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Severe neutropenia: a prognosticator in patients with advanced/recurrent colorectal cancer *under* oral trifluridine-tipiracil (TAS-102) chemotherapy

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Background/aim: The effect of oral trifluridine-tipiracil (TAS-102)-induced neutropenia on survival of patients with advanced/recurrent colorectal cancer was investigated. *Patients and methods*: Between August 2014 and May 2016, 41 patients underwent TAS-102 monotherapy at Ogaki Municipal Hospital. Risk factors for survival were examined by univariate and multivariate analyses. *Results*: In 41 patients, mild neutropenia (grade 1–2) occurred in 10 patients (24.4%), severe neutropenia (grade 3–4) occurred in 13 (31.7%), and 18 (43.9%) did not experience neutropenia. The median overall survival times in the absent, mild, and severe groups were 120 days (95% confidence interval [CI], 67–179), 184 days (95% CI, 94–274), and 299 days (95% CI, 192–404), respectively (p = 0.045). In patients with severe neutropenia, the death hazard ratio was 0.442 (95% CI, 0.201–0.974; p = 0.042). *Conclusion*: In patients with advanced/recurrent colorectal cancer, TAS-102-induced severe neutropenia was associated with superior survival.

1. Introduction

The recommended first- and second-line chemotherapies for colorectal cancer (CRC) include fluorouracil (FU) or leucovorin (LV) and oxaliplatin (FOLFOX), or capecitabine and oxaliplatin (CapeOX) with or without bevacizumab, or FU/LV and irinotecan (FOLFIRI) with or without cetuximab, or FOLFOX with or without cetuximab (Saltz et al. 2008; Van Cutsem et al. 2011; Bokemeyer et al. 2011). For later lines, for the treatment of advanced/recurrent CRC, the American Society of Clinical Oncology and the National Comprehensive Cancer Center Network recommend regorafenib or the trifluridine-tipiracil combination tablet (TAS-102). In Japan, TAS-102 is widely used to treat advanced/recurrent CRC (Japanese Society for Cancer of the Colon and Rectum 2015). TAS-102 use is based on the results of a randomized, double-blind, phase 3 study of TAS-102 plus best supportive care versus placebo plus best supportive care in patients with metastatic CRC refractory to standard chemotherapies (the RECOURSE study) (Mayer et al. 2015). The main TAS-102-induced adverse events (AEs) included leucopenia (76.5%), neutropenia (73.1%), decreased haemoglobin (63.9%), nausea (63.0%), and anorexia (55.5%). In addition, myelosuppression, infections, and interstitial lung disease have been reported as serious AEs (Yoshino et al. 2012). TAS-102 induces a high incidence of myelosuppression including neutropenia, which can result in treatment delays (Kimura et al. 2016). Therefore, the influence of neutropenia on survival outcome (prognosis) is a major concern.

Neutropenia has been reported as a prognosticator in patients undergoing cancer chemotherapy (Hatori et al. 2014; Shitara et al. 2009, 2010, 2011; Ikagawa et al. 2016). However, the relationship of neutropenia and prognosis in advanced/recurrent CRC patients undergoing TAS-102 therapy has not been clinically evaluated. In the present retrospective study, the association of neutropenia with survival and treatment continuation in CRC patients undergoing TAS-102 therapy was evaluated.

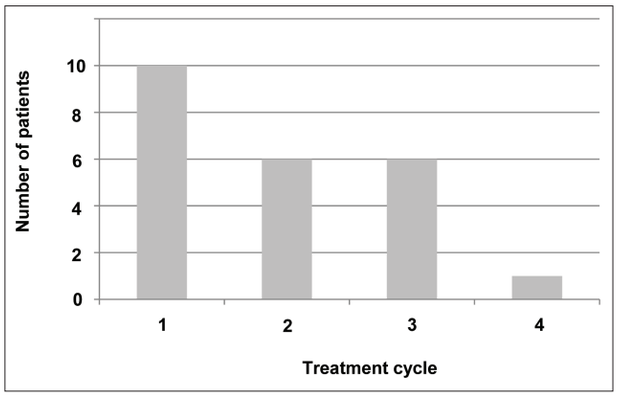

Fig. 1: The timing of the occurrence of neutropenia with the highest grade

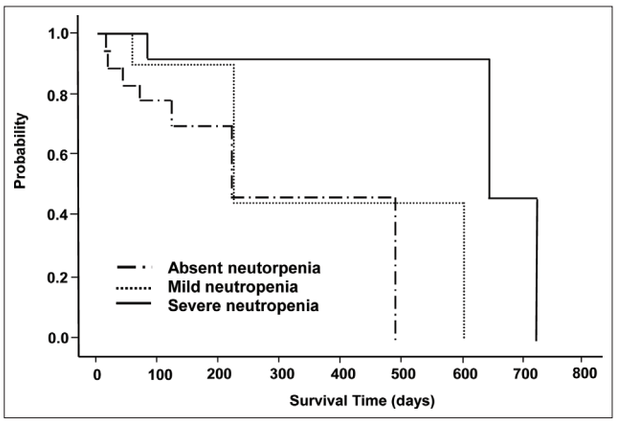

Fig. 2: Kaplan-Meier survival curves according to neutropenia

Table 1: Patient characteristics

Characteristics	All (n = 41)	Absent (n = 18)	Mild (n = 10)	Severe (n = 13)	P value
Age (range), years	68 (37–83)	67 (37–77)	65 (56–81)	70 (52–83)	0.654[a)]
Sex (male/female)	24/17	10/8	6/4	8/5	0.940[a)]
ECOG PS					
0	32	11	9	12	0.229[a)]
1	8	6	1	1	
2	1	1	0	0	
Disease status					
Advanced/Recurrent	3/38	3/15	0/10	0/13	0.126[a)]
Metastatic site					
Lungs	20	8	4	8	0.597[a)]
Lymph nodes	16	7	5	4	
Peritoneum	12	7	3	2	
Liver	23	12	7	4	
Skin	4	3	0	1	
Bones	1	0	0	1	
Previous chemotherapy lines					
1	1	0	1	0	0.327[a)]
2	18	8	3	7	
3	19	9	6	4	
4	3	1	0	2	
Pretreatment neutrophils, /μL	3100 (1590–7360)	4285 (1780–6460)	3055 (1590–7360)	4160 (1970–4990)	0.058[b)]
Number of treatment cycles[c)]	3 (1–18)	2 (1–6)	2 (1–6)	5 (1–18)	0.006[*b)]
BSA, m^2	1.57 (1.09–1.75)	1.47 (1.09–1.96)	1.6 (1.45–1.70)	1.60 (1.15–1.75)	0.958[b)]
CrCl, mL/min	79.2 (40.0–158.0)	77.4 (45.3–158.0)	93.4 (56.0–134.0)	71.5 (40.0–105.0)	0.400[b)]
RDI, %[d)]	90.0 (28.6–100.0)	100.0 (28.6–100.0)	87.0 (50.0–100.0)	77.0 (55.0–100.0)	0.180[b)]

a) Chi-square for independence test, b) Kruskal-Wallis test
c) Median (range) of the total number of treatment cycles between August 2014 and May 2016. Seven out of 41 patients are being treated currently. Four patients discontinued during the first course of treatment.d) RDI of all courses
BSA, body surface area; RDI, relative dose intensity; PS, performance status; CrCl, creatinine clearance
* $p < 0.05$

2. Investigations and results

2.1. Patients' characteristics

Patients' characteristics are shown in Table 1. Of the 41 patients, mild neutropenia (grade 1–2) occurred in 10 patients (24.4%), and severe neutropenia (grade 3–4) occurred in 13 patients (31.7%). The other 18 patients (43.9%) did not experience neutropenia. The median number of treatment cycles was significantly different between the 3 groups ($p = 0.006$).

2.2. Discontinuation and postponement frequencies

The causes and frequencies for discontinuation or postponement are shown in Table 2. Treatment was postponed in 73.1% (30/41 patients) and discontinued in 82.9% (34/41 patients).

2.3. Onset of the occurrence of the highest neutropenia grade

The onsets of the occurrence of highest-grade neutropenia are shown in Fig. 1. The highest grade of neutropenia occurred within two cycles in 65.2% of patients.

2.4. Overall survival according to the highest neutropenia grade

Kaplan-Meier survival curves according to the highest neutropenia grade in all patients are shown in Fig. 2. The median OS times in the absent (n = 18), mild (n = 10), and severe (n = 13) groups were 120 days (95% CI, 67–179 days), 184 days (95% CI, 94–274 days), and 299 days (95% CI, 192–404 days), respectively (Log-rank test, p = 0.045).

2.5. Survival analyses including neutropenia

The univariate and multivariate analyses of baseline and clinical characteristics as prognosticators are shown in Table 3. In the univariate analysis, severe neutropenia, PS, number of treatment cycles, and RDI were significantly associated with survival. Neutropenia alone was independently and significantly associated with survival in the multivariate analysis. For severe neutropenia, the hazard ratio for death was 0.442 (95% CI, 0.201-0.974; p = 0.042), compared with when neutropenia was not present.

3. Discussion

In the present study, patients with advanced/recurrent CRC, who developed severe neutropenia while on TAS-102, had significantly superior OS times compared to those who did not develop severe neutropenia. Univariate analysis revealed that severe neutropenia, PS, number of treatment cycles, and RDI were significantly associated with survival in these patients, whereas multivariate analysis revealed that severe neutropenia alone was a significant independent prognosticator.

In the present study, the neutropenia incidence was 56.1% (23/41 cases), which was slightly less than that observed in a Japanese phase II trial in patients with metastatic CRC (Yoshino et al. 2012). In that trial, the neutropenia frequencies in patients receiving TAS-102 were 73.1% (neutropenia, all grades) and 51.3% (grade ≥3). AEs could result in treatment postponement, which would reduce the RDI, therefore, it was proposed that TAS-102-induced neutropenia might affect prognosis. In the present study, TAS-102 treatment was postponed in 73.1% of patients, with bone marrow suppression (primarily neutropenia) accountable for 60.0% of postponements. In patients with lymphoma undergoing CHOP-21 chemotherapy, Pettengell et al. (2008) reported that the RDI had

Table 2: Frequencies of discontinuations and delays

n = 41		Numbers (%)
Delay		30 (73.1)
Reasons for delay	Myelosuppression	18 (60.0)
	Holiday	6 (20.0)
	Private affairs / patient convenience	2 (6.7)
	Adverse events	2 (6.7)
	Decrease in PS	1 (3.3)
	Liver dysfunction	1 (3.3)
Reasons for discontinuation	Decrease in PS	19 (46.4)
	PD	11(26.8)
	Adverse events	2 (4.9)
	Patient's request	1 (2.4)
	Other	1 (2.4)
	Ongoing	7 (17.1)

PS, performance status; PD, progressive disease

a major influence on prognosis. However, in the present study, RDI was not an independent prognosticator. Furthermore, in patients with unresectable pancreatic cancer who were administered gemcitabine, Hatori et al. (2014) reported that RDI was not a significant prognosticator, and regardless of the RDI, the patients who continued gemcitabine had a good prognosis. In the present study, the number of treatment courses was significantly longer in patients who developed severe neutropenia compared with that in those who did not develop neutropenia; therefore, the total dose in those with severe neutropenia was greater. In the present study univariate analysis revealed that MST was longer in patients with a low RDI (<90%) compared to that in those with a high RDI (≥90%). We speculated that this might be because when the administration frequency of TAS-102 was high, then the RDI might have been decreased because of significant treatment delays due to bone marrow suppression and holidays. Regarding neutropenia and treatment duration, patients with grade >3 neutropenia had long treatment durations and good prognoses. The relationship between neutropenia and prognosis has been reported in patients with gastric cancer on weekly paclitaxel, and in patients with leukaemia or colon cancer on FOLFOX (Shitara et al. 2009, 2010,

Table 3: Univariate and multivariate analyses

	Univariate analysis				Multivariate analysis		
	MST	95%CI	log-rank (P value)	AUC ROC curves	HR	95% CI	P value
Neutropenia							
Absent (n = 18)	123	67–179					
Mild (n = 10)	184	94–274	0.217	0.733			
Severe (n = 13)	298	192–404	0.045*	0.816	0.442	0.201–0.974	0.042*
ECOG PS							
0 (n = 32)	191	132–249					
≥1 (n = 9)	147	41–253	0.042*	0.634	2.012	0.853–4.744	0.110
No. of metastatic sites							
1 (n = 14)	210	108–312					
≥2 (n = 27)	154	97–211	0.123	0.542			
Status							
advanced (n = 3)	129	69–189					
recurrent (n = 38)	69	16–122	0.112	0.700			
Age							
<68 (n = 20)	138	59–217					
≥68 (n = 21)	192	132–252	0.163	0.651			
BSA							
<1.75 (n = 35)	183	9–357					
≥1.75 (n = 6)	125	21–229	0.930	0.426			
CrCl							
>99.8 (n = 12)	184	106–262					
≥99.8 (n = 29)	125	104–253	0.190	0.626			
Number of treatment cycles							
<3 (n = 18)	123	64–182					
≥3 (n = 23)	272	202–342	0.002*	0.831	0.511	0.242–1.081	0.079
RDI							
<90% (n = 20)	219	116–296					
≥90% (n = 21)	129	49–121	0.019*	0.614	2.111	0.953–4.674	0.065
Regorafenib use							
no (n = 35)	128	72–184					
yes (n = 6)	95	4–186	0.7481	0.700			

MST, median survival time; CI, confidence interval; ROC, receiver operating characteristic; AUC, area under the blood concentration-time curve; HR, hazard ratio; ECOG PS, Eastern Cooperative Oncology Group performance status; BSA, body surface area; CrCl, creatinine clearance; RDI, relative dose intensity
AUC indicates the relevance of survival and each factor. AUC indicates a value of 0.5–1; the greatest relevance is observed at 1, whereas 0.5 indicates a lack of relevance.

2011). However, the present study is the first to report the association of neutropenia and prognosis in patients with advanced/recurrent CRC undergoing TAS-102 chemotherapy. Shitara et al. (2009) reported that neutropenia was a surrogate marker for adequate antitumour doses of chemotherapeutic agents. Therefore, a lack of neutropenia might indicate a weak biological effect of chemotherapy, which might reflect inadequate dosing in an individual patient (Shitara et al. 2010). Therefore, when TAS-102 treatment is postponed because of recurrent neutropenia, there might be a need to avoid using lower doses of TAS-102 (dose reduction), taking into account the positive prognostic effect of treatment.

In the present study, most of the highest neutropenia grade occurred within two cycles. Therefore, by monitoring neutrophils, the therapeutic effect could be inferred at an early stage during treatment. In other words, neutrophil count might be a useful biomarker of treatment response. In patients with advanced/recurrent CRC, who are undergoing TAS-102 chemotherapy and who possess the prognostic factors revealed here, it would be important to observe treatment progress for consideration of the need for alternative or subsequent treatments such as regorafenib.

In conclusion, grade ≥3 neutropenia in patients with advanced and recurrent CRC who underwent TAS-102 chemotherapy was associated with good prognosis. This might indicate that TAS-102-induced neutropenia could be monitored as a biomarker of both therapeutic response and survival in patients with advanced/recurrent CRC.

4. Experimental

4.1. Patients

Between August 2014 and May 2016, 41 patients underwent oral TAS-102 monotherapy at Ogaki Municipal Hospital, Japan. Patients transferred to other hospitals during treatment were excluded. Overall survival (OS), AEs (neutropenia), neutropenia duration, relative dose intensity (RDI), and reasons for dose reduction or temporary suspension of TAS-102 were surveyed, retrospectively. Discontinuation and AE data were extracted from electronic charts. AE severity was classified according to the Common Terminology Criteria for Adverse Events, version 4.0. The TAS-102 RDI was calculated as the ratio between the actual dose intensity and scheduled dose intensity. The actual dose intensity was defined as the total dose of drug delivered per body surface area unit per time unit (mg/m^2/week).

Blood was drawn every 4 weeks prior to each chemotherapy cycle and on day 21 of each cycle. Patients were divided into 3 categories to according to neutropenia grade: absent (grade 0), mild (grade 1–2), and severe (grade 3–4). Granulocyte-colony stimulating factor (G-CSF) was not used during treatment.

4.2. Method of TAS-102 administration

Oral TAS-102 was administered twice daily, after morning and evening meals, 5 days a week, with 2 days of rest, for 2 weeks, followed by a 14-day rest period, thus completing 1 treatment cycle. Administration criteria were as follows: an Eastern Cooperative Oncology Group performance status (PS) of 0 or 1; sufficient bone marrow function (neutrophil count ≥1500/mm^3, platelet count ≥75000/mm^3, haemoglobin ≥8.0 g/dL, aspartate aminotransferase/alanine aminotransferase ≤100 IU/L, total bilirubin ≤1.5 mg/dL, creatinine ≤1.5 mg/dL, peripheral neuropathy ≤ grade 2, diarrhoea ≤ grade 1, other nonhaematologic toxicities ≤ grade 1. Dose reductions were made if neutrophil count was <500/mm^3 or platelet count was <50000/mm^3.

4.3. Statistical analyses

The primary objective was OS. OS was defined as from the date of treatment onset to the date of death or discontinuation from any cause. Survival curves were extracted using the Kaplan-Meier method, and the survival period was evaluated using the log-rank test. To determine factors associated with survival, those significant in the univariate analysis ($p < 0.05$), were entered into a multivariate analysis using the Cox proportional hazards model, and hazard ratios and their 95% confidence intervals (95% CIs) were calculated. To separate patients into two groups, receiver operating characteristic (ROC) curves were drawn to determine the optimal cut-off values for each factor. Distributions of subject characteristics were assessed using the Chi-squared test or Fisher exact test. A p-value of <0.05 was considered statistically significant. All analyses were performed using JMP 8 software (SAS Institute Inc., Cary, NC, USA).

4.4. Ethical considerations

The present study was approved by the Institutional Review Board of Ogaki Municipal Hospital.

Conflicts of interest: None declared.

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