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Risk factors for severe neutropenia induced by combination therapy of S-1 and cisplatin in patients with advanced/recurrent gastric cancer

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S-1 and cisplatin therapy (SP therapy) is widely used as the first-line of advanced/recurrent gastric cancer. However, severe neutropenia is often observed (40%) during this therapy. Therefore, the risk management of neutropenia is important. From September 2014 to April 2017, we investigated 76 patients who underwent SP therapy as primary treatment for advanced/recurrent gastric cancer at Ogaki Municipal Hospital. Risk factors for grade 3/4 neutropenia were examined by univariate and multivariate analyses. In SP therapy, 19 patients (25%) experienced grade 3/4 neutropenia. The results of multivariate analysis of factors with $p < 0.05$ in the univariate analysis indicated that less than 10.6 g/dL of the haemoglobin value before the course at the lowest neutrophil count (odds ratio: 7.900; 95% CI: 1.280–48.60; $p = 0.026$), more than six courses of the total course (odds ratio: 9.13; 95% CI: 2.13–39.1; $p = 0.003$), and less than 3140 m^2 neutrophil counts (odds ratio: 5.33; 95% CI: 1.47–19.3; $p = 0.011$) before chemotherapy were risk factors of grade 3/4 neutropenia. A low haemoglobin value before the course at the lowest neutrophil count was revealed as a risk factor causing severe neutropenia in SP therapy.

1. Introduction

Gastric cancer is the third leading cause of cancer-related mortality worldwide (Torre et al. 2015) and the second in Japan (Sobue et al. 2012). Since the 1980s, several therapy trials for advanced/recurrent gastric cancer have been performed. In Japan, S-1 was used in many clinical studies. S-1 (Taiho Pharmaceutical Company, Tokyo, Japan) is an oral anticancer drug that is a combination of tegafur, a prodrug of fluorouracil, 5-chloro-2,4-dihydropyrimidine, and potassium oxonate. Cisplatin (Rozencweig et al. 1977), an inorganic platinum chemotherapeutic drug, is widely used for lung, gastric, oesophageal, bladder, and head and neck cancer. The SPIRITS (S-1 plus cisplatin *vs* S-1 in RCT in the Treatment for Stomach cancer, Koizumi et al. 2008) trials for advanced gastric cancer reported that a combination of S-1 and cisplatin therapy (SP therapy) was superior to S-1 alone. SP therapy was superior in terms of median survival (13 months *vs* 11 months) and success rate (54% *vs* 31%) in the phase III study (Koizumi et al. 2008). Thus, SP therapy is the first-line chemotherapeutic in advanced/recurrent gastric cancer based on the SPIRITS study.

Recently, the combination of S-1 and oxaliplatin has been found to be as effective as the combination of S-1 and cisplatin in a phase III study (Yamada et al. 2015). However, to date, SP therapy is preferred in advanced/recurrent gastric cancer. In the SPIRITS study, neutropenia (40 %), anaemia (26 %), nausea (11 %), and fatigue (30 %) were observed as grade 3/4 adverse effects (Koizumi et al. 2008). The most common adverse effect necessitating a delay of treatment was bone marrow suppression (Lenz et al. 2007). In addition, neutropenia increases the risk of infection and could be fatal if antibiotic therapy is not initiated immediately. Therefore, the risk management of neutropenia is important (Chan et al. 2014; Kuderer et al. 2006; Chan et al. 2013). In this study, the factors influencing the severity of neutropenia in SP therapy as treatment for advanced/recurrent gastric cancer were evaluated.

2. Investigations and results

2.1. Patients' characteristics

Patient's characteristics are shown in the Table 1. A total of 76 patients were included in this study. In SP therapy, 19 patients (25 %) experienced grade 3/4 neutropenia. The number of total courses (5.3 and 3.4 courses, $p = 0.007$) and courses at the lowest neutrophil count (3.7 and 2.4 courses, $p = 0.030$) was significantly increased in patients who had grade 3/4 neutropenia compared with patients with grade 2 or less. In addition, the haemoglobin level before the course at the lowest neutrophil count was significantly decreased (9.4 and 10.2 g / dL, $p = 0.048$).

2.2. Univariate and multivariate analyses

The univariate and multivariate analyses of baseline and clinical characteristics as factors influencing the severity of neutropenia are shown in Table 2. The cut-off value was calculated *via* the ROC. In univariate analysis, neutrophil counts less than 3140 m^2 before chemotherapy ($p = 0.005$) and in more than six courses ($p = 0.002$), and a haemoglobin value less than 10.6 g/dL before the course at the lowest neutrophil count ($p = 0.028$) were significantly different. The results of multivariate analysis of factors with $p < 0.05$ in the univariate analysis indicated that less than 10.6 g/dL of the haemoglobin value before the course at the lowest neutrophil count (odds ratio: 7.900; 95% CI: 1.280–48.60; $p = 0.026$), more than six courses of the total course (odds ratio: 9.13; 95% CI: 2.13–39.1; $p = 0.003$), and less than 3140 m^2 neutrophil counts (odds ratio: 5.33; 95% CI: 1.47–19.3; $p = 0.011$) before chemotherapy were risk factors of grade 3/4 neutropenia.

2.3. Comparison of laboratory data and dose of S-1 and cisplatin

The numbers of patients who received one, two, three, four, and five courses of SP therapy were 76, 63, 47, 32, and 24, respectively. As shown in Table 3, the haemoglobin level ($p = 0.028$) and the cisplatin dose ($p = 0.046$) significantly decreased over several courses.

3. Discussion

The result of multivariate analysis indicated that the haemoglobin value before the course at the lowest neutrophil count ($p = 0.026$), neutrophil counts before chemotherapy ($p = 0.011$), and total course of SP therapy ($p = 0.003$) were risk factors of grade 3/4 neutropenia.

Table 1: Patients` characteristics

Parameter	Neutropenia		p value
	Grade 0-2 n = 57 Median (range)	Grade 3-4 n = 19 Median (range)	
Age, years	63 (39-78)	66 (41-75)	0.238[b)]
Gender (male/female)	38/19	11/8	0.583[a)]
ECOG PS (0/1/2)	45/9/2/1	16/3/0/0	1[a)]
Clinical stage (IV /IIIB/ IIIC)	52/2/3	15/2/2	0.395[a)]
Disease status			
Advanced	42	12	0.37[a)]
Recurrent	15	7	
Total courses of SP therapy	3.4 (1-10)	5.3 (1-10)	0.007*[b)]
Number of metastatic sites (0/1/2/3/4/5)	2/27/21/6/1	3/10/3/3/0	0.162[a)]
BSA, m^2	1.5 (1.15-1.93)	1.5 (1.26-1.8)	0.512[b)]
Before chemotherapy			
Serum creatinine, mg/dL	0.71 (0.34-1.21)	0.73 (0.35-1.22)	0.677[b)]
Ccr, mL/min	80.9 (43.5-124.3)	74 (34.1-114.8)	0.243[b)]
Haemoglobin, g/dL	11.1 (5.8-15.1)	10.9 (8.8-13.7)	0.687[b)]
Albumin, g/dL	3.8 (2.1-4.9)	3.7 (2.4-4.5)	0.792[b)]
Neutrophils, /mm^3	4856.5 (1680-14650)	3855.8 (1270-17440)	0.187[b)]
Cisplatin dose, mg/day	89.6 (43.2-115.8)	90.0 (66.7-120)	0.927[b)]
S-1 dose, mg/day	108.1 (80-120)	110.5 (100-120)	0.499[b)]
Before the course at the lowest neutrophil count			
Serum creatinine, mg/dL	0.71 (0.41-1.82)	0.75 (0.43-1.22)	0.498[b)]
Ccr, mL/min	79.7 (38.6-142.6)	69.7 (37.1-128.3)	0.08[b)]
Haemoglobin, g/dL	10.2 (6.1-14.4)	9.4 (7.8-11.1)	0.047*[b)]
Albumin, g/dL	3.8 (1.8-4.8)	3.7 (1.9-4.7)	0.557[b)]
The number of course	2.4 (1-10)	3.7 (1-9)	0.03*[b)]
Cisplatin dose, mg/day	86.5 (43.2-115.8)	84.9 (65.3-108)	0.682[b)]
S-1 dose, mg/day	106 (80-120)	102.1 (60-120)	0.335[b)]

a) Fishrs exact test
b) student`s t test
BSA, body surface area; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Ccr, creatinine clearance
*p<0.05

The total courses of SP therapy are recognised as risk factors for grade 3/4 neutropenia in advanced gastric cancer (Tanizawa et al. 2010). As such, a delayed recovery of the bone marrow cells during every course of chemotherapy should be considered. The relationship between neutrophil counts before chemotherapy and grade 3/4 neutropenia has been reported previously (Ikesue et al. 2015; Matsubara et al. 2009; Jenkins et al. 2009; Lyman et al. 2014). In this study, the haemoglobin value before the course at the lowest neutrophil count was clarified for the first time. The haemoglobin level gradually decreases with each course because the half-life of erythrocytes is approximately 120 days. Therefore, the total course of SP therapy can be possibly related to the decrease of haemoglobin value before the course at the lowest neutrophil count. However, as shown in Table 2, the results of multivariate analysis indicated that the haemoglobin value before the course at the lowest neutrophil count is an independent risk factor for grade 3/4 neutropenia.

This result is probably because haemoglobin reduction is not only caused by myelosuppression but also cisplatin, which reduces haemoglobin levels by suppressing erythropoietin production in the kidney (Jerome et al. 1999). As shown in Table 3, renal function can be preserved because cisplatin has been significantly reduced. In addition, forced diuresis through appropriate hydration and furosemide (Ries et al. 1986) and magnesium administration (Mizuno et al. 2016; Kidera et al. 2014) were performed to prevent renal function. When the cisplatin dose was not reduced accordingly, the deterioration of renal function was accelerated, and further reduction of haemoglobin resulted in a more severe neutropenia (Lyman et al. 2014).

In addition, as gastric cancer progresses, bleeding from the original disease is increased, which is hypothesised to decrease chemotherapy reactivity and PS to less than 10 g/dL of haemoglobin. Thus, we considered that deterioration of the original disease is related to haemoglobin reduction (Park et al. 2006). A low baseline haemoglobin value and neutrophil counts were significantly associated with the occurrence of grade 3/4 neutropenia in combination therapy of pemetrexed and carboplatin in non-small-cell lung cancer. In this study, a negative correlation was found between Hb levels and IL-6, a pro-inflammatory factor, which contributes to the worsening of neutropenia (Ikesue et al. 2015; Alexandre et al. 2003; Phippen et al. 2011; Maccio et al. 2005; Kuroda et al.2007). Haemoglobin decrease from the first cycle to the second cycle caused by CMF, AC, and AC-T therapy in ovarian cancer patients became FN or an indication for hospitalization (Hurria et al. 2005). Moreover, oxygen cannot be used efficiently in low haemoglobin levels, and the heart rate increases to compensate, thus stressing the heart. A cardiovascular disease is known as a risk factor for FN (Salar et al. 2012). We concluded that deterioration of cardiac function and original disease could be causes of grade 3/4 neutropenia.

Erythropoiesis-stimulating agents (Thomaidis et al. 2014) and transfusion therapy are used in many countries, mainly in Europe and the United States, to manage anaemia; however, in Japan, only transfusion is used. According to a questionnaire-based survey on chemotherapy-induced anemia (Tanaka et al. 2013), the use of erythrocyte preparations in gastric cancer causes no adverse effects. Even if the haemoglobin level is less than 6.9 g/dL, red

Table 2: Univariate and multivariate analyses

Parameter	Univariate analysis				Multivariate analysis		
	OR	95%CI	*P*-value	AUC ROC curves	OR	95% CI	*P*-value
Age≥65 years (n=45)	3.37	0.997-11.4	0.051	0.583			
Gender, male	0.688	0.237-1.99	0.49				
ECOG PS≥1 (n=15)	0.703	0.176-2.82	0.619	0.47			
Clinical stage, IIIB, IIIC (n=9)	2.77	0.66-11.6	0.163	0.56			
Disease status, recurrent (n=22)	1.63	0.542-4.92	0.383				
Total courses of SP therapy, ≥6 (n=16)	6.43	1.94-21.3	0.002*	0.657	9.13	2.13-39.1	0.003*
Number of metastatic sites, ≥3 (n=10)	1.34	0.309-5.8	0.696	0.43			
BSA≥1.63 m^2 (n=25)	1.26	0.426-3.75	0.673	0.457			
Before chemotherapy							
Ccr≥89.7 mL/min (n=23)	0.533	0.155-1.83	0.318	0.564			
Haemoglobin≥12.4 g/dL (n=22)	0.218	0.046-1.04	0.056	0.56			
Albumin≥4.5 g/dL (n=12)	0.553	0.11-2.78	0.472	0.528			
Neutrophils≥3140 /mm^3 (n=49)	4.8	1.59-14.5	0.005*	0.699	5.33	1.47-19.3	0.011*
Cisplatin dose≥77.4 mg (n=64)	4.3	0.517-35.8	0.177	0.501			
S-1 dose≥105 mg (n=41)	0.932	0.329-2.64	0.894	0.49			
Before the course at the lowst neutrophil count							
Ccr≥75.4 mL/min (n=39)	0.61	0.214-1.74	0.356	0.638			
Haemoglobin≥10.6 g/dL (n=25)	5.75	1.21-27.3	0.028*	0.652	7.9	1.28-48.6	0.026*
Albumin≥3.9 g/dL (n=43)	1.07	0.376-3.07	0.894	0.521			
The number of course≥2 (n=44)	2.52	0.801-7.930	0.114	0.637			
Cisplatin dose≥80.4 mg (n=47)	0.45	0.157-1.29	0.138	0.551			
S-1 dose>80 mg (n=64)	1	0.241-4.15	1	0.437			

OR, odds ratio; CI, confidence interval; ROC, receiver operating characteristic; AUC, area under the blood concentration-time curve AUC indicates the relevance of grade 3/4 neutropenia 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.
*p<0.05

Table 3: Comparison of laboratory data and dose of S-1 and cisplatin

Parameter	Before administration					
	1 course (n=76)	2 courses (n=63)	3 courses (n=47)	4 courses (n=32)	5 courses (n=24)	p-value
	Median (range)	Median (range)	Median (range)	Median (range)	Median (range)	
Ccr, mL/min	79.3 (34.1-124.3)	76.5 (32.1-140.2)	76.2 (41.1-130.6)	79.6 (38.0-140.2)	72.6 (35.2-102)	0.683
Albumin, g/dL	3.8 (2.1-4.9)	3.9 (2.3-4.7)	3.9 (2.4-4.8)	3.9 (2.1-4.9)	4.0 (3-4.8)	0.567
Haemoglobin, g/dL	11.1 (5.8-15.1)	11.0 (8-13.8)	10.4 (7.7-13.2)	10.2 (6.3-12.8)	10.3 (6.1-13.1)	0.028*
Cisplatin dose, mg	89.7 (43.2-115.8)	85.1 (43.2-115.8)	83.5 (43.2-115.8)	83.3 (43.2-108)	82.1 (63.8-108)	0.046**
S-1 dose, mg	108.7 (80-120)	104.1 (60-120)	101.7 (60-120)	102.5 (60-120)	104.2 (80-120)	0.083

*first course vs third course; p=0.024, first course vs forth course; p=0.018, first course vs fifth course; p=0.043, second course vs forth course; p=0.048
**first course vs third course; p=0.018, first course vs forth course; p=0.033, first course vs fifth course; p=0.023

blood cell transfusion has not been performed in some cases. Therefore, appropriate red blood cell transfusions also need to be taken into account. Maintaining the haemoglobin level at more than 10 g/dl helps improve PS and quality of life (QOL) in patients with gastric cancer, but even if it is 12 g/dl or higher, PS and QOL, including overall survival and progression-free survival, will not change. Thus, we believe that increasing the haemoglobin level to more than 12 g/dl is unnecessary (Park et al. 2008).

Considering the above results, monitoring the haemoglobin value before starting each course of SP therapy and considering the start time of chemotherapy is necessary. In some cases, red blood cell transfusion is one method to maintain normal haemoglobin level.

This study has some limitations. First, the number of patients who had grade 3/4 neutropenia was not high enough for a result that can be applied to the general population. Second, because this is a retrospective study, the possibility that toxicity, such as nausea, is related to neutropenia is not sufficiently considered. Further studies on whether grade 3/4 neutropenia can be inhibited by maintaining the haemoglobin level above 10.6 g/dL are needed.

In conclusion, a low haemoglobin value before the course at the lowest neutrophil count was revealed as a risk factor causing severe neutropenia in SP therapy.

4. Experimental

4.1. Subjects and methods

From September 2014 to April 2017, we investigated 82 patients who underwent SP therapy as primary treatment for advanced/recurrent gastric cancer at Ogaki Municipal Hospital. One patient who had SP therapy as preoperative chemotherapy, two patients whose neutrophil count was not evaluated before administration, two patients whose neutrophil count was note evaluated after administration, and one patient who had SP therapy with radiation therapy were excluded. Finally, 76 patients were examined retrospectively using electronic medical records (Actis version, Toshiba, Tokyo, Japan). The patients were divided into two groups according to grade 3/4 neutropenia (n=19) and grade 2 or less neutropenia (n=57). Age, gender, Eastern Cooperative Oncology Group Performance Status (ECOG PS), clinical stage, advanced or recurrent disease, total

courses of SP therapy, number of metastatic sites, body surface area (BSA), dose of S-1 and cisplatin, and laboratory data before chemotherapy and before course at the lowest neutrophil count were compared between the two groups. The laboratory data included the levels of serum albumin, serum creatinine, neutrophil count, and haemoglobin level. Creatinine clearance (Ccr) was calculated using the Cockcroft-Gault equation. Laboratory values of albumin, Ccr, and haemoglobin before chemotherapy and dose of S-1 and cisplatin in each patient were collected from courses one to five for comparison.
The lowest neutrophil count was the lowest value until the next course or the lowest value within one month after SP therapy was terminated. The severity of neutropenia was classified according to the Common Terminology Criteria for Adverse Events, version 4.0. Granulocyte-colony stimulating factor (G-CSF) was not used during treatment.
SP therapy was given as continuous oral administration of S-1 twice a day for 21 consecutive days, withdrawal for 14 days, and intravenous administration of cisplatin on day 8.

4.2. Statistical analysis

Differences in continuous data were compared using the student`s t test, and differences in categorical data were compared using Fisher's exact test. Thereafter, multivariate logistic regression analysis was performed using factors with $p < 0.05$ in univariate analysis. To separate patients into two groups in the univariate analysis, the area under receiver operator characteristic (ROC) curves was calculated to estimate the sensitivity, specificity, accuracy, and cut-off values for each factor. To compare the data for each course (Table 3), Fisher's PLSD was used. In all statistical analyses, $p<0.05$ was considered to indicate significance. All statistical analyses were performed with the commercial software EZR. (Saitama Medical Center, Jichi Medicine University,
http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html),
which is a graphical user interface for R (the R Foundation for Statistical Computing, version 2.13.0).

4.3. Ethical considerations

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

Conflicts of interest: None of the authors have a conflict of interest to declare.

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