Retrospective Study on Occurrence of Myelosuppression in S-1 plus Cisplatin Combination Therapy for Treatment of Advanced Gastric Cancer

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S-1 + cisplatin (CDDP) combination therapy is recognized as a standard regimen for the treatment of gastric cancer. Though myelosuppression often occurs afterwards, a detailed investigation on this had not been conducted up till now. We conducted a retrospective study on myelosuppression following S-1 + CDDP combination therapy in patients receiving such therapy for advanced gastric cancer at Gifu Prefectural General Medical Center from June 2006 to April 2008 based on electronic records

We conducted the investigation on 119 courses of therapy in 36 patients, consisting of 22 men (70 courses) and 14 women (49 courses). The median age was 64 years (range, 34 - 82 years). The incidences of notable adverse events above grade 3 were : neutropenia (5.0%), thrombocytopenia (3.3%), and anemia (1.6%). Neutropenia occurred more frequently in female patients ($p = 0.0031$), those over 70 years old ($p = 0.0191$) and those having more than two courses ($p = 0.036$), and these findings were significant. The minimum number of neutrophils was observed mostly from day 20 ? day 29, but occurred from day 30 - day 39 in about 23% of the patients. It is therefore necessary to conduct blood tests from day 20 ? day 29 in S-1 + CDDP combination therapy.

Key words S-1 plus cisplatin combination therapy, myelosuppression, neutropenia, advanced gastric cancer.

Introduction

From 1980s, many trials of cancer chemotherapy for inoperable advanced gastric cancer have been suggested. However, good results were not provided, and the standard therapy of advanced gastric cancer was not readily established. S 1(Taiho Pharmaceutical Company, Tokyo, Japan) is an oral anticancer drug that combines tegafur, a prodrug of fluorouracil, with 5-chloro-2, 4-dihydropyrimidine(CDHP) and potassium oxonate. Koizumi et al.⁽¹⁾, reporting the results of SPIRITS trial in 2008, have shown that the treatment results for advanced gastric cancer was superior in combination therapy of TS-1[®](S 1) + cisplatin (CDDP) than with S 1 alone. Therefore S 1 + CDDP combination therapy has been recognized as one of the standard therapies for advanced gastric cancer.

Koizumi et al.⁽¹⁾ has shown that the frequency of adverse event with myelosuppression above grade 3 that occurred in this treatment amounted to neutropenia(40%), thrombocytopenia(49%) and anemia(68%). The detailed investigation that which time a myelosuppression occur in is not per-

formed whether the characteristic of what kind of patient has an influence on the expression of the myelosuppression. Therefore the treated blood test is performed by the policy of the chief physician individual on various days. However, there were sometimes the cases that it seems that it caused a serious myelosuppression because enforcement day and the number of times of the blood test are inappropriate. We carried out retrospective investigation on patients who underwent S 1 + CDDP combination therapy, by examining the characteristics of patients and correlation with the myelosuppression, and the time frame on the development of myelosuppression.

Patients and Methods

Advanced gastric cancer patients who underwent S 1 + CDDP combination therapy in Gifu Prefectural General Medical Center from June, 2006 to April, 2008 were studied.

The eligibility criteria were as follows : age 20 years ; adequate organ function, defined as haemoglobin > 8.0 g/dL, leucocyte count > 4,000 / μ L, platelet count >

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10,000/ μ L, serum bilirubin <1.5 mg/dL, serum transaminase(aspartate aminotransferase and alanine aminotransferase) <100 U/L, alkaline phosphatase(ALP) <twice the upper limit of normal range(ULN), serum creatinine level less than the ULN.

In patients assigned to receive S 1 + CDDP, S 1 was given orally twice daily for the first 3 weeks of a 5-week cycle. Administration of dose of S 1 was calculated according to the patient's body surface area as follows: 40 mg (<1.25 m²), 50 mg(1.25–1.5 m²), 60 mg(>1.5 m²). CDDP was given as an intravenous infusion of 60 mg/m² on day 8 of each cycle. The treatment less than treated blood test three times in a course was excluded. We investigated the gender of the patient, age, body surface, dose, presence of the previous treatment, performance status (the following PS) of ECOG(Eastern Cooperative Oncology Group), a clinical stage of disease, purpose of the treatment and the number of treatment courses from the electronic chart record. In addition, we investigated the neutrophil, platelets and hemoglobin of treatment before and after. Neutropenia, thrombocytopenia, hemoglobin decrease symptom that developed after the commencement of treatment regimen distinguished disease severity by CTCAE(Common Terminology Criteria for Adverse Events) ver.3.0. We judged disease severity grade 1 to be myelosuppression. The patient data and the correlation with the myelosuppression was examined by a logistic multivariate analysis of variance (StatView ver.5.0).

Results

The treatment of 119 courses was carried out in 36 patients, consisting of 22 men(70 courses) and 14 women(49 courses). The median age was 64 years (range, 34–82 years). Patients details and treatment parameters are shown in **Table 1**. Appearance rate of neutropenia, thrombocytopenia, anemia are shown in **Table 2**. Overall the incidence of neutropenia were 53.8%(above grade 1) and 5.0%(above grade 3). Likewise thrombocytopenia were 10.0%(above grade 1) and 3.3%(above grade 3). The anemia were 40.3%(above grade 1) and 1.6%(above grade 3).

The expression of the myelosuppression and correlative official approval with various kinds of characteristics by a logistic multivariate analysis of variance, show that women ($p=0.0031$), over 70 years($p=0.0191$) and more than two course($p=0.036$) has significantly higher incidence of neutropenia(**Fig. 1**). The dose of cisplatin was regulated from 83.9% to 107.9% by the full dose ratio. It seems that though the dose of cisplatin influenced the appearance of neutropenia, but it failed to have a difference between in each cohort sorted by gender (97.2% vs 99.1%), age (98.3% vs 99.0%), treatment course (97.0% vs 96.1%). Thrombocytopenia incidence increased with patients more than PS 1($p=0.039$) significantly (**Fig. 2**). As for the anemic expression, meaningful correlation was accepted with neither characteristics (**Fig. 3**).

We divided a treatment period into 10 day intervals (day

Table 1 . Patients and Treatment Parameters

Parameters	Number of patients	Number of treatment
Gender		
Men	22	70
Women	14	49
Age		
70<	26	83
70 $\geq$	10	36
Disease stage		
II	1	2
III	2	8
IV	31	99
undetermined	2	10
Prior chemotherapy		
Yes	5	26
No	31	93
Adjuvant chemotherapy		
Yes	9	25
No	27	94
Performance status		
0	30	96
1	5	21
2	1	2
Treatment cycles		
1~2	7	61
3~4	11	29
5~6	11	18
7~8	3	7
9 $\geq$	4	4

0 day 9, day 10 day 19, day 20 day 29, day 30 day 39) and show the enforcement rate of the blood test of each period in **Table 3**. It is evident that the distribution on the day when minimum of the neutrophil of the whole treatment period was observed in 42 courses that performed a blood test in all periods in total in **Fig. 4**. Neutropenia appeared to 73.8% in 42 courses. The minimal distribution range was spread over day 20–day 29 and occupied 28.6%. We did not investigate the distribution of the minimum observation day for thrombocytopenia, because those expression was marginal during 11 courses. In addition, anemia 48 developed in the course, but did not investigate the distribution on minimum observation day because recovery was slow, and a low value continued it for a long term.

Discussion

As of now, the phase III trial of the various chemotherapy regimens intended for unresectable advanced gastric cancer patient have been reported²⁻⁷⁾. However, for many of those regimens, good results on the curative effect such as survival rates were not provided in comparison with the 5-FU independent treatment. Therefore establishing a standard chemotherapy of gastric cancer is overdue. Hyodo et al.⁸⁾ has reported a success rate 44–54% in phase I trial of the S 1 independent dosage for the advanced gastric cancer patient in 2003. Furthermore, according to Koizumi et al.¹⁾ the S 1 +

Table 2 . Incidence of Haematological Toxicity

Parameters	grade1	grade2	grade3	grade4
neutropenia	22 (18.5%)	36 (30.3%)	5 (4.2%)	1 (0.8%)
thrombocytopenia	7 (5.9%)	1 (0.8%)	3 (2.5%)	1 (0.8%)
anacmia	44 (37.0%)	2 (1.7%)	1 (0.8%)	1 (0.8%)

Fig 1 . Odds ratios for neutropenia and 95% CIs

It is shown odds ratio and 95% confidence interval in the right side, in the p value of each characteristics in the left. As the condition that a neutropenia occurred frequently significantly, women patient ($p = 0.0031$), over 70 years old ($p = 0.0191$), more than two course ($p = 0.036$), was found.

Fig 2 . Odds ratios for thrombocytopenia and 95% CIs

It is shown odds ratio and 95% confidence interval in the right side, in the p value of each characteristics in the left. Thrombocytopenia increased with patients more than PS 1 ($p = 0.039$) significantly.

Fig 3 . Odds ratios for anemia and 95% CIs
It is shown odds ratio and 95% confidence interval in the right side, in the p value of each characteristics in the left. Meaningful correlation was accepted with neither characteristics.

Table 3 . Blood test enforcement rate of every treatment day

10 days intervals	n (%)
d0–d9	113(95.0)
d10–d19	81(68.1)
d20–d29	79(66.4)
d30–d39	83(69.7)

CDDP combination therapy could be superior in comparison to S 1 alone for the duration of survival median (13 months vs 11 months) and success rate (54% vs 31%) in a phase III trial for the unresectable gastric cancer patient. As a result, the S 1 + CDDP combination therapy has attracted attention as promising a standard first-line treatment for the advanced gastric cancer.

For S 1 + CDDP combination therapy, some regimens⁹⁻¹³⁾ on how to combine S 1 and the dosage days of CDDP are available. However, we conducted an investigation into Koizumi et al. s¹⁾ regimen. In this regimen, patients receive a large quantity of hydration at the time of the CDDP dosage of the 8 th day. Therefore they have to be hospitalized for several days in this time, but become the treatment in being at home on a day except it. And the chief physician pressed a patient for consultation on an appropriate day, and it is necessary to monitor the myelosuppression. FOLFOX

and FOLFIRI, standard chemotherapy of colon cancer, have a short period of one course with 14 days, and it is thought that the day before the next treatment is near in the time of nadir after the treatment in the last time, and continuation of rational treatment is enabled. On the other hand, nadir of the S 1 + CDDP combination therapy is not clear. Nadir of the S 1 independent treatment was reported as 22 days¹⁴⁾, and for CDDP as 10 14 days¹⁵⁾. Because the S 1 + CDDP combination therapy needs a long treatment periods, it may be over nadir on a treatment start day of next course. Therefore we investigated the rational setting time of the blood test day.

Other than phase II¹⁶⁾, phase III¹⁾ trials of Koizumi et al. myelosuppression at the time on the S 1 + CDDP combination therapy has been reported by Heinz et al.⁷⁾, and lwase et al.¹⁷⁾. The incidence of myelosuppression above grade 3 was the numerical value that our findings was lower than them of the phase III trial of Koizumi et al.¹⁾ as shown earlier.

It may be inappropriate to compare findings of Koizumi et al.¹⁾ to our results. This is because they had investigated the incidence of myelosuppression in a patient continued until one of the following outcomes occurred : progressive disease or unacceptable toxicity or withdrawal of consent by them or termination of treatment. But we investigated these according to a treatment course. Therefore, naturally it seems that the numerical value that we obtained is smaller. The minimum of the number of the neutrophil was observed in day 20 day 29(28.6%), and subsequently day 30 day 39 (23.8%), as shown in Fig. 4.

In their phase II trial, Koizumi et al¹⁶⁾ reported in that the median number of days at which grade 3 neutropenia occurred was 29 days at level 1(CDDP : 60 mg/m²), and the

Fig 4 . Distribution of the observation day of the neutropenia

We divided a treatment period into 10 days intervals (day 0 day 9, day 10 day 19, day 20 day 29, day 30 day 39). And it is shown the distribution on the day when minimum of the neutrophil of the whole treatment period was observed in 42 courses that performed a blood test in all periods in total. It was distributed most from day 20 to day 29.

median neutrophil nadir was on day 25 at level 2(CDDP : 70 mg/m²). Our findings were in agreement to these results. And neutropenia was seen in 50% of all treatment when we added up day 20 day 29 and day 30 day 39. The blood test enforcement rate of these periods is not high with 66.4%, 69.7% as shown in **Table 3**. We infer that patients should take a blood test several times in these periods for the purpose of the early detection of neutropenia.

The neutropenia incidence was high in patients over 70 years, women patients, after the second treatment, as noted in the result. It is necessary for a doctor and the pharmacist to be careful of the expression of the myelosuppression in particular at the time of the treatment of these patients. Sloan et al.⁽¹⁸⁾ have reported that the side effect incidence of the anticancer agent of the women patient is significantly higher than a men patient. They reported significantly higher incidence of side effects such as leukopenia, stomatitis, alopecia in women patients undergoing 5-FU + leucovorin treatment to colon cancer. However, they reported no difference in the success rate of the treatment between men and women, without identifying the specific reason.

In conclusion, S 1 + CDDP combination therapy that includes S 1 a fluorouracil derivative, results in higher expression of neutropenia in women patients. This regimen supports the findings of Sloan et al⁽¹⁸⁾. It will be necessary to study more details in future to elucidate why such a difference is seen between sexes.

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