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Prognostic factors in patients with advanced and recurrent colorectal cancer receiving last-line chemotherapy

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For patients with advanced/recurrent colorectal cancer, the trifluridine/tipiracil combination tablet (TAS 102) and regorafenib are last-line treatments. This study aimed to clarify prognostic factors in patients receiving last-line chemotherapy. Between April 2014 and December 2016, 47 patients received last-line chemotherapy at Ogaki Municipal Hospital, Japan. The primary outcome was overall survival. To determine factors associated with survival, those considered significant in the univariate analysis (p <0.10), were entered into a multivariate Cox proportional hazards model. KRAS type and the use of opioid formulations were independently and significantly associated with survival in the multivariate analysis. For patients with KRAS-wild relative to KRAS-mutation cancers, the hazard ratio for death was 0.478 (95% CI, 0.249-0.919; p = 0.03). For patients taking opioid formulations, relative to those not, the hazard ratio for death was 3.557 (95% CI, 1.032-12.257; p = 0.04). The median overall survival duration for patients with KRAS-wild (n = 24) and KRAS-mutation (n = 23) cancers were 223.5 days (range: 115-703) and 154 days (range: 51-503), respectively (p = 0.05). This finding provides a useful index to make an early decision on discontinuation of treatment and to guide decisions around agents to use in last-line chemotherapy.

1. Introduction

Chemotherapy has been shown to contribute to tumour size reduction and to improve prognosis in colon cancer (Aiba et al. 2014). Chemotherapy regimens used in colon cancer include FOLFOX/CapeOX±bevacizumab and FOLFOX+cetuximab/panitumumab as first-line treatments (Henley et al. 2015; Siegel et al. 2011; Bailey et al. 2015), and FOLFIRI±bevacizumab/ziv-aflibercept/ramucirumab, FOLFIRI+cetuximab/panitumumab, and irinotecan+cetuximab/panitumumab as second-line treatments (Hemminki et al. 2004; Hemminki et al. 2004; Ahsan et al. 1998; Bonelli et al. 1998; Hampel et al. 2008). These chemotherapy regimens help to prolong survival. The trifluridine/tipiracil combination tablet (TAS-102) and regorafenib are used as third-line treatment; clinical trial drugs or best supportive care is used for subsequent lines of treatment (Watanabe et al. 2017). Therefore, TAS-102 and regorafenib are, essentially, last-line treatments.

Patients requiring last-line treatment are usually in a poor clinical state. Nausea and bone marrow suppression caused by TAS-102 and hand-foot syndrome caused by regorafenib may decrease the patient's quality of life (QOL) (Kimura et al. 2016). As cancer disease progresses, the harmful effects of chemotherapy may outweigh the benefits, possibly resulting in hospitalization and, if severe, in death (Näppä et al. 2011; Bjordal et al. 2004; Martoni et al. 2007). Therefore, for patients requiring last-line treatment, much consideration is needed to determine treatment and continuation. In order to ensure adherence to treatment, therapeutic responses and adverse events (AEs) must both be closely monitored (Bjordal et al. 2004; Kim et al. 2005). Monitoring the performance status is very useful, as it is one of the strongest predictors of survival (Näppä et al. 2011). In a study of patients with lung cancer, it was shown that survival and QOL improve if aggressive cancer chemotherapy is stopped and palliative care is introduced at an early stage (Temel et al. 2010). Näppä et al. (2011) reported that the use of chemotherapy in the last month of life shortens the survival duration.

For these reasons, it is necessary to evaluate whether a patient requiring last-line chemotherapy is a good candidate for and would benefit from further chemotherapy (in terms of survival duration). Therefore, to identify prognostic factors for patients receiving last-line chemotherapy as treatment for colorectal cancer, the survival period after staring last-line treatment was examined. Further, we examined the effect of treatment discontinuation on prognosis.

Table 1: Patients' characteristics

Variable	
Number	47
Age, years, median (range)	67 (37–83)
Male/female, n	29/18
ECOG performance status, median (range)	0 (0–2)
Number of treatment lines completed, median (range)	3 (2–7)
Body surface area, m^2, median (range)	1.59 (1.14–1.96)
CrCl, mL/min, median (range)	79.2 (40.0–139.0)
Disease status: Unresectable/recurrent, n	23/24
Number of metastatic sites, median (range)	2 (1–3)
Overall survival duration, median (range)	184 (51–805)
Receiving an opioid, Yes/No, n	5/42
Adjuvant chemotherapy, Yes/No, n	20/27
KRAS type: Wild/Mutation, n	23/24

ECOG, Eastern Cooperative Oncology Group; CrCl, creatinine clearance; TAS-102, trifluridine/tipiracil combination tablet.

2. Investigations and results

2.1. Patients' characteristics

The patients' characteristics are shown in Table 1. The median age was 67 years (range, 37–83 years), the median number of treatment lines completed was 3 (range, 2–7), and the overall survival duration was 184 days (range, 51–805).

2.2. Prognostic factors in patients with advanced/recurrent colorectal cancer receiving last-line chemotherapy

The results of the univariate and multivariate analyses of baseline and clinical characteristics as prognosticators are shown in Table 2. In the univariate analysis, performance status, KRAS type, and the use of opioid formulations were significantly associated with survival. KRAS type and the use of opioid formulations were independently and significantly associated with survival in the multivariate analysis. For patients with KRAS-wild cancers, relative to KRAS-mutation cancers, the hazard ratio for death was 0.478 (95% CI, 0.249–0.919; p = 0.027). For patients who received opioid formulations, the hazard ratio for death was 3.557 (95% CI, 1.032–12.257; p = 0.044), compared with patients who did not receive opioid formulations.

2.3. Reasons for and timing of last-line chemotherapy discontinuation

19.1% of cancer patients treated with last-line chemotherapy received such a treatment within the last month of life. The reasons for discontinuing last-line chemotherapy, shown in Table 3, included a decrease in performance status (n = 24 [51.1%]), progressive disease (n = 16 [34.0%]), AEs such as nausea and malaise (n = 5 cases [10.6%]), and other reasons (n = 2 [4.3%]).

2.4. Overall survival

The survival period from the start of last-line chemotherapy to death for patients who received chemotherapy within 1 month of death (n = 10) was 148 (range: 60–805) days. Patients who stopped chemotherapy more than 1 month before death (n = 37) had a median survival period of 200 (range: 71–670) days (p = 0.637).
The median overall survival durations in the KRAS-wild (n = 24) and KRAS-mutation (n = 23) groups were 223.5 days (range: 115–703) and 154 days (range: 51–503), respectively (log-rank test p = 0.046), as shown in the Fig.

3. Discussion

This study found that 19.1% of cancer patients treated with last-line chemotherapy received such a treatment within the last month of life. This proportion falls within the range of other reported results (18–33%) (Hemminki et al. 2004; Näppä et al. 2011; Bjordal et al. 2004; Kim et al. 2005). Näppä et al. (2011) reported that patients who received chemotherapy within the last month of life had a short survival period from the start of treatment. In the present study of patients with advanced/ recurrent colorectal cancer, taking TAS-102 or regorafinib within the last month of life did not affect survival duration. The most common reason for discontinuing last-line chemotherapy, cited in 24/47 (51.1%) patients, was a decrease in performance status. Although it is impossible to conclude from this research whether this decline was the result of disease progression or was due to the final round of chemotherapy, previous reports found that AEs caused by TAS-102 or regorafenib decrease patients' QOL (Kimura et al. 2016). Keam et al. (2008) reported that patients who received chemotherapy in the last month of life had a shorter survival period, were hospitalized more frequently, and were less likely to die at home (i.e., were more likely to die in hospital) than those who did not. Lewin et al. (2005) reported that patients enrolled in hospice care spent more time at home and incurred fewer medical expenses. The authors also noted that aggressive chemotherapy was more expensive and did not prolong survival. Therefore, it is conceivable that chemotherapy contributes to a decrease in QOL, at least for a patient whose end of life is approaching. Näppä et al. (2011) reported that treatment lines, patient's wishes, and medical services must be considered when deciding on last-line treatment.
Early detection of patients approaching the end of life allows provision of better quality of care and more appropriate use of resources (Hemminki et al. 2007; Ahsan et al. 1998; Asola et al. 2006; Thorne et al. 2005). In this study, we clarified that patients with KRAS-wild type colorectal cancers had a better prognosis than those with KRAS-mutation type cancers, and that use of opioid formulations was associated with a poor prognosis in patients receiving last-line chemotherapy.
Evaluation of molecular markers, such as KRAS, NRAS, and BRAF, in patients with colorectal cancer has become one of the most important factors in developing more accurate and individualized treatment plans. Although anti-EGFR antibody drugs are key in the treatment of advanced/recurrent colorectal cancer, they have been shown to be ineffective in KRAS-mutant type cancers; hence, KRAS is an effective marker for selecting therapeutic targets (Taniguchi et al. 2015; Kito et al. 2015). There are many reports on the relationship between the KRAS gene and prognosis in patients with stage III and stage IV colorectal cancer (Dienstmann et al. 2017; Taieb et al. 2016). In a review by Yokota (2012) that included the review of a trial of cetuximab treatment, the relationship between KRAS mutation and prognosis was summarized. It was shown that KRAS mutations at codons 12 and 13 result in various biological, biochemical, and functional changes that affect prognosis in patients with advanced/recurrent colorectal cancer (Yokota 2012). In a report of 226 patients receiving cetuximab treatment in whom KRAS, NRAS, BRAF, and PIK3CA mutations were examined, KRAS and NRAS mutations were found not to be useful as predictive markers in a univariate analysis (Pentheroudakis et al. 2013). A review article that extracted data on anti-EGFR antibody treatment reported that various studies' findings regarding whether the RAS mutation is a prognostic factor, were controversial (Lo Nigro et al. 2016). Thus, the KRAS gene mutation is a predictive factor for the effect of anti-EGFR antibody treatment, such as cetuximab, but it is not considered to be a prognostic factor. However, Adenis et al. (2016) reported survival and safety outcomes in patients treated with regorafenib in a real-life setting. Multivariate analysis showed that overall survival was incident affected by ECOG (Eastern Cooperative Oncology Group) performance status, time since initial diagnosis, initial dose, number of metastatic sites, presence of liver metastases, and KRAS mutation It seems necessary to consider further whether KRAS gene mutations are a problem with EGFR inhibitor agents only.
In this study, the use of opioids was found to be an indicator of prognosis; patients receiving opioid formulations were found to have a shorter survival duration than those who had not. Although there is no study comparing an opioid non-use group with an opioid use group, there is no evidence that use of opioids shortens the survival duration (Portenoy et al. 2006). Hence, it is considered unreasonable to withhold opioids for analgesia because of concerns about reducing the patient's lifespan (Portenoy et al. 2006). Furthermore, it has been reported that there is no association between the individual opioid doses administered and survival (Bercovitch et al. 1999; Morita et al. 2001; Alsirafy et al. 2013).
In conclusion, these findings suggest that KRAS type may be a useful index to guide early decisions on discontinuation of last-line chemotherapy and choice of chemotherapeutic agent, taking the therapeutic effect and prognosis into account.

4. Experimental

4.1. Subjects and methods

Between April 2014 and December 2016, 47 patients received last-line chemotherapy (TAS-102 or regorafenib) at Ogaki Municipal Hospital, Japan. Patients who were transferred to other hospitals while undergoing treatment were excluded. Overall survival, reasons for discontinuing chemotherapy, and the timing of discontinuing last-line chemotherapy were retrospectively examined. Discontinuation data were extracted from electronic charts.
Identified patients were divided in two groups: One group had received chemotherapy in the last month of life, the other group had not. The patients were also divided into

Table 2: Univariate and multivariate analyses of prognostic factors associated with last-line chemotherapy

	Univariate analysis				Multivariate analysis		
	HR	95% CI	*p*-value	AUC	HR	95% CI	*p*-value
Age, years							
<73 (*n* = 34)							
≥73 (*n* = 13)	1.007	0.976–1.038	0.679	0.548			
Sex							
Male (*n* = 29)							
Female (*n* = 18)	1.09	0.586–2.029	0.786	0.865			
ECOG performance status							
<0 (*n* = 36)							
≥1 (*n* = 11)	2.369	1.311–4.282	0.004*	0.342	1.635	0.824–3.247	0.159
Disease status							
Recurrent (*n* = 24)							
Advanced (*n* = 23)	1.529	0.817–2.860	0.184	0.574			
No. of metastatic sites							
<2 (*n* = 16)							
≥2 (*n* = 31)	1.228	0.818–1.845	0.322	0.362			
BSA, m^2							
<1.850 (*n* = 45)							
≥1.850 (*n* = 2)	0.970	0.215–4.386	0.969	0.478			
CrCl, mL/min/1.73m^2							
<70.8 (*n* = 19)							
≥70.8 (*n* = 28)	0.997	0.986–1.007	0.536	0.549			
Hemoglobin level, g/dL							
<13.2 (*n* = 37)							
≥13.2 (*n* = 10)	0.995	0.973–1.016	0.621	0.514			
Pretreatment neutrophil count, /µL							
<2890 (*n* = 11)							
≥2890 (*n* = 36)	1.000	1.000–1.000	0.091	0.613	1.000	1.000–1.000	0.109
KRAS type							
Mutation (*n* = 24)							
Wild (*n* = 23)	0.520	0.277–0.976	0.042*	0.618	0.478	0.249–0.919	0.027*
Previously treated with regorafenib							
No (*n* = 41)							
Yes (*n* = 6)	0.359	0.127–1.017	0.054	0.375	0.347	0.118–1.024	0.055
Previous no. of treatment lines							
<2 (*n* = 3)							
≥2 (*n* = 44)	0.872	0.579–1.312	0.511	0.496			
Received an opioid formulation							
No (*n* = 42)							
Yes (*n* = 5)	3.865	1.469–10.169	0.006*	0.588	3.557	1.032–12.257	0.044*
Adjuvant chemotherapy							
No (*n* = 27)							
Yes (*n* = 20)	0.577	0.302–1.103	0.096	0.576	0.484	0.233–1.007	0.052

HR, hazard ratio; CI, confidence interval; AUC, area under the (receiver operating characteristic) curve; CrCl, creatinine clearance; ECOG Eastern Cooperative Oncology Group; BSA, body surface area.

Table 3: Reasons for treatment discontinuation, stratified by KRAS type *n*=47)

Reason for discontinuing last-line chemotherapy	*n* (%)	KRAS wild (*n*=23)	KRAS mutation (*n*=24)	*p*-value
Decrease in performance status	24 (51.1)	11	13	0.532
Progressive disease	16 (34.0)	7	9	
Adverse events	5 (10.6)	4	1	
Other	2 (4.3)	1	1	

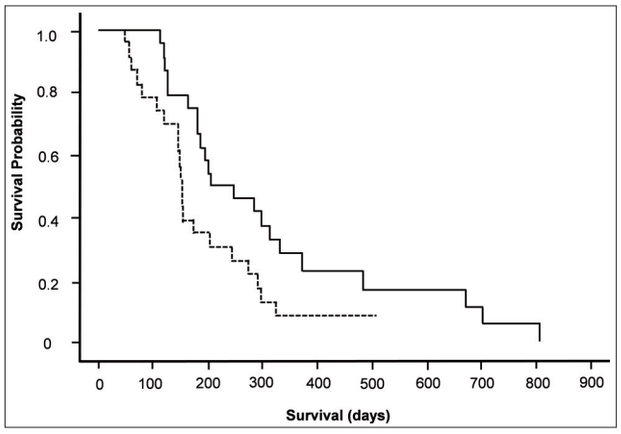

Fig.: Kaplan-Meier survival curves according to KRAS type.
Solid line, KRAS-wild: Median survival time, 223.5 (range: 115–703) days.
Dotted line, K-RAS-mutation: Median survival time, 154 (range: 51–503) days.

2 groups according to whether they had KRAS-wild type or KRAS-mutation type colorectal cancers.

Oral TAS-102 was administered twice daily (after morning and evening meals) for 5 consecutive days, followed by 2 days of rest, for 2 weeks, followed by a 14-day rest period; this constituted 1 treatment cycle. Legolafenib (160 mg after a meal) was administered orally once every day for 3 weeks, followed by a 1-week rest period; this constituted 1 treatment cycle.

4.2. Statistical analysis

The primary outcome was overall survival, defined as survival from the date of treatment onset to the date of death from any cause or discontinuation for any reason. Survival curves were created using the Kaplan-Meier method, and the survival period was evaluated using the log-rank test. To determine factors associated with survival, variables with a p-value <0.10 in the univariate analysis were entered into a multivariate analysis using the Cox proportional hazards model, and hazard ratios and their 95% confidence intervals (95% CI) were calculated. To separate patients into 2 groups, receiver operating characteristic curves were drawn to determine the optimal cut-off values for each factor. Distributions of reasons for treatment discontinuation were assessed using the chi-square test of independence (Fisher's exact probability test). Significance was set at p <0.05 and all statistical analyses were performed using EZR software (v1.30, Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

4.3. Ethical considerations

This analysis was done under the Institutional Review Board of Ogaki Municipal Hospital for the retrospective analysis of de-identified colorectal cancer patient records.

Conflicts of interest: None declared.

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