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Correlation between Serum Albumin and Myelosuppression in Patients with Esophageal Cancer Treated with Chemoradiation Therapy

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ABSTRACT

Concurrent chemoradiation therapy (CRT) with 5-fluorouracil (5-FU), cisplatin, and external radiation is a standard treatment for advanced local-regional esophageal cancer. Because the binding of cisplatin to albumin in the serum affects the distribution and excretion of cisplatin, hypoalbuminemia during CRT may affect the pharmacological antitumor activity of cisplatin and lead to side effects. Therefore, we analyzed the relationship between serum albumin levels and side effects, such as myelosuppression and nephrotoxicity, during CRT. A total of 115 patients with esophageal cancer who underwent CRT were divided into those with hypoalbuminemia (serum albumin <3.5 g/dL before CRT) and those without hypoalbuminemia (serum albumin ≥ 3.5 g/dL during CRT). Seven patients were included in the hypoalbuminemia group, whereas 11 patients were included in the nonhypoalbuminemia group. The toxicity profiles of the two groups suggested that myelosuppression was more evident in the hypoalbuminemia group than that in nonhypoalbuminemia group, although a significant difference was observed only in platelet counts. In contrast, there was no significant difference in nephrotoxicity between the groups. These results suggest that hypoalbuminemia in patients with esophageal cancer undergoing CRT with low-dose cisplatin and 5-FU may be associated with more-severe myelosuppression rather than with nephrotoxicity and that myelosuppression should be monitored carefully during CRT, particularly in patients with hypoalbuminemia. (Jikeikai Med J 2008 ; 55 : 7-14)

Key words : serum albumin, low-dose cisplatin, myelosuppression, chemoradiation therapy, esophageal cancer

Introduction

The benefits of multimodality therapy for esophageal cancer have become broadly accepted over the past 2 decades. Concurrent chemoradiation therapy (CRT) using 5-fluorouracil (5-FU), cisplatin, and external radiation has demonstrated survival benefits over radiotherapy alone and has become a standard treatment for local-regional esophageal cancer[1-3]. CRT enables maximal tumor control because the

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combined local antitumor effect is more than additive and because chemotherapy may provide an opportunity for the control of micrometastatic disease[4–6]. Esophageal cancer treated with CRT is, however, accompanied by several complications, such as pain, gastrointestinal symptoms, and myelosuppression[7]. Of these complications, dysphagia, related either to the disease itself or to treatment, frequently appears during CRT, resulting in malnutrition or hypoalbuminemia. One study has found that almost 80% of patients are malnourished to some degree at presentation[8].

Because cisplatin binds tightly to albumin in the serum, hypoalbuminemia during CRT may affect the distribution and excretion of cisplatin and alter antitumor activity and toxicity[9–11]. de Jongh et al. have reported that hypoalbuminemia is associated with increased nephrotoxicity induced by weekly high-dose cisplatin for various solid tumors[12]. However, to the best of our knowledge, no studies have examined the relationship between serum albumin and toxicity induced by either daily low-dose cisplatin or CRT. Because cisplatin is administered in various doses and with various schedules, in the present study we define low-dose cisplatin as 3 to 7.5 mg/m^2 and standard-dose cisplatin as 60 to 85 mg/m^2.

In the present study, we examined myelosuppression and nephrotoxicity during CRT in patients who had or did not have hypoalbuminemia.

PATIENTS AND METHODS

Patients and treatments

The subjects of the study were selected from among patients with esophageal cancer who underwent CRT as inpatients at The Jikei University Hospital from March 2001 through January 2006. Patients were selected if they received 4 to 6 weeks of chemotherapy consisting of cisplatin (4 mg/m^2) administered intravenously for 5 consecutive days each week and 5-FU (750 mg/m^2) by 24-hour infusion on days 1, 3, and 5 each week. Concurrent with chemotherapy, patients were treated with external radiation (10 Gy per week in 5 fractions) to a locoregional lesion or lesions. Patients received 60 Gy of external radiation over 6 weeks. To test the hypothesis that serum albumin plays a role in the toxicity of cisplatin, we extracted 2 groups from entire patient population: those with hypoalbuminemia and those without hypoalbuminemia. Hypoalbuminemia was defined as a serum albumin concentration less than 3.5 g/dL before the start of CRT, and nonhypoalbuminemia was defined as a serum albumin concentration of 3.5 g/dL or more before and during CRT. Because free cisplatin levels in serum during low-dose cisplatin chemotherapy are reportedly too low to be measured with atomic absorption spectrometry[13,14], we did not determine free cisplatin levels. Of 115 patients who underwent CRT, 7 patients were placed in the hypoalbuminemia group and 11 patients were placed in the nonhypoalbuminemia group. The toxicity profile of CRT in these groups was analyzed retrospectively in this study. The study protocol was reviewed and approved by the institutional review boards of The Jikei University School of Medicine and of Kyoritsu University of Pharmacy. The study was conducted in accordance with the guidelines.

Toxicity assessment

Throughout CRT, patients were examined for myelosuppression with blood tests, including those measuring the white blood cell (WBC) count, the absolute neutrophil count (ANC), the hemoglobin level, and the platelet count. Patients receiving granulocyte-colony stimulating factor (G-CSF) because of severe neutropenia were excluded from the analysis of the WBC count and the ANC, because G-CSF affects both variables. The patients who had received a red blood cell transfusion were also excluded from the analysis of hemoglobin, because such a transfusion affects hemoglobin levels. Nephrotoxicity was assessed with the serum creatinine level, the 24-hour creatinine clearance (Ccr), and urinary N-acetyl-β-D-glucosaminidase (NAG) before and after CRT.

Statistical methods

The software program of SPSS 11.5 J for Windows (SPSS Inc., Chicago, IL, USA) was used for inferential statistics. Statistical comparisons of cate-

gorical data between groups were performed with Fisher's exact test. For the statistical comparison of population means, the Shapiro-Wilk test was first performed to determine whether a parametric or nonparametric approach should be used. If data were normally distributed, Student's t-test was used. If the data were not normally distributed, the Mann-Whitney U-test was used. To analyze the repeated measures data, repeated-measures analysis of variance was used.

Results

Patient characteristics

The 2 groups were well balanced in terms of age, sex, location of the lesion, clinical stage, presence of recurrent disease, histologic classification, performance status, dose intensity of both cisplatin and 5-FU, and total dose of 5-FU but differed in body weight and body mass index (BMI) before CRT and in the total dose of cisplatin (Table 1; $p=0.021$, 0.045, and 0.033, respectively). In some patients with hypoalbuminemia, de-escalation of the cisplatin dose was performed from the start of CRT because of poor performance status, leukopenia, and renal impair-

Table 1. Patient characteristics

	hypoalbuminemia	nonhypoalbuminemia	p value
Number of patients	7	11	
Age (years)	65.6±2.8	65.0±2.4	$p=0.880$
Sex (male/female)	5/2	9/2	$p=1.000$
Location of the lesion			$p=1.000$
Cervical esophagus	1	1	
Cervical and upper thoracic esophagus	0	1	
Upper thoracic esophagus	2	1	
Upper and middle thoracic esophagus	1	0	
Upper and lower thoracic esophagus	0	1	
Middle thoracic esophagus	0	1	
Middle and lower thoracic esophagus	1	0	
Lower thoracic esophagus	1	2	
Clinical stage			$p=0.155$
II	1	4	
III	2	3	
IVa	3	0	
Recurrent disease	1	4	$p=0.596$
Histologic classification of primary tumor			
squamous cell carcinoma (recurrent disease)	7 (1)	11 (4)	
Performance status (ECOG)			$p=0.419$
0	3	8	
1	3	3	
2	1	0	
Body weight (before starting CRT) (kg)	47.3±5.0	62.8±3.6	$p=0.021$
BMI (before starting CRT) (kg/m^2)	18.3±1.3	22.8±1.4	$p=0.045$
Dose intensity (mg/m^2/week)			
5-FU	1,944±115	2,004±64	$p=0.618$
cisplatin	14.4±1.7	18.6±0.4	$p=0.077$
Total dose (mg/m^2)			
5-FU	12,199±1,031	11,971±440	$p=0.819$
cisplatin	88.9±9.3	111.3±4.0	$p=0.033$

Abbreviations: ECOG, Eastern Cooperative Oncology Group. All plus-minus values shown represent means±SE.

Table 2. Characteristics of patients without G-CSF support

	hypoalbuminemia	nonhypoalbuminemia	p value
Number of patients	6	9	
Dose intensity (mg/m^2/week)			
5-FU	1,922±134	1,988±78	$p=0.656$
cisplatin	15.1±1.9	18.6±0.5	$p=0.140$
Total dose (mg/m^2)			
5-FU	12,112±1,215	12,059±526	$p=0.965$
cisplatin	93.2±9.8	113.4±4.4	$p=0.045$

Data are presented means±SE.

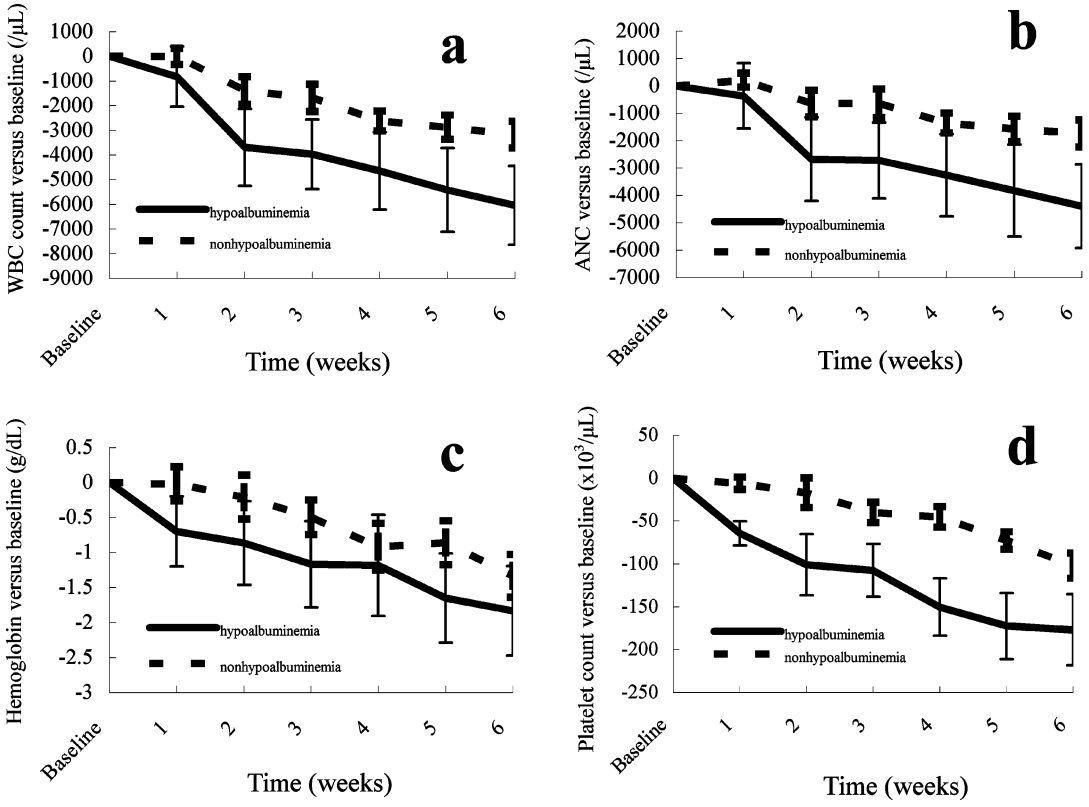

Figure 1a-d. a. Changes in the WBC count over time during CRT ; b. Changes in the ANC over time during CRT ; c. Changes in hemoglobin level over time during CRT ; d. Changes in platelet count over time during CRT. Data are means±SE. In the analysis of WBC count and the ANC, patients receiving G-CSF support were excluded. In the analysis of hemoglobin, the patients that had received a red blood cell transfusion were excluded. Changes in the WBC count, the ANC, and the hemoglobin level over time in patients with hypoalbuminemia tended downward compared with those in patients without hypoalbuminemia, although there were no significant differences ($p=0.116$, 0.137, and 0.337, respectively). However, the platelet count differed significantly ($p=0.014$).

ment, resulting in decreases in the total delivered dose of cisplatin. Some patients needed G-CSF support because of neutropenia during CRT. Characteristics, especially those related to dosage, of patients that did not receive G-CSF support are summarized in Table 2. A significant difference was observed only in the total dose of cisplatin ($p=0.045$).

Cisplatin-induced toxicity

Myelosuppression

Longitudinal changes related to myelosuppression were compared between the groups. Fig. 1a-d shows

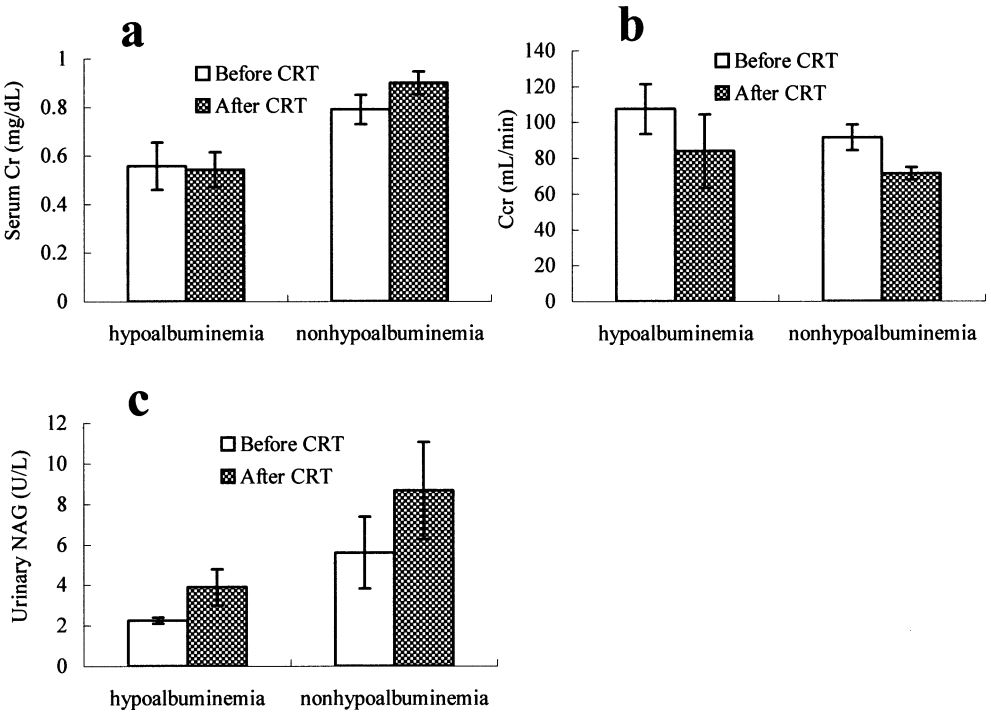

Figure 2a–c. a. Changes before and after CRT in serum creatinine level; b. Changes before and after CRT in 24-hour Ccr; c. Changes before and after CRT in urinary NAG. Data are means±SE. There were no significant differences in serum creatinine, Ccr, or urinary NAG between the groups ($p=0.142$, 0.787, and 0.564, respectively)

changes in the WBC count, the ANC, the hemoglobin level, and the platelet count during the initial 6 weeks of CRT. Myelosuppression, represented by 4 variables, was more evident in the hypoalbuminemia group than in the nonhypoalbuminemia group; however, of the 4 variables, only the platelet count differed significantly between the groups.

Renal Toxicity

Nephrotoxicity profiles were also compared between the groups using such variables as serum creatinine, Ccr, and urinary NAG. No significant differences were observed between the groups (Fig. 2a–c).

Discussion

In our study, we found that hypoalbuminemia was associated with more-severe myelosuppression, particularly thrombocytopenia, but not with nephrotoxicity in esophageal cancer treated with CRT using a low-dose cisplatin and 5-FU regimen. At least 3 reasons for the association between hypoalbuminemia and myelosuppression can be considered.

First, the more-severe myelosuppression might be due to an increase in free cisplatin. In the presence of hypoalbuminemia, the level of free cisplatin is expected to be higher than that in the absence of hypoalbuminemia. Therefore, myelosuppression would be more severe in patients with hypoalbuminemia than in patients without hypoalbuminemia. In fact, we found that platelet counts were significantly lower in patients with hypoalbuminemia ($p=0.014$). Although the WBC count, the ANC, and the hemoglobin level tended to be lower in patients with hypoalbuminemia ($p=0.116$, 0.137, and 0.337, respectively), the differences were not significant. According to this hypothesis, more-severe nephrotoxicity could also develop. However, in our study, hypoalbuminemia was not correlated with the severity of nephrotoxicity (Fig. 2a–c). The previous fact might be related to the different toxicity profile due to the different dose and schedule of cisplatin administration described later. Although few studies of the mechanism of cisplatin-

induced thrombocytopenia have been published, the latest studies have stressed that cisplatin impairs the earlier cell stages in megakaryopoiesis, such as megakaryoblasts and promegakaryocytes[15].

Second, the difference in toxicity profiles might be due to the administered dose and schedule of cisplatin. Cisplatin is well known be nephrotoxic. de Jongh et al. have reported the side effects of a regimen including weekly standard-dose cisplatin[12]. They have demonstrated that hypoalbuminemia is associated with a high incidence of nephrotoxicity but not of myelosuppression. Thus, our result was unexpected because myelosuppression without more severe nephrotoxicity appeared mostly in patients who had hypoalbuminemia. However, our dosage schedule for cisplatin was significantly different from that used by de Jongh et al.. We administered 5-FU and a very low-dose of cisplatin (4 mg/m²/day) for 5 consecutive days each week during CRT. The most commonly used dose and schedule of the so-called low-dose cisplatin and 5-FU regimen, which is the preferred treatment regimen for gastrointestinal cancer in Japan[16], could be as follows : cisplatin is given at a dose of 3 to 5 mg/m²/day over 30 minutes to 1 hour, and 5-FU is given at a dose of 200 to 300 mg/m²/day by means of 24-hour continuous infusion on days 1 to 5 for 4 to 6 weeks depending on whether the setting is preoperative or definitive. In contrast, de Jongh et al. gave a standard-dose of cisplatin (70 to 85 mg/m²) over 3 hours once per week for 6 intended administrations[12]. Regarding the pharmacokinetics of cisplatin, some studies have reported that the area under the concentration×time curve (AUC) of free cisplatin is significantly higher with daily bolus infusion (15 mg/m²/day, days 1 to 5) than with drip infusion (35 to 40 mg/m², twice on day 1)[17] and that myelosuppression is dependent on the AUC of free cisplatin rather than on the peak plasma level[18]. According to these studies, myelosuppression may be more prevalent with lower-dose daily cisplatin therapy than with standard-dose cisplatin therapy. Therefore, one explanation is that the administration schedule might be responsible for the toxicity profile and might contribute to the toxicity discrepancy in patients with hypoalbuminemia. Ohsawa et al. have compared toxicity profiles between a standard-dose cisplatin regimen and a daily low-dose cisplatin regimen, which is similar to the regimen used in the present study[14]. Ohsawa et al. concluded that the standard-dose cisplatin regimen is more likely to induce nausea, vomiting, appetite loss, and nephrotoxicity. Meanwhile, they showed that thrombocytopenia is the only significant toxicity with the daily low-dose cisplatin regimen. Chung et al. have also reported that thrombocytopenia of greater than grade 3 (World Health Organization [WHO] criteria) occurred in 19.2% of patients (5 of 26 patients) receiving 7.5 mg/m² of cisplatin over 1 hour on days 1 to 5 every week and 350 mg/m² of 5-FU continuously infused each day for 4 weeks[19].

Several clinical studies of CRT suggest that a low-dose cisplatin and 5-FU regimen might be as effective as the standard-dose cisplatin and 5-FU regimen[14,20,21] but might have a lower rate of toxicities, including nephrotoxicity[14,20–22]. In particular, to our knowledge, no study has found that a low-dose cisplatin and 5-FU regimen produces nephrotoxicity greater than grade 3 (National Cancer Institute-Common Toxicity Criteria version 2.0, WHO criteria, Japan Clinical Oncology Group Toxicity criteria, the criteria of the Japan Society for Cancer Therapy or the criteria provided by Japan Society Clinical Oncology)[14,19,22–25]. With the so-called standard-dose cisplatin and 5-FU regimen, 60 to 80 mg/m² of cisplatin is given over 2 hours on day 1 and 800 to 1,000 mg/m² of 5-FU is continuously infused over 24 hours on days 1 to 4 or 5 and repeated every 3 to 4 weeks. Accordingly, the theoretical dose intensities of cisplatin and 5-FU in a standard-dose regimen could be 20 mg/m²/week and 1,600 mg/m²/week, respectively. With our regimen, the theoretical dose intensities of cisplatin and 5-FU are 20 mg/m²/week and 2,250 mg/m²/week, respectively. Despite the theoretical dose intensities seeming to be similar in the 2 regimens, the toxicities of our regimen were generally mild to moderate compared with those of the standard-dose cisplatin and 5-FU regimen[14,20,21]. However, more-severe myelosuppression, especially thrombocytopenia, has been observed in patients with hypoalbuminemia, as shown in Figure 1a-d.

The mechanism of action of daily low-dose cisplatin might differ somewhat from that of the standard-dose of cisplatin, as daily low-dose cisplatin may stimulate the formation of ternary complexes among thymidylate synthase, reduced folate, and 5-FU metabolites[26,27].

A third possible reason for the increased severity of myelosuppression in patients with hypoalbuminemia is the correlation of the serum albumin levels with the patient's general condition. In the present study, patients with hypoalbuminemia showed significant decreases in both body weight and BMI before the start of CRT and tended to have a more-advanced clinical stage than did patients without hypoalbuminemia. A single patient with a poor performance status of 2 had hypoalbuminemia in our study. Belinson et al. have also reported a strong correlation between the serum albumin level before chemotherapy and disease stage[28]. Thus, the patient's general condition might be more likely to deteriorate in the presence of hypoalbuminemia and also be associated with the severity of toxicities in patients with hypoalbuminemia, especially myelosuppression, in patients treated with a low-dose cisplatin and 5-FU regimen. Some patients with esophageal cancer who undergo CRT have malnutrition because of the disease itself or because of esophagitis due to CRT. In such patients, maintaining the nutritional status with percutaneous endoscopic gastrostomy feeding or total parenteral nutrition might ameliorate the side effects of CRT and increase tolerance.

In conclusion, our present results suggest that myelosuppression, especially thrombocytopenia, is more prevalent in patients with hypoalbuminemia and that serum albumin levels should be strictly controlled during CRT with a low-dose cisplatin and 5-FU regimen for esophageal cancer.

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