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Prediction of better clinical outcomes based on the development of neutropenia during the first course of trifluridine/tipiracil treatment for advanced/recurrent colorectal cancer

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Trifluridine/tipiracil is a standard treatment after the third-line treatment for advanced/recurrent colorectal cancer (CRC). This study aimed to clarify whether trifluridine/tipiracil-induced neutropenia (degree and time of onset) is predictive of better clinical outcomes in patients with CRC. We retrospectively identified 130 patients who received trifluridine/tipiracil for treating CRC at Ogaki Municipal Hospital (Ogaki, Japan) between July 2014 and July 2021. Kaplan-Meier and log-rank tests and multivariate analysis were performed to evaluate overall survival (OS) according to the degree and time of onset of neutropenia. The median OS of patients who developed Grade 1–2 neutropenia (n=27) and those who developed Grade 3–4 neutropenia (n=51) was 185 days (95% confidence interval [CI]: 154–223) and 279 days (95% CI: 214–301), respectively (log-rank test, p=0.002). The median OS of patients who developed ≥ Grade 3 neutropenia during the first course of treatment (n=25) and those who developed ≥ Grade 3 neutropenia after the second course (n=26) was 300 days (95% CI: 246–458) and 211 days (95% CI: 173–299), respectively (log-rank test, p=0.137). Compared with that of patients who did not develop neutropenia, the hazard ratio for death of patients who developed neutropenia during the first course of treatment was 0.608 (95% CI, 0.385–0.958; p=0.032). Although the timing of severe neutropenia during trifluridine/tipiracil administration was not related to OS, the presence or absence of neutropenia during the first course of trifluridine/tipiracil administration can predict prolongation of OS in patients with CRC.

1. Introduction

Chemotherapy-induced neutropenia is one of the most common adverse events during chemotherapy and often results in postponement of treatment or dose reduction. A link between neutropenia and better clinical outcomes in cancer patients has been reported in various cancer types including breast cancer (Cameron et al. 2003), gastric cancer (Yamanaka et al. 2007), pancreatic cancer (Kurihara et al. 2015), non-small cell lung cancer (Di Maio et al. 2005), and advanced/recurrent colon cancer (CRC) (Shitara et al. 2009; Kasi et al. 2016).

The standard treatment after third-line treatment for CRC is trifluridine/tipiracil or regorafenib; the drug choice is at the discretion of the clinician. Therefore, it is important to identify patients who are likely to benefit from chemotherapy. Many studies have reported the relationship between neutropenia and overall survival (OS) in patients treated with trifluridine/tipiracil (Kasi et al. 2016; Hamauchi et al. 2017; Kimura et al. 2017; Yoshino et al. 2020), and these have demonstrated a longer OS in patients with neutropenia. There are also reports that severe neutropenia prolongs OS (Kimura et al. 2017). Jang et al. (2013) reported that the timing of neutropenia may be a good predictor of prognosis in patients with non-small cell lung cancer. However, the relationship between the time of onset of neutropenia and OS in patients receiving trifluridine/tipiracil has not been reported.

Therefore, we hypothesised that early onset of neutropenia is associated with OS in patients treated with trifluridine/tipiracil and that severe neutropenia during the first course of treatment is a predictor of good prognosis in patients with CRC. While clinically beneficial predictors of OS in patients receiving trifluridine/tipiracil have not been fully elucidated, our study may help identify patients who are likely to benefit from chemotherapy early and can guide treatment choices. Although previous studies have reported that neutropenia in patients treated with trifluridine/tipiracil for CRC is a predictor of OS (Kasi et al. 2016; Hamauchi et al. 2017), these evaluated ≥ Grade 2 neutropenia and did not include Grade 1 neutropenia.

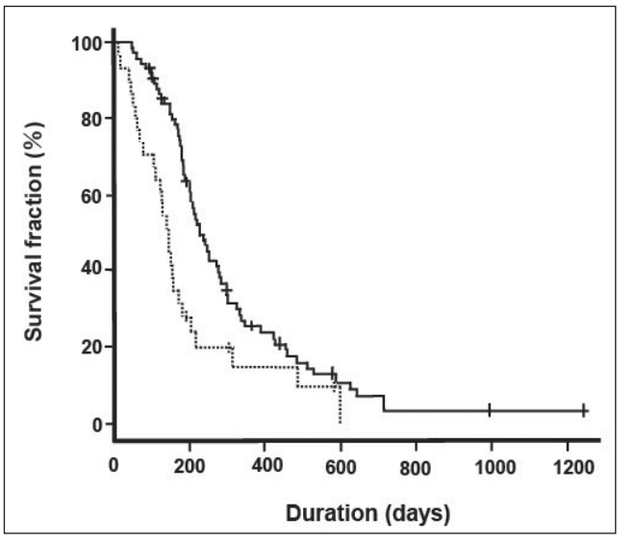

Fig. 1: Kaplan-Meier survival curves of overall survival following trifluridine/tipiracil treatment in the two patient groups (those who developed neutropenia and those who did not develop neutropenia)
.... Patients who did not develop neutropenia
____ Patients who developed neutropenia

The purpose of this study was to clarify the clinical significance of trifluridine/tipiracil-induced neutropenia (degree and time of onset) in patients with CRC. Further, we evaluated the development of neutropenia during the first course of treatment to examine whether it can be a predictor of better clinical outcomes in patients.

2. Investigations and results

2.1. Patient characteristics

Patient characteristics are shown in Table 1. The median age was 69 (range, 36–83) years, median body surface area was 1.55 (range, 1.09–2.04) m^2, and median pre-treatment neutrophil count was 3210/mm^3 (range, 1,300–13040/mm^3).

2.2. Overall survival

Seventy-eight of 109 patients developed neutropenia during trifluridine/tipiracil therapy. Figure 1 shows the Kaplan–Meier survival curves for patients after therapy with trifluridine/tipiracil and illustrates the OS of patients who did (n=78) and did not (n=31) develop neutropenia. The median OS of patients who developed neutropenia was 228 days (95% CI: 200–282) and 147 days (95% CI: 107–173) for those who did not develop neutropenia (log-rank test, p=0.002).

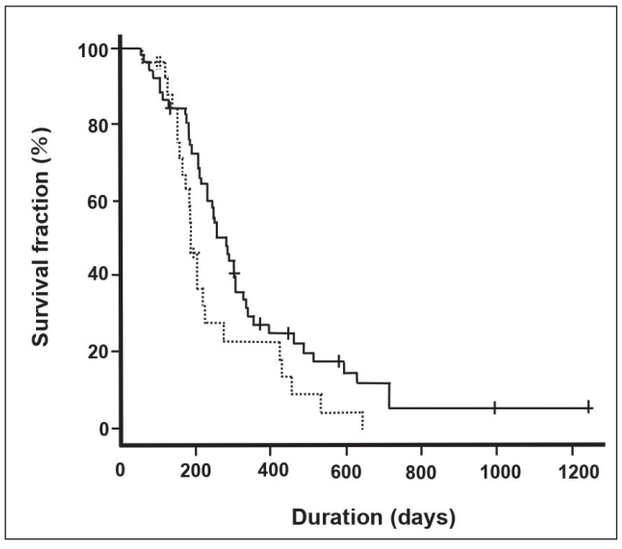

Fig. 2: Kaplan-Meier survival curves of overall survival following trifluridine/tipiracil treatment in the two patient groups (those who developed Grade 1–2 neutropenia and those who developed Grade 3–4 neutropenia)
.... Patients who developed Grade 1–2 neutropenia
____ Patients who developed Grade 3–4 neutropenia

Figure 2 shows the Kaplan-Meier survival curves for patients after therapy with trifluridine/tipiracil and demonstrates the OS of patients who developed Grade 1–2 neutropenia (n=27) and those who developed Grade 3–4 neutropenia (n=51). The median OS of patients who developed Grade 1–2 neutropenia was 185 days (95% CI: 154–223) and that of patients who developed Grade 3–4 neutropenia was 279 days (95% CI: 214–301) (log-rank test, p=0.002).

Figure 3 shows the Kaplan-Meier survival curves for patients after therapy with trifluridine/tipiracil and demonstrates the OS in patients who developed ≥ Grade 3 neutropenia during the first course of treatment (n=25) and those who developed ≥ Grade 3 neutropenia after the second course (n=26). The median OS of patients who developed ≥ Grade 3 neutropenia during the first course was 300 days (95% CI: 246–458) and that of patients who developed ≥ Grade 3 neutropenia after the second course was 211 days (95% CI: 173–299) (log-rank test, p=0.137).

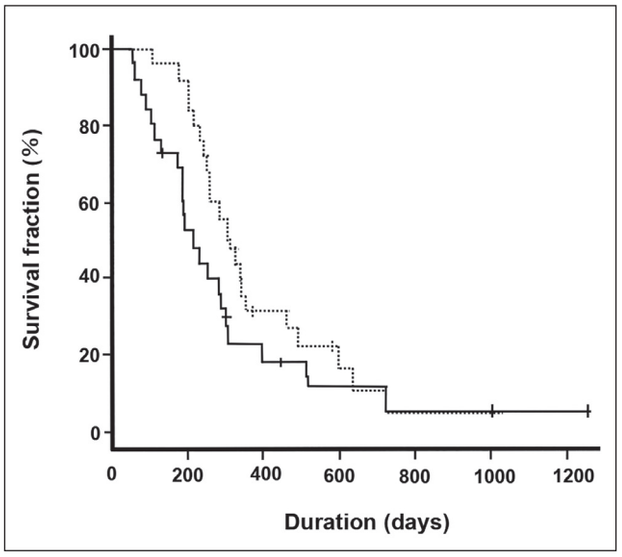

Fig. 3: Kaplan-Meier survival curves of overall survival following trifluridine/tipiracil treatment in the two patient groups (those who developed ≥ Grade 3 neutropenia during the first course and those who developed ≥ Grade 3 neutropenia after the second course)
.... Patients who developed ≥ Grade 3 neutropenia during the first course
____ Patients who developed ≥ Grade 3 neutropenia after the second course

Table 1: Patient characteristics

Variable	
No. of patients	109
Age, years, median (range)	69 (36-83)
Gender, n, Male/Female	57/52
Height, cm, median (range)	158 (56-183)
Weight, kg, median (range)	54 (32-95)
Body surface area, m^2, median (range)	1.55 (1.09-2.04)
Creatinine clearance, mg/mL, median (range)	71.6 (12.6-171.1)
Pretreatment neutrophil count, /μL, median (range)	3,210 (1,300-13,040)
Performance status, 0/1/2, n	77/32/1
Metastatic site, n	
Liver	68
Lymph node	39
Lung	39
Peritoneal	32
Bone	5
Skin	1
Recurrence	1
Others	2
Treatment lines, n	
2nd	7
3rd	58
4th	36
5th	4
6th	4
Previus chemotherapy, n	
FOLFIRI+bevacizumab	28
FOLFIRI+cetuximab	11
FOLFIRI+ramucirumab	4
FOLFIRI+aflibercept	5
FOLFIRI+panitumumab	3
FOLFIRI	5
IRIS+cetuximab	1
IRIS	2
FOLFOX	2
FOLFOX+bevacizumab	8
FOLFOX+cetuximab	6
FOLFOX+panitumumab	1
XEROX	1
XELOX+bevacizumab	5

SOX+bevacizumab	3
SOX	1
Irinotecan+cetuximab	1
Irinotecan	3
Capecitabine+bevacizumab	1
XELIRI+bevacizumab	2
Capecitabine	2
Regorafenib	5
Cetuximab	1
Panitumumab	1
Tegafur/uracil	1
Tegafur/gimeracil/oteracil potasium	6

FOLFOX fluorouracil, leucovorin, and oxaliplatin, FOLFIRI fluorouracil, leucovorin, and irinotecan, IRIS irinotecan and tegafur/gimeracil/oteracil potassium, XEROX capecitabine plus oxaliplatin, SOX tegafur/gimeracil/oteracil potassium and oxaliplatin, XELIRI irinotecan and capecitabine

Table 2: Univariate analysis of prognostic factors associated with overall survival in patients with advanced and recurrent colorectal receiving chemotherapy

Factors	Hazard ratio	95% confidence interval	*p* value
Age	1.004	0.985-1.023	0.674
Body surface area	1.042	0.390-2.778	0.935
Creatinine clearance	0.999	0.997-1.001	0.443
Performance status	1.271	0.819-1.971	0.284
Gender (Male)	1.307	0.864-1.976	0.204
Number of metastatic	1.273	0.931-1.742	0.130
Disease status (Unresectable)	0.884	0.578-1.353	0.572
Treatment lines	1.025	0.818-1.284	0.828
Neutropenia Grade in the first course (Grade 3-4) **	1.143	0.700-1.867	0.592
Neutropenia in the first course (yes)	0.603	0.388-0.938	0.024*
Pretreatment neutrophil count	1	0.999-1	0.361

* $p<0.05$
**Neutropenia Grade in the first course (Grade 1-2 vs. Grade 3-4)

Table 3:Multivariate analysis of prognostic factors associated with overall survival in patients with advanced and recurrent colorectal receiving chemotherapy

Factors	Hazard ratio	95% confidence interval	*p* value
Body surface area	1.791	0.629-5.105	0.275
Creatinine clearance	0.999	0.997-1.001	0.454
Pretreatment neutrophil count	1.000	0.999-1	0.435
Neutropenia in the first course (yes)	0.608	0.385-0.958	0.032*
Treatment lines	0.892	0.688-1.156	0.385
Performance status	1.389	0.871-2.215	0.167

* $p<0.05$

2.3. Prognostic factors of patients with advanced/recurrent colorectal cancer receiving trifluridine/tipiracil treatment

The results of univariate and multivariate analyses of baseline and clinical characteristics as prognosticators are shown in Table 2 and Table 3, respectively. Development of neutropenia during the first course of treatment was independently and significantly associated with survival. Compared with that of patients who did not develop neutropenia during the first course, the hazard ratio for death of patients who did develop neutropenia during the first course was 0.608 (95% CI, 0.385–0.958; p=0.032). Body surface area, creatinine clearance, pre-treatment neutrophil count, treatment lines, and performance status during the first course were not independently and significantly associated with survival in the multivariate analysis.

2.4. Timing of onset of ≥ Grade 3 neutropenia

Grade 3 or higher neutropenia was observed for the first time in 31 cases during the first course of treatment, 11 cases during the second course, and 10 cases during the third course; no cases of neutropenia occurred after the fourth course of treatment.

3. Discussion

In this study, we clarified the clinical significance of trifluridine/tipiracil-induced neutropenia (degree and time of onset) in patients with CRC and examined whether the onset of neutropenia during the first course could be a predictor of better clinical outcomes. Neutropenia observed during trifluridine/tipiracil administration was associated with good OS, and OS was significantly longer in patients with more severe neutropenia. In contrast, although the timing of severe neutropenia was not related to OS, prolonged OS could be predicted based on the presence or absence of neutropenia during the first course of trifluridine/tipiracil administration.

Previous studies have shown an association between the incidence of neutropenia and improved prognosis of patients receiving chemotherapy (Cameron et al. 2003; Di Maio et al. 2005; Yamanaka et al. 2007; Shitara et al. 2009; Jang et al. 2013; Kurihara et al. 2015; Kasi et al. 2016; Kasi et al. 2016; Hamauchi et al. 2017; Kimura et al. 2017; Yoshino et al. 2020). Our results are consistent with those of previous studies on trifluridine/tipiracil (Jang et al. 2013; Kasi et al. 2016; Hamauchi et al. 2017; Yoshino et al. 2020), namely, the median OS of patients experiencing neutropenia was longer than that of patients without neutropenia (OS: 147 days vs. 228 days, p=0.002). Therefore, the occurrence of neutropenia during trifluridine/tipiracil administration may be associated with prolonged survival of patients with CRC. Furthermore, patients with severe neutropenia had a longer OS than those without severe neutropenia (185 days vs. 279 days, p=0.002).

Several mechanisms may explain the longer OS of patients with neutropenia during administration of trifluridine/tipiracil. Shitara et al. (2009) reported that neutropenia was a surrogate marker for appropriate antitumor doses of chemotherapeutic agents. The lack of neutropenia indicates that the biological effects of chemotherapy are weak. This may be owing to the dose administered to the patient being too low (Shitara et al. 2010). Gurney (1996) showed that there was a 4- to 10-fold variation in cytotoxic drug clearance between individuals. There are also reports that increasing the dose based on the pharmacokinetics of the corresponding regimen is effective (Gamelin et al. 2008). Thus, the use of pharmacokinetic-adjusted chemotherapy is considered ideal for the treatment of CRC. However, in real-world clinical practice, it is not practical to adjust the chemotherapy dose for an individual patient because of the complexity of the measurements.

In addition, several other factors should be considered, including the relationship between neutrophils and cancer metastasis. Neutrophils in the tumour microenvironment have been shown to promote tumour growth and metastasis through several mechanisms (Fridlender and Albelda 2012; Dumitru et al. 2013; Mishalian et al. 2013; Tazzyman et al. 2013; Moses and Brandau 2016). This is because cancer cells induce the production of neutrophils and release special traps (neutrophil extracellular traps) (Park et al. 2016; Erpenbeck and Schön 2017; Snoderly et al. 2019). In other words, patients with neutropenia may have suppressed tumour growth due to the therapeutic effect.

Previous studies have not demonstrated that earlier timing of neutropenia during trifluridine/tipiracil therapy improves prognosis of patients with CRC. During the mFOLFOX6 therapy for CRC, Chan et al. (2017) reported that the early-onset neutropenia group (within two cycles) showed significantly better OS than the late-onset group (3–6 cycles) (Chen et al. 2016). However, in this study, patients with severe neutropenia had a longer OS than patients without severe neutropenia, but the time of onset of neutropenia was not related to OS. We believe this is mainly owing to differences in chemotherapy regimens. In addition, most cases of neutropenia during trifluridine/tipiracil treatment were observed early, i.e., within the first three courses. Therfore, probably an

effective cut-off value could not be obtained. However, in our study, univariate and multivariate analyses revealed that neutropenia during the first course of trifluridine/tipiracil treatment was predictive of prolonged OS.

This study confirms that the onset of neutropenia during the first course of trifluridine/tipiracil treatment can be a predictor of good prognosis of patients with CRC. This allows early identification of patients who are likely to benefit from chemotherapy and can help clinicians determine whether switching from trifluridine/tipiracil to regorafenib is appropriate. However, the association of neutropenia with OS should also be verified in patients receiving regorafenib. Currently, several other biomarkers, such as KRAS, are also used by clinicians to determine the optimal treatment for CRC patients, and their association with chemotherapy responses and clinical outcomes has been previously confirmed (Alhopuro et al. 2005; De Roock et al. 2010; Sinicrope et al. 2011). However, we did not evaluate these biomarkers owing to lack of data, which may be considered a limitation of the current study.

In conclusion, the results of this study demonstrate that the presence or absence of neutropenia during the first course of trifluridine/tipiracil therapy can predict the therapeutic effect and identify patients who are likely to benefit from chemotherapy. This may help physicians and pharmacists make informed choices regarding optimal treatment for patients with CRC.

4. Experimental

4.1. Subjects and methods

We retrospectively identified 130 patients who received trifluridine/tipiracil for treating CRC at Ogaki Municipal Hospital (Ogaki, Japan) between July 2014 and July 2021. We excluded 21 patients who were transferred to another hospital or who completed only one course of treatment. Thus, 109 patients were considered eligible for this study. Patient data were extracted from anonymised patient records. Patient characteristics, OS, grade of neutropenia during the first course of treatment, and timing of occurrence of worst grade of neutropenia were analysed retrospectively using data collected from the electronic charts and pharmacy service records. OS was defined as the time from the date of initial treatment to date of death.

4.2. Assessment of neutropenia

Blood samples were routinely collected prior to chemotherapy (Day 0 or 1) and every 14 days. Neutropenia absence was defined as neutrophil count > 2000/mm^3. According to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) (US Department Of Health And Human Services 2010), neutropenia grade was defined as follows: Grade 1, neutrophil count 1500–2000/mm^3; Grade 2, neutrophil count 1500–1000/mm^3; Grade 3, neutrophil count 1000–500/mm^3; and Grade 4, neutrophil count 0–500/mm^3.

4.3. Treatment

Trifluridine/tipiracil (each at a dose of 35 mg/m^2) was administered twice daily after morning and evening meals for 5 days, followed by 2 days of rest, then again for 2 weeks, followed by a 14-day rest period. This regimen constituted one treatment cycle and was repeated every 4 weeks. If ≥ Grade 3 neutropenia was observed, treatment was postponed until improvement to ≤ Grade 2 neutropenia was observed, and if Grade 4 neutropenia was observed, the dose was reduced by 10 mg/day in the next course.

4.4. Statistical analysis

Univariate analyses were performed to evaluate the relationships between patients' baseline characteristics and the development of neutropenia. Significant variables, as well as previously reported factors that affect OS, were entered into a multivariate logistic regression model. Optimal cut-off values for the significant variables were determined based on receiver operating characteristic curve analyses. The Kaplan–Meier and log-rank tests were used to compare OS. Differences were considered statistically significant at p-values < 0.05. All analyses were performed using EZR software (version 1.30, Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R software (The R Foundation for Statistical Computing, Vienna, Austria) (Kanda 2013).

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Competing interests: The authors declare that they have no conflicts of interest.

Author contributions: MK contributed to the study design, collected and provided the data, was the principal author of the report, and is the guarantor of the article and all data. EU, and TY contributed to the study design, reviewed the article, and supervised drafting the report and the submission process. All authors approved the final version of the article.

Data availability: All relevant data are included in the manuscript and its associated files.

Ethics approval: The study protocol was approved by the Institutional Review Board of Ogaki Municipal Hospital (Ogaki, Japan; 20211223-11).

Consent to participate: The requirement for informed consent was waived due to the retrospective study design.

Consent to publish: Consent to publish has been received from all participants.

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