Prediction of Severe Cisplatin-Induced Neutropenia Using Serum Albumin Concentration: A Retrospective Study

Yusuke Nakazawa (✉ y_nakazawa@jikei.ac.jp)

The Jikei University Hospital <https://orcid.org/0000-0001-9817-2684>

Akira Kageyama

The Jikei University Hospital

Masaki Kitamura

The Jikei University Hospital

Norio Mitsumori

Jikei University School of Medicine: Tokyo Jikeikai Ika Daigaku

Takashi Kawakubo

The Jikei University Hospital

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Abstract

Background: Hypoalbuminemia may occur in patients with gastric cancer because of reduced food intake and gastric dysfunction. Cisplatin that is used in the treatment of gastric cancer not only has gastrointestinal side effects but also has a high serum protein-bound fraction, which causes alteration in pharmacokinetics, especially reduction of serum albumin concentration that may increase the risk of cisplatin-induced neutropenia. Hence, alteration of serum albumin concentration poses a major safety issue during anticancer therapy. We examined whether fluctuations in serum albumin concentration is a risk factor for predicting the development of severe neutropenia.

Methods: This retrospective study included patients with gastric cancer undergoing cisplatin plus S-1 combination therapy to analyze their serum albumin concentration and the frequency of grade 3–4 neutropenia. We then investigated the relationship between the serum albumin concentration before cisplatin administration in the treatment course during which the neutrophil count reached nadir and the neutrophil count fluctuation after cisplatin administration.

Results: Grades 3–4 and 0–2 neutropenia developed in 24 and 48 patients, with a mean serum albumin concentration of 3.60 ± 0.54 and 3.77 ± 0.51 g/dL, respectively, before chemotherapy ($P = 0.23$). During chemotherapy when the neutrophil count reached nadir, the serum albumin concentration levels before cisplatin administration were 3.39 ± 0.60 and 3.85 ± 0.59 g/dL, respectively; the grade 3–4 neutropenia group had a significantly lower concentration of serum albumin than the grade 0–2 neutropenia group ($P = 0.006$). Lower serum albumin concentrations before cisplatin administration were significantly correlated with a decrease in neutrophil count after cisplatin administration ($r = 0.463$, $P < 0.001$). According to the receiver operating characteristic curve analysis, patients with serum albumin concentrations below 3.25 g/dL before cisplatin administration exhibited a significantly higher incidence of grade 3–4 neutropenia (odds ratio: 4.33).

Conclusions: The risk of cisplatin-induced neutropenia is significantly high in patients with hypoalbuminemia. Thus, serum albumin concentration should be evaluated before cisplatin administration to anticipate the development of severe neutropenia.

Background

Serum albumin is a typical marker of nutritional status. A decrease in albumin synthesis caused by reduced food intake and gastric dysfunction can lead to hypoalbuminemia. Patients with gastric cancer may be susceptible to hypoalbuminemia, not only because of organic disease but also because of gastrointestinal side effect induced by anticancer drugs. The 2018 Japanese gastric cancer guidelines (version 5) recommends cisplatin plus S-1 combination therapy as the first-line treatment for advanced/recurrent or unresectable gastric cancer; the recommendation is based on the trial results of SPIRITS [1] and JCOG 9912 [2]. Cisplatin is a therapeutic anticancer drug with a high emetic risk, commonly causing poor appetite after administration. It also exhibits a high serum protein-bound

fraction (> 90%) [3, 4]. Therefore, patients with decreased serum albumin concentration receiving cisplatin are highly prone to cisplatin-induced side effects, particularly hematological toxicity caused by altered pharmacokinetics. Among hematological toxicities, severe neutropenia is a serious condition that has been frequently observed and it may progress to febrile neutropenia. Altered serum albumin concentration can be a major safety concern during anticancer therapy. However, this concentration is not currently recognized as a reference for optimizing chemotherapy. Clarifying this potential association may facilitate appropriate chemotherapy; hence, this study aimed to examine whether fluctuation in serum albumin concentrations is a risk factor for predicting the development of severe neutropenia induced by cisplatin plus S-1 therapy.

Methods

Study design

Conducted at Jikei University Hospital in Tokyo, Japan, this retrospective observational study investigated the association between serum albumin concentration and the frequency of grade 3–4 neutropenia in patients with gastric cancer undergoing cisplatin plus S-1 combination therapy.

Patients and methods

This study examined the data of patients with advanced/recurrent or unresectable gastric cancer who received cisplatin plus S-1 combination therapy between March 2012 and March 2019. In accordance with the 2018 Japanese gastric cancer guidelines (version 5), these patients received 60 mg/m² concentration of cisplatin intravenously on day 8 plus 80 mg/m² concentration of S-1 orally on days 1–14 in a 21-day cycle every 3 weeks. Patient data were retrospectively retrieved from the electronic medical records. According to the nadir of the neutrophil count during cisplatin plus S-1 combination therapy, the patients were categorized into grade 3–4 neutropenia and grade 0–2 neutropenia groups. Patient characteristics before the start of chemotherapy between the two study groups were then compared. Clinical data included sex, age, body weight, body surface area, body mass index, surgery history, liver metastasis, lymph node metastasis, peritoneal metastasis, laboratory data, and cisplatin and S-1 treatment intensity. Furthermore, we compared the laboratory data between the two groups; these laboratory data were specifically those obtained before cisplatin administration during the treatment course when the neutrophil count reached nadir. We also investigated the correlation between the serum albumin concentration before cisplatin administration as mentioned above and the fluctuation of the neutrophil count after cisplatin administration. The fluctuation in the neutrophil count was compared using the difference in the logarithm of each value. The optimal cutoff value, which was the limit value of serum albumin concentration anticipated to develop grade 3–4 neutropenia, was calculated by receiver operating characteristic (ROC) curve analysis. The severity of neutrophil count decrease (neutropenia) was graded according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE ver. 5.0, Japanese translation JCOG version). A neutrophil count of <1,000/μL indicates grade 3 neutropenia.

Informed consent

This study protocol conformed to the Declaration of Helsinki and was approved by the Ethics Committee of the Jikei University [No. 30-294 (9315)]. This retrospective observational study was conducted using the opt-out method to post its purpose in the Jikei University School of Medicine. Informed consents were not required for this study because the clinical data of each patient who agreed to treatment by a written consent were kept anonymous during the analysis. For full disclosure, the study details are mentioned in an opt-out document in the Jikei University School of Medicine.

Statistical analysis

Continuous and categorical variables were statistically analyzed by Mann–Whitney’s *U* test and chi-square test, respectively. The clinical data of each patient were compared using the Wilcoxon signed-rank test. Furthermore, the correlation between albumin concentration and neutrophil count fluctuation was examined using the Spearman rank correlation coefficient. All statistical data were analyzed using the SPSS® version 21. The significance level of the test was set at 0.05.

Results

A total of 72 patients underwent cisplatin plus S-1 combination therapy. According to the nadir of their neutrophil count, 24 (33%) patients developed grade 3–4 neutropenia (20 with grade 3 and 4 with grade 4), whereas 48 (67%) developed grade 0–2 neutropenia (25 with grade 0, 11 with grade 1, and 12 with grade 2). We excluded those with albumin preparation. Table 1 shows the patient characteristics before chemotherapy. All variables between the two groups were not significantly different. The mean serum albumin concentration levels in the grade 3–4 neutropenia and grade 0–2 neutropenia groups were 3.60 ± 0.54 and 3.77 ± 0.51 g/dL, and 71% (17/24) and 71% (34/48) of them had hypoalbuminemia (<4.1 g/dL by CTCAE version 5.0 Japanese translation JCOG version), respectively.

Table 1 Patient characteristics before treatment

	Neutropenia		<i>P</i> value
	Grade 3–4	Grade 0–2	
Number of patients (male/female)	24 (18/6)	48 (37/11)	1.00 ^{a)}
Median of age	70 (39–84)	68 (33–87)	0.49 ^{b)}
Body weight (kg)	54.4 ± 9.0	52.5 ± 9.9	0.40 ^{b)}
Body surface area (m ²)	1.593 ± 0.154	1.555 ± 0.157	0.25 ^{b)}
Laboratory value			
AST (U/L)	26.5 ± 14.9	22.7 ± 12.4	0.22 ^{b)}
ALT (U/L)	24.2 ± 12.9	20.8 ± 15.8	0.09 ^{b)}
Total bilirubin (mg/dL)	0.78 ± 0.43	0.65 ± 0.27	0.16 ^{b)}
Total Protein (g/dL)	6.48 ± 0.50	6.65 ± 0.55	0.19 ^{b)}
Serum albumin (g/dL)	3.60 ± 0.54	3.77 ± 0.51	0.23 ^{b)}
Hypoalbuminemia (< 4.1 g/dL)	17 (71%)	34 (71%)	1.00 ^{a)}
Urea nitrogen (mg/dL)	12.7 ± 4.5	13.7 ± 3.7	0.35 ^{b)}
Serum creatinine (mg/dL)	0.71 ± 0.18	0.76 ± 0.15	0.28 ^{b)}
CRP (mg/dL)	0.57 ± 0.74	0.70 ± 1.19	0.91 ^{b)}
WBC (/μL)	5346 ± 1771	6240 ± 2355	0.07 ^{b)}
Neutrophil count (/μL)	3408 ± 1823	4215 ± 2250	0.05 ^{b)}
Hemoglobin (g/dL)	11.8 ± 2.0	11.6 ± 2.2	0.99 ^{b)}
Platelet (*10 ⁴ /μL)	25.7 ± 9.6	28.6 ± 8.6	0.07 ^{b)}
Dose intensity			
Cisplatin (%)	94.4 ± 7.9	93.4 ± 10.1	0.86 ^{b)}
S-1 (%)	95.8 ± 7.2	94.7 ± 9.2	0.74 ^{b)}

AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein; WBC, white blood cell.

a) Chi-square test, b) Mann–Whitney *U* test.

Patients in the grade 3–4 neutropenia and grade 0–2 neutropenia groups reached the nadir of neutrophil count after 3.2 ± 2.3 and 3.2 ± 2.6 courses ($P = 0.83$), and the mean neutrophil count was $696 \pm 188/\mu\text{L}$ and $2283 \pm 1074/\mu\text{L}$ ($P < 0.001$), respectively. Table 2 shows the laboratory data obtained before cisplatin administration during chemotherapy when the neutrophil count reached nadir. In the grade 3–4 neutropenia and grade 0–2 neutropenia groups, the mean total protein level was 6.13 ± 0.66 and 6.62 ± 0.67 g/dL, and the mean serum albumin concentration was 3.39 ± 0.60 and 3.85 ± 0.59 g/dL, respectively; both values in the grade 3–4 neutropenia group were significantly lower than those in the grade 0–2 neutropenia group (total protein: $P = 0.009$, serum albumin concentration: $P = 0.006$, Table 2).

Table 2 Outcome before cisplatin administration in the treatment course during which the neutrophil count reached nadir

	Neutropenia		
	Grade 3–4 (n = 24)	Grade 0–2 (n = 48)	P value
Laboratory value			
AST (U/L)	20.2 ± 7.0	23.2 ± 14.3	1.00
ALT (U/L)	16.6 ± 7.3	18.8 ± 15.7	0.51
Total bilirubin (mg/dL)	0.78 ± 0.41	0.66 ± 0.26	0.24
Total Protein (g/dL)	6.13 ± 0.66	6.62 ± 0.67	0.009**
Serum albumin (g/dL)	3.39 ± 0.60	3.85 ± 0.59	0.006**
Urea nitrogen (mg/dL)	13.3 ± 4.8	15.2 ± 4.0	0.12
Serum creatinine (mg/dL)	0.74 ± 0.16	0.81 ± 0.15	0.09
CRP (mg/dL)	0.65 ± 1.29	0.52 ± 1.07	0.45
WBC (/ μL)	5179 ± 2614	5802 ± 2581	0.14
Neutrophil count (/ μL)	3413 ± 2615	3804 ± 2403	0.23
Hemoglobin (g/dL)	11.0 ± 1.8	11.3 ± 1.7	0.40
Platelet ($*10^4/\mu\text{L}$)	21.6 ± 7.4	23.8 ± 9.3	0.35

AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein; WBC, white blood cell.

** $P < 0.01$ Mann–Whitney U test

In patients with grade 3–4 neutropenia from before the treatment to before cisplatin administration in the treatment course during which the neutrophil count reached nadir, the mean total protein level was significantly decreased from 6.48 ± 0.50 g/dL to 6.13 ± 0.66 g/dL ($P = 0.002$; Table 3). Their mean serum albumin concentration also significantly decreased from 3.60 ± 0.54 g/dL to 3.39 ± 0.60 g/dL ($P = 0.028$). Conversely, the total protein and serum albumin concentration levels in the grade 0–2 neutropenia group did not significantly decrease. Furthermore, the logarithmic difference of the fluctuation of total protein was -0.025 ± 0.035 and -0.003 ± 0.035 , while the fluctuation of serum albumin concentration was -0.030 ± 0.058 and 0.008 ± 0.035 , in grade 3–4 and grade 0–2 neutropenia groups, respectively; the fluctuations in the former group were significantly less when compared with the latter group (total protein: $P = 0.005$, serum albumin concentration: $P = 0.009$; Table 3).

Table 3 Fluctuation of total protein and serum albumin concentration

	Neutropenia	Before treatment	Before cisplatin administration	<i>P</i> value	Fluctuation	<i>P</i> value
Total Protein (g/dL)	Grade 3–4	6.48 ± 0.50	6.13 ± 0.66	0.002^{**} a)	-0.025 ± 0.035	0.005^{**} b)
	Grade 0–2	6.65 ± 0.55	6.62 ± 0.67	$0.96^a)$	-0.003 ± 0.035	
Serum albumin (g/dL)	Grade 3–4	3.60 ± 0.54	3.39 ± 0.60	0.028^* a)	-0.030 ± 0.058	0.009^{**} b)
	Grade 0–2	3.77 ± 0.51	3.85 ± 0.59	$0.10^a)$	0.008 ± 0.035	

** $P < 0.01$ * $P < 0.05$; a) Wilcoxon signed-rank test, b) Mann–Whitney *U* test

Figure 1 illustrates the correlation between the serum albumin concentration before cisplatin administration in the treatment course during which the neutrophil count reached nadir and the neutrophil count fluctuation after cisplatin administration. Lower serum albumin concentrations before cisplatin administration were significantly correlated with a decrease in neutrophil count after cisplatin administration ($r = 0.463$, $P < 0.001$).

According to the ROC curve analysis, a cutoff serum albumin concentration of 3.25 g/dL before cisplatin administration in the treatment course during which the neutrophil count reached nadir was associated with grade 3–4 neutropenia (area under the curve [AUC]: 0.698, sensitivity: 81.3%, specificity: 50.0%). Out of 24 patients with serum albumin concentration below the cutoff value of 3.25 g/dL before cisplatin administration, 12 developed grade 3–4 neutropenia (odds ratio for grade 3–4 neutropenia: 4.33). In addition, the frequency of grade 3–4 neutropenia below the cutoff value was significantly high ($P = 0.012$; Table 4).

Table 4 Frequency of neutropenia among patients with serum albumin concentration below the cut-off level

Serum albumin concentration	Neutropenia				
	Grade 3–4 group	Grade 0–2 group	Odds ratio	(95% CI)	P value
	(n = 24)	(n = 48)			
<3.25 g/dL	12	9	4.33	1.47–12.76	0.012 [□]
≥3.25 g/dL	12	39			

Discussion

Hypoalbuminemia worsens the treatment prognosis of patients with gastric cancer [5,6]; thus, maintaining the nutritional status is necessary to achieve a better treatment outcome. The role of hypoalbuminemia as a risk factor for therapy disruption should be fully understood to help optimize patient management. In the current study, the mean serum albumin concentrations of patients before cisplatin plus S-1 combination therapy were 3.60 ± 0.54 and 3.77 ± 0.51 g/dL in the grade 3–4 neutropenia and grade 0–2 neutropenia groups, of which 71% and 71% had hypoalbuminemia, respectively. Therefore, in this study, the serum albumin concentration of numerous patients with gastric cancer suffering from gastric dysfunction decreased before the start of chemotherapy. Furthermore, considering that cisplatin plus S-1 combination therapy is associated with a high frequency of gastrointestinal adverse events, the patients’ nutritional status will worsen after chemotherapy.

Hypoalbuminemia is frequently linked to severe neutropenia [7–10], but it has not been fully evaluated in serum albumin concentration during anticancer drug administration as the optimal observation point. In this study, by observing the albumin concentration before cisplatin administration in the treatment course during which the neutrophil count reached nadir, we evaluated the albumin concentration effect on neutrophil count fluctuation with pharmacokinetic alteration. The total protein and serum albumin concentration levels before cisplatin administration were lower in the grade 3–4 neutropenia group than in the grade 0–2 neutropenia group, and the degree of such reductions from before chemotherapy to before cisplatin administration were significantly greater in the grade 3–4 neutropenia group. Total protein includes serum albumin, globulin, and α_1 acidic glycoprotein, and serum albumin constitutes the highest proportion; hence, serum albumin is a confounding factor in the reduction of total protein, demonstrating a strong relationship. Therefore, patients manifesting hypoalbuminemia as the treatment progressed had a high incidence of grade 3–4 neutropenia. Furthermore, Lower serum albumin concentrations before cisplatin administration were significantly correlated with a decrease in neutrophil count after cisplatin administration. Our findings suggested that patients with hypoalbuminemia before cisplatin administration during cisplatin plus S-1 combination therapy were highly susceptible to severe neutropenia development.

Thus, the drug property that cisplatin is particularly susceptible to alteration in serum albumin concentration during administration should be investigated. At the end of cisplatin infusion, the protein-bound fraction increases to 90% after 2 h [3,4], indicating the irreversible binding of platinum [11–13]. The half-life for the decrease in the concentration values of nonprotein-bound plasma platinum is approximately 23–45 min at the end of the infusion [14,15], with the rapid elimination of free cisplatin from the sera. After approximately 2 h, filterable platinum and cisplatin levels become undetectable [16]. Immediately after the completion of infusion, free cisplatin concurrently affects the pharmacokinetic processes including protein binding, elimination, and tissue distribution. Thus, cisplatin administration to patients with hypoalbuminemia may affect the increase of drug efficacy by the unbound drug fraction increases.

Identifying the border region indicating hypoalbuminemia risk is necessary for patient monitoring. In the current study, the patients with serum albumin concentration below 3.25 g/dL before cisplatin administration, as calculated by ROC curve analysis, showed a significantly high incidence of grade 3–4 neutropenia (odds ratio: 4.33); grade 3–4 neutropenia is a frequent and serious adverse effect of cisplatin plus S-1 combination therapy and may progress to febrile neutropenia. Therefore, a serum albumin concentration below 3.25 g/dL before cisplatin administration should be an important parameter for patient monitoring during chemotherapy.

Considering that severe neutropenia is more frequent in Japanese patients with gastric cancer who received cisplatin combination therapies than in foreigners [1,17–20], the analysis of grade 3–4 neutropenia and related factors from the perspective of Japanese population is essential. Although hypoalbuminemia as a risk factor for chemotherapy-induced neutropenia requires further investigation regarding its application to non-Japanese patient populations, serum albumin concentration may be one of the safety criteria for proper chemotherapy involving cisplatin.

Conclusions

Patients with gastric cancer undergoing cisplatin plus S-1 combination therapy often developed hypoalbuminemia since before chemotherapy, and those with further decrease of serum albumin concentration after chemotherapy exhibited a significantly greater risk of cisplatin-induced neutropenia. Hence, serum albumin concentration needs to be evaluated before each administration of cisplatin to anticipate severe neutropenia development.

Abbreviations

AUC, area under the curve; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; ROC, receiver operating characteristic; WBC, white blood cell.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of the Jikei University [No. 30-294 (9315)].

Consent for publication

This was a retrospective observational study and carried out by the opt-out method to post a purpose in the Jikei University School of Medicine. Patients were not required to give informed consent for the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent. For full disclosure, the details of the study are mentioned in the opt-out document in the Jikei University School of Medicine.

Availability of data and materials

The datasets generated and analyzed during the present study are available from the corresponding author on reasonable request.

Competing interests

Norio Mitsumori who is a coauthor on this study has earned compensation as an outside director of Ootoya Holdings Co. Ltd., and also received study support from Taiho Pharmaceutical Co. Ltd. and Covidien Japan Co. Ltd. This study has no conflict with these companies.

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Authors' contributions

NY designed and performed the research and wrote the paper; KA contributed to the analysis; KM contributed to critical revision of the article for important intellectual content; MN provided clinical advice; KT provided the final approval for this article.

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References

1. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol.* 2008;9:215–21. [https://doi.org/10.1016/S1470-2045\(08\)70035-4](https://doi.org/10.1016/S1470-2045(08)70035-4).

2. Boku N, Yamamoto S, Fukuda H, Shirao K, Doi T, Sawaki A, et al. Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomized phase3 study. *Lancet Oncol.* 2009;10:1063–9. [https://doi.org/10.1016/S1470-2045\(09\)70259-1](https://doi.org/10.1016/S1470-2045(09)70259-1).
3. Vermorken JB, van der Vijgh WJ, Klein I, Gall HE, van Groeningen CJ, Hart GA, et al. Pharmacokinetics of free and total platinum species after rapid and prolonged infusions of cisplatin. *Clin Pharmacol Ther.* 1986;39:136–44. <https://doi.org/10.1038/clpt.1986.24>.
4. DeConti RC, Toftness BR, Lange RC, Creasey WA. Clinical and Pharmacological studies with cis-diamminedichloroplatinum(II). *Cancer Res.* 1973;33:1310–5.
5. Elahi MM, McMillan DC, McArdle CS, Angerson WJ, Sattar N. Score based on hypoalbuminemia and elevated C-reactive protein predicts survival in patients with advanced gastrointestinal cancer. *Nutr Cancer.* 2004;48:171–3. https://doi.org/10.1207/s15327914nc4802_6.
6. Crumley AB, Stuart RC, McKernan M, McMillan DC. Is hypoalbuminemia an independent prognostic factor in patients with gastric cancer? *World J Surg.* 2010;34:2393–8. <https://doi.org/10.1007/s00268-010-0641-y>.
7. Nakazawa Y, Kageyama A, Harada D, Kitamura M, Mitsumori N, Kawakubo T. Effect of hypoalbuminemia on severe neutropenia induced by paclitaxel monotherapy and paclitaxel plus ramucirumab combination therapy in patients with gastric cancer. *Gan To Kagaku Ryoho.* 2019;46:901–5.
8. Kloft C, Wallin J, Henningsson A, Chatelut E, Karlsson MO. Population pharmacokinetic-pharmacodynamic model for neutropenia with patient subgroup identification: comparison across anticancer drugs. *Clin Cancer Res.* 2006;12:5481–90. <https://doi.org/10.1158/1078-0432.CCR-06-0815>.
9. Alexandre J, Gross-Goupil M, Falissard B, Nguyen ML, Gornet JM, Misset JL, et al. Evaluation of the nutritional and inflammatory status in cancer patients for the risk assessment of severe haematological toxicity following chemotherapy. *Ann Oncol.* 2003;14:36–41. <https://doi.org/10.1093/annonc/mdg013>.
10. Lyman GH, Delgado DJ. Risk and timing of hospitalization for febrile neutropenia in patients receiving CHOP, CHOP-R, or CNOP chemotherapy for intermediate-grade non-Hodgkin lymphoma. *Cancer.* 2003;98:2402–9. <https://doi.org/10.1002/cncr.11827>.
11. Siddik ZH, Newell DR, Boxall FE, Harrap KR. The comparative pharmacokinetics of carboplatin and cisplatin in mice and rats. *Biochem Pharmacol.* 1987;36:1925–32. [https://doi.org/10.1016/0006-2952\(87\)90490-4](https://doi.org/10.1016/0006-2952(87)90490-4).
12. Yotsuyanagi T, Ohta N, Futo T, Ito S, Chen DN, Ikeda K. Multiple and irreversible binding of cis-diamminedichloroplatinum(II) to human serum albumin and its effect on warfarin binding. *Chem Pharm Bull.* 1991;39:3003–6. <https://doi.org/10.1248/cpb.39.3003>.
13. Bednarski PJ, Kratochwil NA, Otto AM. Reversible and irreversible interactions of a cisplatin analog bearing a 1,2-diphenylethylenediamine ligand with plasma and plasma proteins in vitro. *Drug Metab Dispos.* 1994;22:419–27.

14. Gullo JJ, Litterst CL, Maguire PJ, Sikic BI, Hoth DF, Woolley PV. Pharmacokinetics and protein binding of cis-dichlorodiammine platinum (II) administered as a one hour or as a twenty hour infusion. *Cancer Chemother Pharmacol*. 1980;5:21–6. <https://doi.org/10.1007/BF00578558>.
15. Gormley PE, Bull JM, LeRoy AF, Cysyk R. Kinetics of cis-dichlorodiammineplatinum. *Clin Pharmacol Ther*. 1979;25:351–7. <https://doi.org/10.1002/cpt1979253351>.
16. Himmelstein KJ, Patton TF, Belt RJ, Taylor S, Repta AJ, Sternson LA. Clinical kinetics on intact cisplatin and some related species. *Clin Pharmacol Ther*. 1981;29:658–64. <https://doi.org/10.1038/clpt.1981.91>.
17. Ajani JA, Rodriguez W, Bodoky G, Moiseyenko V, Lichinitser M, Gorbunova V, et al. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. *J Clin Oncol*. 2010;28:1547–53. <https://doi.org/10.1200/JCO.2009.25.4706>.
18. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet*. 2010;376:687–97. [https://doi.org/10.1016/S0140-6736\(10\)61121-X](https://doi.org/10.1016/S0140-6736(10)61121-X).
19. Ohtsu A, Shah MA, Van Cutsem E, Rha SY, Sawaki A, Park SR, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. *J Clin Oncol*. 2011;29:3968–76. <https://doi.org/10.1200/JCO.2011.36.2236>.
20. Yamaguchi K, Sawaki A, Doi T, Satoh T, Yamada Y, Omuro Y, et al. Efficacy and safety of capecitabine plus cisplatin in Japanese patients with advanced or metastatic gastric cancer: subset analyses of the AVAGAST study and the ToGA study. *Gastric Cancer*. 2013;16:175–82. <https://doi.org/10.1007/s10120-012-0167-0>.

Figures

Figure 1

Correlation between serum albumin concentration before cisplatin administration and the fluctuation of neutrophil count

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