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Identifying prognostic factors associated with overall survival in second-line paclitaxel plus ramucirumab treated human epidermal growth factor receptor 2-negative advanced/recurrent gastric cancer

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This study aimed to identify the overall survival prolongation index in patients who received paclitaxel plus ramucirumab as second line chemotherapy for human epidermal growth factor receptor (HER) 2-negative advanced/recurrent gastric cancer (AGC). We included 77 patients who underwent second line chemotherapy (paclitaxel plus ramucirumab) for AGC at our institution between January 2015 and September 2020. To determine factors associated with survival, univariate and multivariate analyses were performed, and hazard ratios and their 95% confidence intervals (95% CI) were calculated. In the multivariate analysis, grade ≥1 neutropenia (yes) and the number of anti-cancer drugs used (≥5) were independently and significantly associated with survival. Compared to the patients without grade ≥1 neutropenia, patients with grade ≥1 neutropenia had a survival hazard ratio of 0.455 (95% CI: 0.214–0.966; $p = 0.040$). The median second line treatment durations in patients with grade ≥1 neutropenia (n = 54) and in those without grade ≥1 neutropenia (n = 23) were 133 days (95% CI, 98–190 days) and 70 days (95% CI, 41–128 days), respectively (log-rank test, $p = 0.026$). This study demonstrated that AGC patients with initial neutropenia may benefit from paclitaxel plus ramucirumab therapy.

1. Introduction

Currently, there are six effective drugs for gastric cancer: fluoropyrimidine drugs (fluorouracil [5-FU], tegafur/gimeracil/oteracil potassium [S-1], capecitabine [Cape]), platinum drugs (cisplatin [CDDP], oxaliplatin [OX]), paclitaxel (PTX), docetaxel (DTX), nab-paclitaxel (nab-PTX), irinotecan (IRI), ramucirumab (RAM), and nivolumab. Trastuzumab (T-mab) can be used for human epidermal growth factor receptor 2 (HER 2)-positive gastric cancers.

For HER 2-negative unresectable advanced/recurrent gastric cancer (AGC), the recommended

first-line chemotherapy regimen is a combination of fluoropyrimidines (S-1, Cape) and platinum (CDDP, oxaliplatin) drugs (Koizumi et al. 2008; Kang et al. 2009; Yamada et al. 2015; Cunningham et al. 2008). The recommended regimen for second-line chemotherapy is PTX plus RAM therapy (Wilke et al. 2014), regardless of whether HER 2 is negative or positive. In third-line chemotherapy, nivolumab significantly prolonged the overall survival compared to the best supportive care based on the results of a phase III study conducted in Japan, South Korea, and Taiwan (Kang et al. 2017). This made nivolumab the recommended regimen at level A of evidence. In addition, IRI is recommended to be used in third line therapy because PTX is often used as a second-line chemotherapy.

For AGC, it is desirable to consider a treatment strategy that uses up to six drugs, fluorinated pyrimidines, platinum, taxanes, IRI, RAM, and nivolumab (Selim et al. 2019; Smyth et al. 2020). Since four agents are used in second line, it is important to move to the third line or later. Therefore, we focused on the duration of RAM used it as the second-line therapy. In PTX plus RAM therapy as second line, it has been reported that patients with severe neutropenia have a longer overall survival (OS). In other words, it can be predicted that patients with severe neutropenia have significantly transitioned from third line onward. However, Kawasaki et al. reported that the presence or absence of treatment given after PTX plus RAM therapy was not a significant factor for OS. Thus, the relationship between neutropenia and OS has not been fully elucidated. In addition, the relationship between the onset of severe neutropenia and the treatment duration of PTX plus RAM therapy has not yet been clarified. Therefore, there is an urgent need to identify patients who are likely to benefit from PTX plus RAM therapy, which will lead to enhanced clinical decision-making and improved patient outcomes.

The purpose of this study was to clarify the prognostic factors associated with the treatment duration and OS in patients who used PTX plus RAM as second-line therapy for AGC.

2. Investigations and results

2.1. Patient characteristics

Patient characteristics are presented in Table 1. The median age of the patients was 77 years (39–83 years) and the median number of metastatic sites was 1 (0–3). Further, the first-line treatment regimens were S-1 plus CDDP (50 cases), S-1 plus OX (14 cases), Cape plus CDDP (nine cases), and Cape plus OX (four cases).

2.2. Hazard ratio for overall survival among patients with advanced/recurrent gastric cancer who received second line paclitaxel plus ramucirumab treatment

Univariate and multivariate analyses of the baseline and clinical characteristics are presented as prognosticators in Tables 2 and 3. In the univariate analysis, grade 1 or higher neutropenia (yes) and the number of anti-cancer drugs used (≥ 5) were significantly associated with survival. In the multivariate analysis, grade 1 or higher neutropenia (yes) and the number of anti-cancer drugs used (≥ 5) were

Table 1: Patient characteristics

Characteristic	Datum
Patients, n	77
Age, years	
Median (range)	68 (39-83)
Gender, n	
Male/female	58/19
Disease status	
Advanced/recurrent, n	50/27
Height, cm	
Median (range)	163 (142-180)
Weight, kg	
Median (range)	51 (27-90)
Laboratory test values before chemotherapy (second line)	
Serum creatinine, mg/dL	0.74 (0.36-2.04)
Total bilirubin, mg/dL	0.5 (0.2-2.2)
Aspartate aminotransferase, IU/L	27 (11-99)
Alanine aminotransferase, IU/L	16 (5-96)
Alubmin, g/dL	3.6 (1.8-4.6)
Disease status	
Recurrent/unresectable	50/27
Treatment regimen in first line	
SP (S-1 plus CDDP)	50
SOX (S-1 plus Oxaliplatin)	14
XP (Capecitabine plus CDDP)	9
XELOX (Capecitabine plus Oxaliplatin)	4
Metastatic site, n	
Peritoneal	39
Liver	25
Lymph node	24
Lung	6
Bone	3
Others	3

CDDP, cisplatin; S-1, tegafur gimeracil oteracil potassium

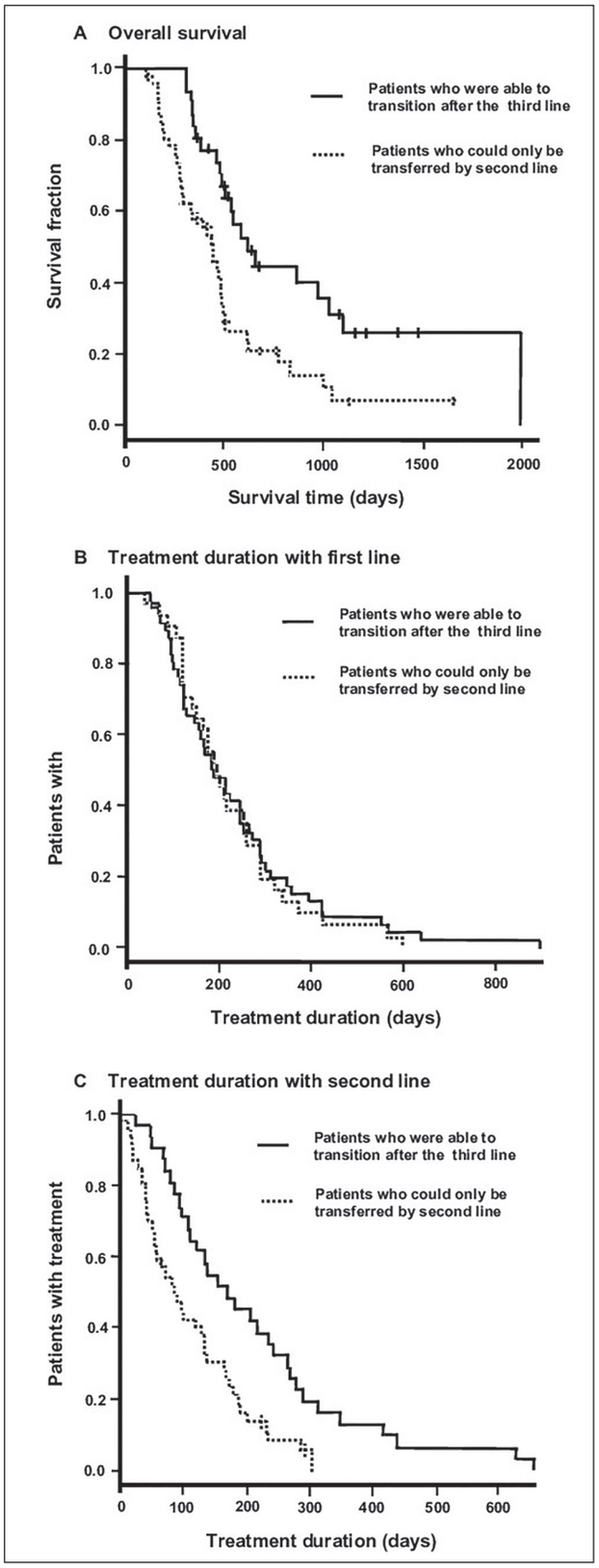

Fig. 1: Treatment duration and overall survival depending on the transferred treatment line. Kaplan-Meier curves of OS in patients who were able to transition after the third line and those who could only be transferred by second line (A) and treatment duration with first line in patients who were able to transition after third line and those who could only be transferred by second line (B), treatment duration with second-line treatment in patients who were able to transition after the third line and those who could only be transferred by second-line treatment (C). Solid lines indicate groups that were able to transition after the third-line treatment, and the dotted lines indicate groups that could only be transferred by second-line treatment. OS, Overall survival

independently and significantly associated with survival. Compared to the patients with no grade 1 or higher neutropenia, patients with grade 1 or higher neutropenia had a death hazard ratio of 0.455 (95% CI: 0.214–0.966; $p = 0.040$). Patients who received ≥ 5 chemotherapy regimens had a death hazard ratio of 0.569 (95% CI: 0.361–0.898; $p = 0.016$), which was lower than that of patients who received ≤ 4.

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

Factor	Hazard ratio	95% CI	P-value
Age, years			
>68	1.003	0.976-1.030	0.854
Gender			
Male	1.218	0.655-2.264	0.533
Height, cm			
<172	0.993	0.960-1.028	0.701
Weight, kg			
<64	0.992	0.968-1.016	0.517
Albumin, g/dL			
<3.3	1.065	0.867-1.307	0.549
Alanine aminotransferase, IU/L			
>17.0	1.004	0.986-1.022	0.635
Aspartate aminotransferase, IU/L			
>46.0	1.002	0.988-1.016	0.755
Total bilirubin, mg/dL			
>2.2	1.253	0.783-2.003	0.347
Serum creatinine, mg/dL			
>0.92	0.890	0.317-2.498	0.825
Disease status			
Advanced/Recurrent	1.158	0.672-1.996	0.597
Pretreatment neutrophil count, /μL			
<2,620	0.879	0.509-1.517	0.644
Grade 3 or higher neutropenia			
Yes	0.654	0.389-1.100	0.109
Grade 1 or higher neutropenia			
Yes	0.436	0.149-0.763	0.004*
Number of metastases			
>2	1.482	0.947-2.318	0.085
Number of anti-cancer drugs used			
≥5	0.528	0.343-0.813	0.003*

CI, confidence interval

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

Factor	Hazard ratio	95% CI	P-value
Grade 3 or higher neutropenia			
Yes	1.063	0.517-2.183	0.869
Grade 1 or higher neutropenia			
Yes	0.455	0.214-0.966	0.040*
Number of metastases			
>2	1.368	0.875-2.137	0.169
Number of anti-cancer drugs used			
≥5	0.569	0.361-0.898	0.016*
Pretreatment neutrophil count, /μL			
<2,620	0.859	0.497-1.483	0.585

CI, confidence interval

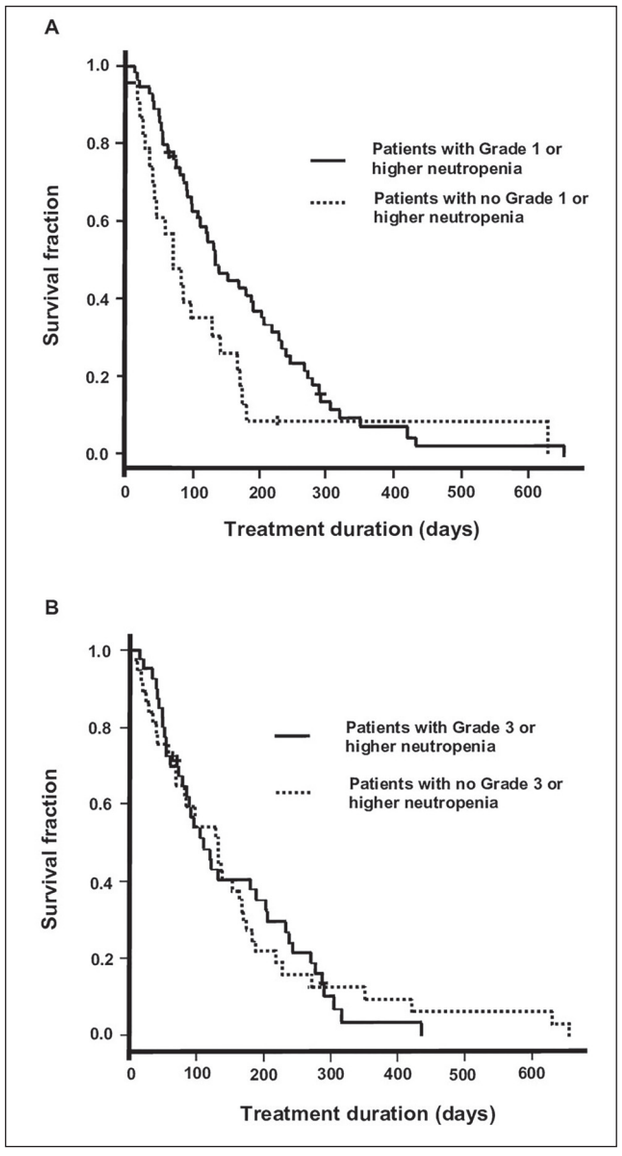

Fig. 2: Neutropenia and treatment duration of second line (paclitaxel plus ramucirumab therapy). Kaplan-Meier curves of treatment duration with second line in patients with grade 1 or higher neutropenia and in patients with no grade 1 or higher neutropenia (A) and treatment duration with second line in patients with grade 3 or higher neutropenia and in patients with no grade 3 or higher neutropenia (B). A: Solid lines indicate groups with grade 1 or higher neutropenia, and the dotted lines indicate groups with no grade 1 or higher neutropenia. B: Solid lines indicate groups with grade 3 or higher neutropenia, and the dotted lines indicate groups with no grade 3 or higher neutropenia.

2.3. Treatment duration and overall survival depending on the transferred treatment line

Kaplan-Meier survival curves according to the transferred treatment line in all patients are shown in Fig. 1. The median OS in patients who were able to transition after the third line (n = 31) and patients who could only be transferred by the second line (n = 46) were 627 days (95% CI, 487–1028 days) and 440 days (95% CI, 291–490 days), respectively (log-rank test, $p = 0.002$) (fig. 1A). The median treatment duration in first line in patients who were able to transition after the third line (n = 31) and patients who could only be transferred by the second line (n = 46) were 195 days (95% CI, 142–253 days) and 186 days (95% CI, 130–246 days), respectively (log-rank test, $p = 0.815$) (fig. 1B). The median treatment duration in second line in patients who were able to transition after the third line (n = 31) and those who could only be transferred by the second line (n = 46) were 170 days (95% CI, 105–242 days) and 85 days (95% CI, 55–133 days), respectively (log-rank test, $p = 0.002$) (Fig. 1C).

2.4. Degree of neutropenia and second-line treatment duration

Kaplan-Meier survival curves according to the degree of neutropenia in all the patients are shown in Fig. 2. The median treatment duration in second-line treatment in patients with grade 1 or higher neutropenia (n = 54) and in those with no grade 1 or higher neutropenia (n = 23) were 133 days (95% CI, 98–190 days) and 70 days (95% CI, 41–128 days), respectively (log-rank test, $p = 0.026$) (Fig. 2A). The median treatment duration in second-line treatment in patients with grade 3 or higher neutropenia (n = 40) and in those with no grade 3 or higher neutropenia (n = 37) were 111 days (95% CI, 79–190 days) and 133 days (95% CI, 70–168 days), respectively (log-rank test, $p = 0.957$) (Fig. 2B).

3. Discussion

The purpose of this study was to identify the index of OS prolongation in patients who were given PTX plus RAM as the second-line treatment for AGC. The OS was long in patients with neutropenia in the initial course of PTX plus RAM therapy and in cases when the number of anti-cancer drugs used was five or more. The fact that the number of anti-cancer drugs used was five or more means that the transition to the third line or later was possible. Severe neutropenia was observed when using PTX plus RAM was not related to OS, but patients with neutropenia had a longer treatment duration of PTX plus RAM therapy and a longer OS. Therefore, patients with initial neutropenia in PTX plus RAM therapy may benefit from this chemotherapy.

In this study, the hazard ratio to OS in patients receiving PTX plus RAM therapy was calculated. The OS is long in patients with neutropenia in the first course of PTX plus RAM therapy and when the number of anti-cancer drugs used is five or more. This confirms that it is desirable to consider a treatment strategy that uses up to six drugs, pyrimidine fluoride, platinum, taxane, IRI, RAM, and nivolumab, for AGC. In this study, we focused on neutropenia during the first course. This is because the onset of neutropenia of grade 3 or higher accounts for the majority (79.8%) in the first course (Kawasaki et al. 2019). In addition, if the treatment duration of PTX plus RAM therapy is long, the frequency of neutropenia may increase due to the increase in the number of courses. By observing neutropenia in the first course, it is possible to identify patients who are likely to benefit from anti-cancer drug treatment at an early stage.

Regarding the continuation of first- and second-line therapies, there was no difference in the continuation of treatment on the first line between patients who were able to shift to the third line or later and those who could not, and the difference in the effect of PTX plus RAM therapy on the second line affected the subsequent OS (figure 1). Therefore, it is of great significance to identify patients who are likely to benefit from PTX - RAM therapy on the second line. On the other hand, Kawasaki et al. (2019) reported that the presence or absence of treatment given after PTX plus RAM therapy was not a significant factor for OS. The cause of this difference is considered to be that the number of cases (n = 49) is limited and the detection power is insufficient.

Regarding the relationship between neutropenia and treatment continuation, severe neutropenia, that occurred with the use of PTX plus RAM therapy, was not related to OS, but patients with neutropenia (grade 1 or higher) had a longer treatment duration of PTX plus RAM therapy and a longer OS than patients without neutropenia (Fig. 2). In other words, the short duration of PTX plus RAM therapy means that the effect of PTX plus RAM therapy was low. The relationship between neutropenia and prognosis has also been reported in patients receiving gastric cancer (weekly paclitaxel therapy), leukaemia, and colorectal cancer chemotherapy (Shitara et al. 2010, 2009, 2011). Mild and severe neutropenia have been reported as important prognostic factors. Shitara et al. (2009) reported that neutropenia is a surrogate marker for appropriate antitumor doses of chemotherapeutic agents. The lack of neutropenia indicates that the biological effects of chemotherapy are near or weak. This may be because the dose given to individual patients

is too low (Shitara et al. 2010). On the other hand, Kawasaki et al. (2019) reported that the onset of severe neutropenia is involved in the prolongation of OS in the same regimen as in our study. In addition, in trifluridine/tipiracil combination tablet therapy for colorectal cancer patients, it has been clarified that patients with grade 3 or higher neutropenia (severe) have a long treatment duration and a good prognosis (Kimura et al. 2017). In the case of mild neutropenia, it was not different from absolute neutropenia (Kimura et al. 2017). In our study, the prolongation of OS was related to the presence or absence of neutropenia rather than severe neutropenia. It is speculated that the cause of this difference was the number of cases, and there was a difference in the proportions of severe and mild neutropenia.

The association between neutrophils and cancer metastasis has been reported. Neutrophils in

the tumour microenvironment have been shown to promote tumour growth and metastasis through several mechanisms (Mishalian et al. 2013; Dumitru et al. 2013; Moses et al. 2013; Tazzyman et al. 2013; Fridlender et al. 2012). This means that cancer cells utilise the normal function of neutrophils, which make up the largest proportion of white blood cells, to form metastatic tumours. This is because cancer cells induce neutrophils and release special traps (neutrophil extracellular traps (NETs)) (Erpenbeck et al. 2017; Snoderly 2019; Park et al. 2016). Neutrophils usually use NETs to capture and kill pathogens. On the other hand, cancer cells released from the primary tumour and migrated to distant tissues try to form a tumour (metastatic tumour) in the tissue. That is, it can be seen that patients with neutropenia suppress tumour growth due to the therapeutic effect.

The results of this study have the potential for enhanced clinical decision-making and improved patient outcomes. For example, when PTX plus RAM therapy is performed on the second line, patients who do not have neutropenia in the initial course may move to the third line early if treatment is postponed due to non-haematological toxicity. Alternatively, the patient can be instructed as having a poor prognosis from an early stage.

This study has some limitations. First, this study was not a standardised prospective test. Second, high pre-treatment neutrophil counts can contribute to a poor prognosis, and these patients may be less likely to experience neutropenia during treatment. However, multivariate analysis, including pre-treatment neutrophil counts, showed that neutropenia during chemotherapy was independently associated with prognosis. Finally, the medium sample size in this study may have been limited. Therefore, further well-designed research is needed to address these factors and validate the results. In conclusion, the purpose of PTX plus RAM therapy for AGC is to prolong OS. Therefore, it is important to identify patients who are likely to benefit from anticancer drug treatment to enhance clinical decision-making and patient outcomes.

4. Experimental

4.1. Patients and methods

Between January 2015 and September 2020, 82 patients who underwent second-line chemotherapy (PTX plus RAM) for AGC at Ogaki Municipal Hospital, Japan, were initially included in the study. Patients who completed treatment in the middle of one course and patients who were transferred to another hospital during treatment were excluded (n = 5). Thus, 77 patients were considered eligible for this study, OS and treatment duration of the first- and second-line therapies were analysed retrospectively. Patient characteristics were extracted from anonymized patient records. Patient characteristics, adverse events (neutropenia), and OS were analysed retrospectively using the data collected from electronic charts and pharmacy service records. The occurrence of neutropenia was evaluated in the first course of PTX plus RAM therapy. The grades of adverse events were evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0 (US Department of Health and Human Services 2017).

The study's retrospective protocol was approved by the Institutional Review Board of Ogaki Municipal Hospital, Ogaki, Japan (Ogaki, Japan; 20201224-4). The requirement for informed consent was waived by the ethics committee. With regard to patient consent, an opt-out option was presented in the clinical trial protocol and published on the website, in accordance with the principles of ethical guidelines on medical and health research on human subjects.

4.2. Statistical analysis

The primary outcome was OS, which was defined as the period from the date of treatment onset to the date of death from any cause. To determine factors associated with survival, univariate and multivariate analyses using the Cox proportional hazards model were performed, and hazard ratios and their 95% confidence intervals (95% CI) were calculated. Significant variables, as well as previously reported risk factors, were entered into a multivariate logistic regression model. Optimal cut-off values for the significant variables were determined based on receiver operating characteristic (ROC) curve analyses. The Kaplan-Meier log-rank test was used to compare OS and treatment duration. Differences were considered statistically significant at p-values <0.05. All analyses were performed using the 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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