	21	7	25	0.414
Bone	7	0	5	0.094
Ovaries	1	2	0	0.029 ^b
Brain	1	0	1	1
Skin	1	0	0	0.479
Others	3	5	3	0.043 ^b
Neutrophil count, /mm ³	3,580 (1,880-13,040)	2,905 (1,560-8,490)	2,910 (1,300-1,2440)	0.064
Treatment after TAS-102				
No	50	20	64	0.368
Regorafenib	11	7	20	0.682
Others	0	1	4	0.239

Data are presented as n (%) or median (range). ^aThe Cockcroft-Gault equation was used to estimate creatinine clearance based on serum creatinine and patient characteristics. ^bP<0.05. Ccr, creatinine clearance; FOLFOX, combination of fluorouracil/leucovorin and oxaliplatin; BV, bevacizumab; Pan, panitumumab; Cet, cetuximab; AFL, aflibercept; Ram, ramucirumab; XELOX, combination of capecitabine and oxaliplatin; SOX, S-1 plus oxaliplatin; FOLFIRI, combination of fluorouracil/leucovorin and irinotecan; CPT-11, irinotecan; S-1, tegafur/gimeracil/oteracil potassium.

the incidence of severe neutropenia and overall survival (OS). Our results showed that patients who developed severe neutropenia had longer OS, consistent with previous reports linking chemotherapy-induced neutropenia to better prognosis (7,10-14).

Despite a history of severe neutropenia from prior chemotherapy, initial dose reduction of TAS-102 did not reduce the incidence of severe neutropenia, nor did it improve progression-free survival (PFS) or OS compared to standard dosing.

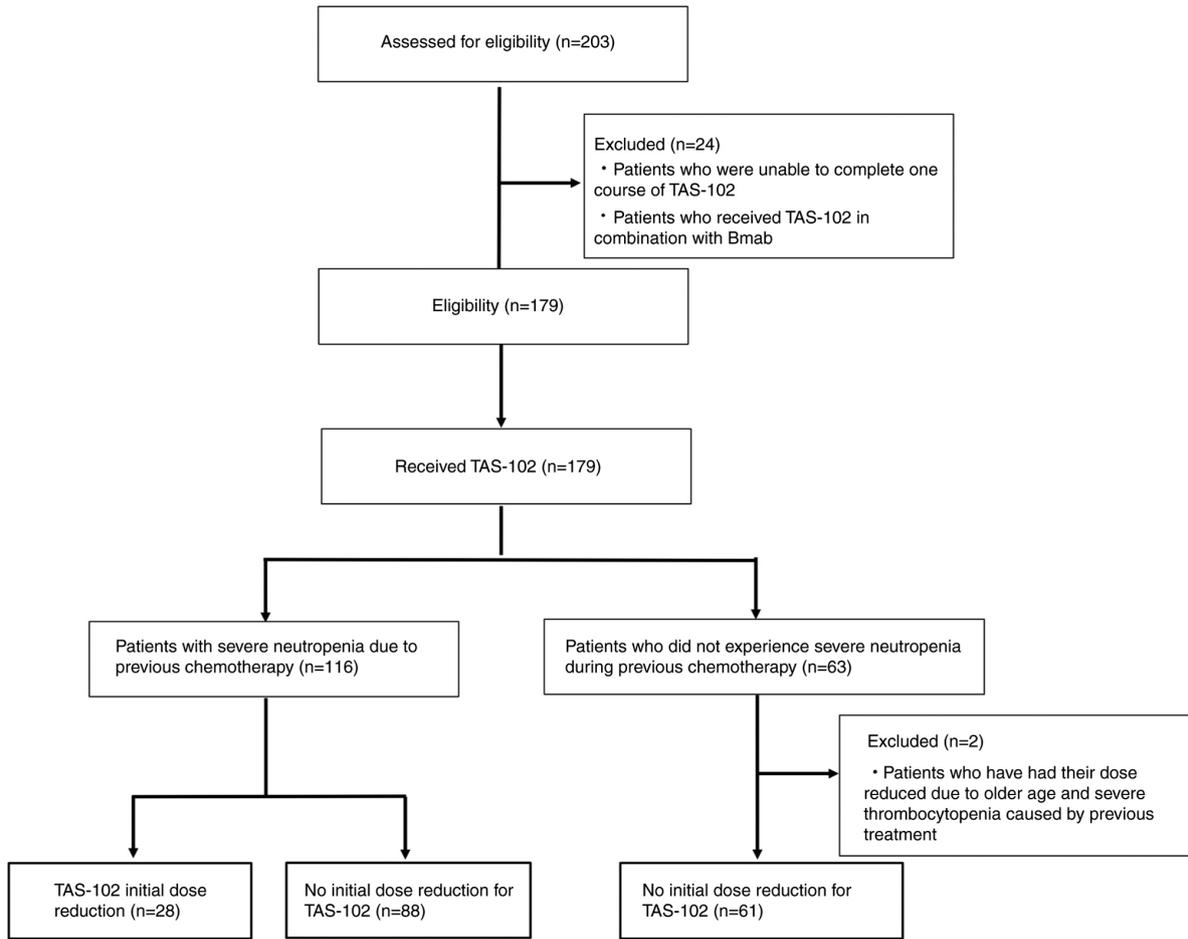


Figure 1. Flow diagram. TAS-102, trifluridine/tipiracil combination tablet; Bmab, bevacizumab.

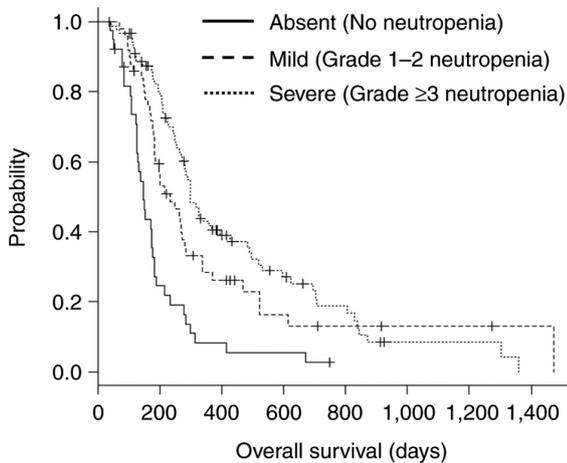


Figure 2. Kaplan-Meier survival curves for overall survival based on neutropenia severity. The Kaplan-Meier survival curves illustrate overall survival following therapy with TAS-102 in 3 patient groups, including absent, mild (grade 1 or 2 neutropenia), and severe (grade 3 or 4 neutropenia). A significant difference was observed among the 3 groups ($P<0.001$). TAS-102, trifluridine/tipiracil combination tablet.

Neutropenia may serve as a surrogate marker of adequate drug exposure and antitumor activity (15-19). However, factors such as prior treatment regimens, baseline comorbidities, renal function, and actual dose intensity may also influence

outcomes. We considered performing multivariate analysis including creatinine clearance (Ccr); however, due to the small sample size and limited number of events in the B1 subgroup ($n=28$), it was challenging to ensure the reliability of a multivariate model. Nonetheless, we acknowledge the importance of further investigation, and future large-scale prospective studies incorporating multivariate analyses including Ccr are warranted to better elucidate its potential confounding effect. We therefore performed subgroup analyses stratified by Ccr, which showed no significant differences in neutropenia incidence or survival, suggesting renal function was unlikely to confound our main findings. In addition, prior treatment regimens were comparable across groups, as shown in Table I, indicating that this factor was unlikely to bias the results. By contrast, detailed comorbidity profiles and relative dose intensity were not systematically evaluated in this study, which should be acknowledged as limitations.

Consistent with this, no differences in severe neutropenia or survival outcomes were observed between dose-reduction and non-dose-reduction groups. A borderline trend in PFS ($P=0.053$) may reflect the association between neutropenia and improved OS but did not translate into significant group differences.

Baseline absolute neutrophil count (ANC) has been reported as a prognostic factor, with higher ANC correlating with poorer outcomes and lower ANC predicting increased

Table II. Neutropenia grade during TAS-102 administration.

Neutropenia grade	A Group (n=61)	B1 Group (n=28)	B2 Group (n=88)	P-value
Grade 3-4, n (%)	30 (49.2)	15 (53.6)	44 (50.0)	0.958
Grade 1-2, n (%)	12 (19.7)	11 (39.3)	26 (29.5)	0.126
Grade 0, n (%)	19 (31.1)	2 (7.1)	18 (20.5)	0.033 ^a

^aP<0.05.

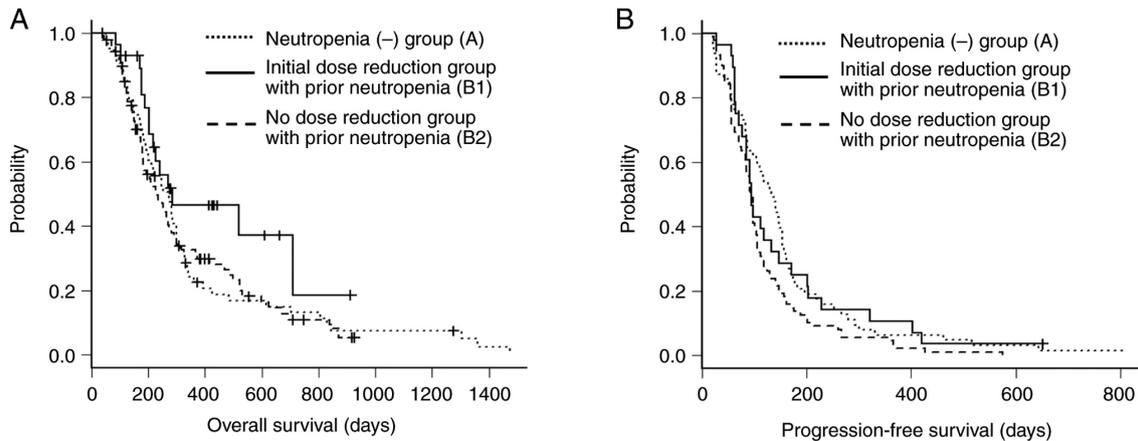


Figure 3. Kaplan-Meier survival curves for overall and progression-free survival among three groups. The Kaplan-Meier survival curves depict (A) overall survival and (B) progression-free survival following therapy with TAS-102 in the 3 patient groups: (A group) individuals who did not experience severe neutropenia during previous chemotherapy and did not undergo dose reduction (n=61); (B1 group) those who experienced severe neutropenia during previous chemotherapy and received an initial dose reduction of TAS-102 (n=28); (B2 group) those who had severe neutropenia but did not receive a dose reduction (n=88). No significant difference in survival was observed among the groups. TAS-102, trifluridine/tipiracil combination tablet.

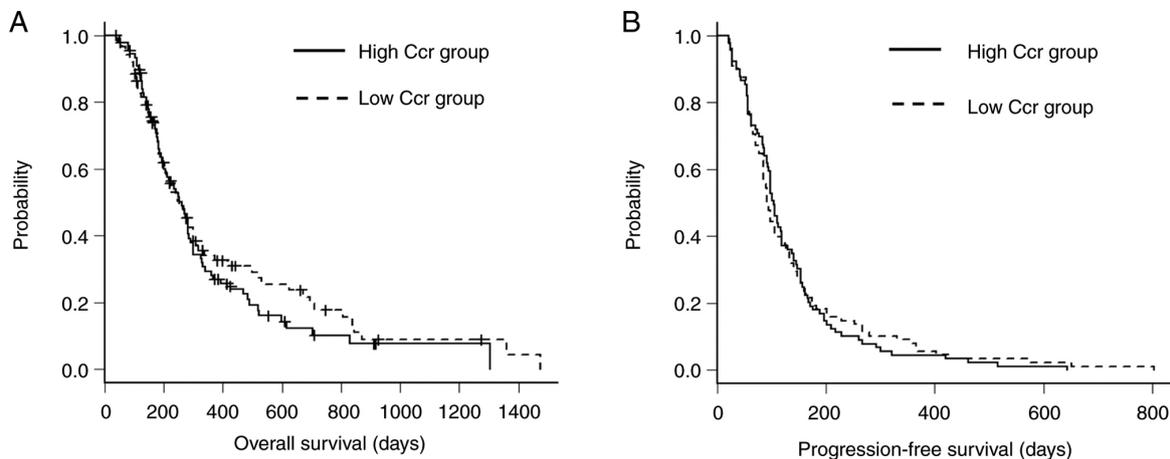


Figure 4. Kaplan-Meier survival curves for overall and progression-free survival between the high and low Ccr groups. The Kaplan-Meier survival curves illustrate (A) overall survival and (B) progression-free survival following TAS-102 therapy in the high and low Ccr groups. No significant difference in survival was observed between the groups. Ccr, creatinine clearance; TAS-102, trifluridine/tipiracil combination tablet.

neutropenia risk and better survival (20-22). In our cohort, baseline ANC did not differ significantly between dose groups, even among patients with prior severe neutropenia, supporting the notion that initial dose reduction was not guided by baseline ANC.

While TAS-102 pharmacokinetics can be affected by renal function due to the renal excretion of tipiracil, 3 our

analyses did not detect a significant impact of renal function on toxicity or efficacy, aligning with previous studies (23,24).

Traditional chemotherapy dosing based on body surface area (BSA) may not fully account for interindividual variability; lean body mass (LBM) and body composition analyses are emerging tools for dose individualization (25-27). However, these factors were not directly

assessed in our study and should be explored in future research.

Limitations of this study include its single-center retrospective design, which may introduce selection bias and limit generalizability. Additionally, patients receiving TAS-102 combined with bevacizumab, a common regimen that may increase neutropenia incidence, were excluded. The relatively small sample size in certain subgroups and absence of multivariate analysis also limit definitive conclusions. Therefore, future studies with larger sample sizes are needed to confirm these findings.

Current NCCN and ESMO guidelines recommend initiating TAS-102 at full approved doses, with dose modifications guided by observed toxicities rather than preemptive reductions (28,29). Our findings support this approach, suggesting that initial dose reduction based solely on prior severe neutropenia may not be necessary. Standard dosing with close monitoring remains the preferred clinical strategy.

In conclusion, although grade ≥ 3 neutropenia frequently leads to treatment interruptions during TAS-102 monotherapy, preemptive initial dose reduction does not reduce neutropenia incidence or improve survival outcomes. Careful monitoring and appropriate dose adjustments during treatment are essential to optimize efficacy and safety.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

CS and MK contributed to the study design, collected and provided the data, served as the principal authors of the report, and are the guarantors of the article and all associated data. MG, YI and EU contributed to the study design, reviewed the manuscript, and supervised the drafting of the report and the submission process. CS and MK confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of Ogaki Municipal Hospital (Ogaki, Japan; approval no. 202520227-22). Consent to participate was waived by the Institutional Review Board of Ogaki Municipal Hospital owing to the retrospective study design.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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