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Risk factors contributing to the development of neutropenia in patients receiving oral trifluridine-tipiracil (TAS-102) chemotherapy for advanced/ recurrent colorectal cancer

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Elucidating the factors influencing severe neutropenia could aid in earlier management of neutropenia during oral trifluridine-tipiracil (TAS-102) chemotherapy in advanced and recurrent colorectal cancer (CRC). This study was conducted to assess the risk of TAS-102-induced grade 3 or more neutropenia. Between August 2014 and July 2017, 60 patients underwent oral TAS-102 monotherapy at Ogaki Municipal Hospital, Japan. The patients were divided into two groups based on the development of grade 3 or more neutropenia (9 patients) or not (51 patients). Risk factors for grade 3 or more neutropenia were examined by univariate and multivariate analyses. Creatinine clearance rate (CrCl) before TAS-102 administration significantly correlated with the incidence of Grade 3 or more neutropenia after TAS-102 administration (odds ratio 6.5, 95% confidence interval 1.14–30.00; p = 0.02). Multivariate analysis revealed that a CrCl of lower than 57.1 mL/min before TAS-102 administration (odds ratio 54.06, 95% confidence interval 2.14—1364.2; p = 0.02) was an independent risk factor significantly contributing to the development of grade 3 or more neutropenia, induced by TAS-102. CrCl < 57.1 mL/min in patients with advanced and recurrent CRC who underwent TAS-102 chemotherapy was associated with grade 3 or more neutropenia.

1. Introduction

In recent times, the use of combination-based chemotherapy has significantly improved prognosis in colorectal cancer (Aiba et al. 2015). Second line treatments of advanced and recurrent colorectal cancer (CRC) include regorafenib or a trifluridine-tipiracil combination (TAS-102), as recommended by the American Society of Clinical Oncology and the National Comprehensive Cancer Network. This line of treatment is also recommended in Japan (Watanabe et al. 2015). Major adverse events (AEs) associated with TAS-102 treatment include neutropenia (73.1 %), decreased haemoglobin (63.9 %), nausea (63.0 %), and anorexia (55.5 %). Myelosuppression has also been reported as one of the serious AEs (Yoshino et al. 2012; Mayer et al. 2015). Therefore, severe neutropenia and febrile neutropenia (FN) could be predictive factors for the postponement of treatment sessions, eventually lowering the quality of life (QOL).

TAS-102 is an antimetabolite that contains trifluridine and tipiracil hydrochloride at a molar ratio of 1:0.5, and is a renal excretion type drug. Trifluridine is a thymidine-based nucleoside analog, and tipiracil hydrochloride is a novel thymidine phosphorylase inhibitor that improves the bioavailability of trifluridine (Lenz 2015). In a multicentre, double-blind, randomized phase II comparative study (Yoshino et al. 2012) and a multicentre double-blind, randomized phase III comparative study in a global population (Mayer et al. 2015), patients with severe kidney dysfunction (creatinine clearance rate (CrCl): 15 - 29 mL/min) were not included. To the best of our knowledge, clinical trials for patients with impaired renal function have not been conducted yet. Thus, there is no information available on the safety profile of the drug in patients with impaired kidney dysfunction. In addition, the liver is the main site of metabolism for trifluridine, and it is presumed that the drug pharmacokinetics may be influenced by reduction in liver function. However, there is limited safety information in patients with liver dysfunction, as compared to patients with impaired renal function. Therefore, it is essential to identify risk factors for TAS-102-induced neutropenia. Elucidating the influence of the risk factors for severe neutropenia can help in planning an early response to neutropenia during the treatment period. In the present retrospective study, the risk factors for TAS-102-induced grade 3 or more neutropenia was evaluated in order to assess the safety of this treatment regime.

2. Investigations and results

2.1. Patients' characteristics

Patients' characteristics are shown in Table 1. Among the patients who developed grade 3 or more neutropenia and patients who did not, those with grade 3 or more neutropenia had lower CrCl (median 49.4 mL/min) than those without grade 3 or more neutropenia (median 80.2 mL/min) (p = 0.02). Similarly, the median AST levels were 25 U/L (range, 15–115 U/L) and 27 U/L (range, 10–85 U/L), Alanine aminotransferase (ALT) levels were 17 U/L (range, 9–52 U/L) and 16 U/L (range, 7–55 U/L), and the TBI levels were 11.4 g/dL (range, 8.5–15.2 g/dL) and 11.9 g/dL (range, 0.2–1.2 g/dL), respectively. No significant differences were found between the two groups with regard to the other factors investigated.

2.2. Assessment of risk factors for neutropenia after TAS-102 administration

The results of univariate logistic regression analysis regarding the potential influence of the patients' baseline characteristics on the development of grade 3 or more neutropenia after TAS-102 administration are shown in Table 2. The CrCl before TAS-102 administration significantly correlated with the incidence of grade 3 or more neutropenia after TAS-102 administration (odds ratio 6.5, 95% confidence interval 1.14–30.00; p = 0.02), whereas the AST, ALT, and TBI levels did not correlate with this incidence.

Table 1: Patient characteristics

Factors	Grade 0-2 neutropenia	Grade 3 or more neutropenia	*p* value
Number	51	9	
Age, years	67 (37-81)	73 (58-83)	0.18 [a)]
Sex,			
Male/Female	29/22	5/4	0.95 [b)]
ECOG performance status	0 (0-2)	0 (0-2)	0.65 [a)]
Number of treatment cycles	3 (1-7)	3 (2-4)	0.45 [a)]
Body surface area, m^2	1.6 (1.14-1.96)	1.6 (1.44-1.81)	0.63 [a)]
Creatinine clearance rate, mL/min	80.2 (24.0-158.0)	49.4 (25-104.0)	0.02 [a)]
Disease status			
Unresectable/Recurrent	24/27	3/6	0.45 [b)]
Number of metastatic sites	2 (1-4)	2 (1-3)	0.94 [a)]
Aspartate aminotransferase, U/L	26 (10-115)	16 (7-70)	0.97 [a)]
Alanine aminotransferase, U/L	16 (6-70)	17 (11-55)	0.56 [a)]
Total bilirubin, mg/dL	0.6 (0.2-1.3)	0.5 (0.3-1.1)	0.84 [a)]
Haemoglobin, g/dL	11.4 (8.5-15.2)	12.3 (9.4-14.4)	0.57 [a)]
Pre-treatment neutrophil count, /μL	4060 (1700-9250)	3670 (2310-8360)	0.82 [a)]
Previous adjuvant chemotherapy			
Yes/No	19/33	2/7	0.38 [b)]

[a)] Data are expressed as median (maximum - minimum) and the differences between the two groups were determined by Mann-Whitney's U test. b) Differences between the two groups were determined by chi-square test or Fisher's exact test. * $p < 0.05$
ECOG: Eastern Cooperative Oncology Group

By ROC curve analysis, the area under the ROC curves was 0.739. The cut-off value calculated by the ROC curve was 57.1 mL/min. The results of the multivariate logistic regression analysis, to assess the risk factors contributing to the development of grade 3 or more neutropenia after TAS-102 administration, are shown in Table 3. The multivariate analysis revealed that a CrCl lower than 57.1 mL/min before TAS-102 administration (odds ratio 54.06, 95% confidence interval 2.14–1364.2; $p = 0.02$) was an independent risk factor, contributing significantly to the development of grade 3 or more neutropenia induced by TAS-102.

2.3. Assessment of onset of the highest neutropenia grade and pre-treatment neutrophil count

The onset of occurrence of the highest neutropenia grade is shown in the Fig. Grade 3 or more neutropenia was seen in 45.0 % (27/60) patients. The highest grade of neutropenia occurred within 2 cycles in 26.7 % (16/60) of patients. Grade 3 or more neutropenia was confined to 59.3 % (16/27) patients within 2 courses. In patients who developed grade 3 or more neutropenia and patients who did not, the neutrophil counts before the course and at the highest neutropenia grade were 2980 /μL (1180-8360 /μL) and 2535 /μL (1430-4370 /μL), respectively.

3. Discussion

Severe neutropenia could be a predictive factor for postponement of treatment, FN, and decrease in QOL of patients. The risk factors for TAS-102-induced grade 3 or more neutropenia was evaluated in order to assess the safety of TAS-102 chemotherapy in patients with advanced/recurrent CRC.

Hepatic function and renal function have been reported as factors influencing the development of severe neutropenia in cancer chemotherapy (de Jong et al. 2008; Chen et al. 2013; Armstrong et al. 2009; Alexandre et al. 2000). The major elimination routes of tipiracil hydrochloride (a component of TAS-102) include renal excretion. Therefore, severe neutropenia could develop due to renal dysfunction. In this study, CrCl < 57.1 mL/min was found to be the risk factor for grade 3 or more neutropenia in patients with advanced and recurrent CRC who underwent TAS-102 chemotherapy. In contrast, liver function was not detected as a risk factor. Trifluridine, the antitumor component of TAS-102 is a type of hepatic metabolic drug. Therefore, it is hypothesized that severe neutropenia can be anticipated in cases with reduced liver function or abnormal bile excretion. Based on the National Cancer Institute liver function classification criteria, patients with normal (TBI, AST / ALT ≤ the upper limit of the normal range (ULN)) and mild (TBI ≤ ULN and AST / ALT > ULN or TBI > 1.0–1.5 x ULN) liver dysfunction were included in this study. However, patients with moderate (TBI > 1.5–3 x ULN) or severe (TBI > 3 x ULN) liver dysfunction were not included. Therefore, it may not be possible to analyse the drug effects in patients with moderate or severe liver dysfunction, which could be considered as the subject of future studies.

Lymphocyte count, neutrophil count (Alexandre et al. 2000; Watanabe et al. 2012), sex (Armstrong et al. 2009; Watanabe et al. 2012; Yano et al. 2009; Choi et al. 2014; Chan et al. 2013), performance status (PS, Ozawa et al. 2008; Ahn et al. 2012; Khanfir et al. 2016;

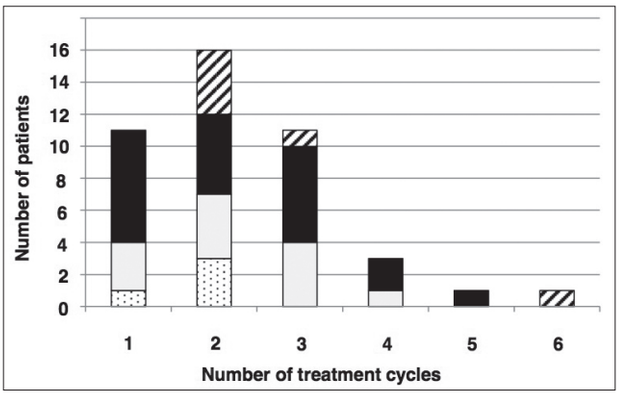

Fig. : Grade 1, Grade 2, Grade 3, Grade 4

Table 2. Univariate Logistic Regression Analysis of the Risk Factors for Neutropenia in the First Treatment Cycle (n = 60)

Factors	Odds ratio	95% confidence interval	p value
Age	1.07	0.97 – 1.18	0.20
Female sex	0.95	0.23 – 3.95	0.94
ECOG Performance status	1.71	0.52 – 5.70	0.38
Body surface area	4.35	0.01 – 205.00	0.46
Number of metastatic sites	0.92	0.39 – 2.19	0.86
Number of treatment cycles	0.68	0.31 – 1.52	0.35
Creatinine clearance rate	6.5	1.41 – 30.00	0.02*
Aspartate aminotransferase	1.01	0.98 – 1.04	0.57
Alanine aminotransferase	1.00	0.96 – 1.05	0.95
Total bilirubin	0.74	0.08 – 7.01	0.80
Haemoglobin	1.75	0.41 – 7.40	0.45
Pre-treatment neutrophil count	1.00	1.00 – 1.00	0.50

* $p < 0.05$
ECOG: Eastern Cooperative Oncology Group

Table 3. Multivariate Logistic Regression Analysis of Risk Factors for Neutropenia in the First Treatment Cycle (n = 60)

Factors	Odds ratio	95% confidence interval	p value
Age	1.10	0.93 – 1.29	0.26
Female sex	1.21	0.04 – 32.95	0.91
ECOG Performance status	0.67	0.11 – 4.02	0.66
Body surface area	0.01	<0.01 – 33.01	0.25
Number of metastatic sites	1.06	0.30 – 3.71	0.93
Number of treatment cycles	2.63	0.68 – 10.25	0.16
Creatinine clearance rate	54.06	2.14 – 1364.20	0.02*
Aspartate aminotransferase	0.92	0.84 – 1.01	0.09
Alanine aminotransferase	1.10	0.97 – 1.25	0.15
Total bilirubin	18.03	0.41 – 788.57	0.13
Haemoglobin	0.73	0.38 – 1.41	0.35
Pre-treatment neutrophils	1.00	1.00 – 1.00	0.90

* $p < 0.05$
ECOG: Eastern Cooperative Oncology Group

Alexandre et al. 2007), and age (Lyman et al. 2003; Rabinowitz et al. 2006) are also reported as risk factors of severe neutropenia and FN. Meanwhile, Khanfir et al. (2016) reported that age did not turn out as a risk factor. In this study, the lymphocyte count, the neutrophil count, sex, PS and age did not turn out as a risk factor in TAS-102 patients. Concerning PS, the study many be problematic, because few patients with PS 2 were included. Moreover, this study may be affected by the small number of cases included.

CrCl < 57.1 mL/min was observed to be the risk factor for grade 3 or more neutropenia during the first course. Grade 3 or more neutropenia was detected in 59.3% of the patients within completion of two courses. It was reported that serious neutropenia and FN tended to occur from days 15 to 21 in the first cycle (Yoshino et al. 2016; Rabinowitz et al. 2006). Therefore, assessment of CrCl prior to the first dose of TAS-102 could lead to earlier and effective management of neutropenia occurring during the course of treatment.

It has been reported that severe neutropenia is associated with good prognosis (Hamauchi et al. 2017; Kimura et al. 2017). Neutropenia may be a surrogate marker for finalizing adequate antitumor doses of TAS-102 (Shitara et al. 2009, 2010). Shitara et al. (2009) have also reported that neutropenia was a surrogate marker for estimation of adequate antitumour doses of chemotherapeutic agents in FOLFOX and weekly paclitaxel (Shitara et al. 2010) regimes. Therefore, the postponement of TAS-102 treatment due to the presence of neutropenia, dose reductions in the ensuing courses should be deliberated upon by taking into account its efficacy.

In conclusion, CrCl < 57.1 mL/min was associated with grade 3 or more neutropenia in patients with advanced and recurrent CRC who had undergone TAS-102 chemotherapy. This study indicates that TAS-102-induced neutropenia could be monitored as a surrogate biomarker for grade 3 or more neutropenia in patients with advanced/recurrent CRC.

4. Experimental

4.1. Subjects and methods

Between August 2014 and July 2017, 60 patients underwent oral TAS-102 monotherapy at the Ogaki Municipal Hospital, Japan. Patients who discontinued treatment during the first course were excluded from the study. AEs, including neutropenia, and the time of occurrence of highest neutropenia grade were surveyed, retrospectively. AE data and patients' characteristics such as age, sex, haematological, or biochemical data were extracted from the existing electronic charts. AE severity was classified according to the Common Terminology Criteria for Adverse Events, version 4.0.

Blood was withdrawn 4 weeks prior to each chemotherapy cycle and on day 21 of each cycle. Patients were divided into two categories to according to the neutropenia grade: normal and mild (grade 0–2), and severe (grade 3–4). Granulocyte-colony stimulating factor was not used during the treatment regime. Using the Cockcroft-Gault method creatinine clearance rate was estimated from the serum creatinine value.

A treatment cycle of oral TAS-102 consisted of the administration of a twice-daily dose, post morning and evening meals, 5 days a week, with 2 days of rest, for 2 weeks, followed by a 14-day rest period. Dose reductions were carried out if the neutrophil or platelet count reduced to $< 500/mm^3$ or $< 50000/mm^3$, respectively.

4.2. Assessment of risk factors for neutropenia following TAS-102 administration

In order to investigate the risk factors for neutropenia after TAS-102 administration, the patients were divided into two groups based on whether grade 3 or more neutropenia had developed (9 patients) or not (51 patients). Between the two groups, we compared various factors including, sex distribution, age, Eastern Cooperative Oncology Group (ECOG) performance status, number of treatment cycles, body surface area, CrCl, disease status, number of metastatic site, aspartate aminotransferase (AST) levels, alanine aminotransferase (ALT) levels, total bilirubin (TBI) levels, haemoglobin values, pre-treatment neutrophil count, and previous adjuvant chemotherapy profiles. We also explored the potential influence of the patients' baseline characteristics on the development of grade 3 or more neutropenia, after TAS-102 administration.

4.3. Assessment of the onset of the highest neutropenia grade and pre-treatment neutrophil count

We monitored the treatment cycles to identify the onset of the highest grade of neutropenia, during TAS-102 administration. In addition, the neutrophil counts ascertained before the onset of the treatment course and at the onset of occurrence of highest neutropenia grade were compared between patients who developed grade 3 or more neutropenia and who did not.

4.4. Statistical analyses

Mann-Whitney's U test, Fisher's exact test or the chi-square test were used to assess differences between patients who developed grade 3 or more neutropenia and those who did not. The correlation between the baseline characteristics of the patients and the development of grade 3 or more neutropenia facilitated by TAS-102 treatment was analysed using univariate and multivariate logistic regression analyses based on a binary response model. We plotted the area under receiver-operator characteristics (ROC) curves to estimate sensitivity, specificity, accuracy, and cut-off values for some factors obtained by univariate logistic regression analysis. Significance was set at $p < 0.05$ and all statistical analyses were performed using the EZR software (v1.30, Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (Kanda Y 2013).

4.5. Ethical considerations

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

Conflicts of interest: None declared.

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