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ORIGINAL ARTICLE

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Phase I/II study of weekly docetaxel dose escalation in combination with fixed weekly cisplatin and concurrent thoracic radiotherapy in locally advanced non-small cell lung cancer

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Abstract *Purpose*: We conducted a phase I study to determine the maximum-tolerated dose (MTD) and dose-limiting toxicities (DLT) of weekly docetaxel and cisplatin (DOC/CDDP) with concurrent thoracic radiotherapy (TRT) in patients with unresectable stage III non-small-cell lung cancer (NSCLC). *Materials and methods*: The DOC/CDDP administration schedules consisted of a split schedule (SS) with administration in 3 out of every 4 weeks, and a continuous schedule (CS) with administration every week. TRT was given to a total dose of 60 Gy at 2 Gy per fraction over 6 weeks. *Results*: Twenty-one patients entered the study. The patient characteristics were: PS 0/1/2, 6/13/2; Sq/Ad, 16/5; stage IIIA/IIIB, 4/17. The principal DLT was grade3 esophagitis. The MTD of DOC on the SS and CS in combination with CDDP (25 mg/m2/week) was 25 and 20 mg/m^2/week, respectively. We determined the RD and schedule of DOC/CDDP on the SS to be 20/25 mg/m^2/week. The serum α-1-acid glycoprotein (AAG) concentration values were found to be negatively correlated with the grade of esophagitis. The median survival time was 23.1 months. *Conclusion*: The chemoradiation regimen tested in this study has promising activity and manageable toxicity. The continuous schedule could not be recommended due to excessive toxicity. The main DLT was esophagitis, and it significantly correlated with the plasma AAG concentration.

Keywords Docetaxel · Cisplatin · Chemoradiation · AAG

Conflicts of interest: The authors indicated no potential conflicts of interest

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Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers, and although surgery offers the best chance of cure and long-term survival, only a small percentage of patients present with resectable disease. In fact, 25–30% of patients with NSCLC present with locally or regionally advanced unresectable tumors. Chest irradiation with modern megavoltage equipment plays a critical role in the treatment of these patients, since it assures good local control of the tumor in most patients. However, the development of distant metastases also affects their prognosis, and the addition of chemotherapy to thoracic radiation therapy (TRT) has been proposed in an attempt to reduce the risk of distant metastases.

Recent studies support the benefit of combined modality therapy in stage III NSCLC. The results of randomized studies that used sequential or concomitant chemotherapy for unresectable non-small cell lung cancer have shown significant differences in survival, local control rates, and distant metastasis rates for chemoradiotherapy over radiotherapy alone [1–5], and a recent meta-analysis of all randomized trials that compared TRT alone with the combined approach showed an unequivocal, although modest, survival advantage when cisplatin-based chemotherapy was added to TRT [6]. Concomitant chemoradiotherapy offers the potential advantage of synergistic interactions for local control

and the added possibility of direct antitumor activity [4, 5]. More recently, there has been accumulating phase III evidence that concomitant chemoradiotherapy probably yields higher response rates and survival in patients with stage III disease [7, 8].

Several novel agents with remarkable radiosensitizing properties have recently been introduced in clinical practice. In preclinical studies the taxanes were found to be potent radiation-enhancers by virtue of their ability to cause cell cycle arrest in the radiosensitive G2/M phase [9, 10]. Preclinical studies further illustrated the taxanes' radiosensitizing effect in tumor-cell lines, with docetaxel exhibiting an effect ten times that of paclitaxel at equimolar concentrations [11]. Four phase I trials of docetaxel and concurrent radiation have been reported [12–15]. Mauer et al. [12] and Koukourakis et al. [14] conducted phase I trials of weekly docetaxel with concurrent thoracic radiotherapy and determined that the maximum-tolerated dose (MTD) of weekly docetaxel was 20–30 mg/m^2 with thoracic radiation. The dose-limiting toxicities (DLTs) were esophagitis and neutropenia. The phase II studies of docetaxel [16, 17] and thoracic radiotherapy have shown an encouraging, high response, but an increased incidence of esophagitis and asthenia was observed.

The use of low daily doses of cisplatin concomitantly with RT seems to be of particular interest, since clear synergism has been demonstrated in vitro [18]. In a European Organization for Research and Treatment of Cancer (EORTC) study, daily administration of cisplatin proved to be more effective than a weekly schedule in potentiating the local tumor control achievable with RT alone, although the difference between the two schedules were not statistically significant [4].

In view of these considerations, we planned this phase I study. The objectives of this study were to determine the MTD, recommended dose (RD) and DLT of cisplatin and docetaxel when given weekly concomitantly with conventional TRT, and evaluate the efficacy of this regimen.

Moreover, since it has reported that serum α-1-acid glycoprotein (AAG) combined with docetaxel extensively [19] and that the AAG levels were significantly associated with time to progression in NSCLC patients and febrile neutropenia [20]. The AAG levels were significantly associated with the toxicity of docetaxel because AAG strongly binds docetaxel in serum. Thus, we examined the relationship between serum AAG level and major toxicities in this regimen.

Patients and methods

Patient eligibility

Previously untreated patients with histologically or cytologically documented inoperable stage IIIA or IIIB NSCLC were eligible for this study. Patients with malignant pleural effusion or any disease that required irradiation of more than half of the hemithorax were ineligible. Other eligibility criteria included: (1) age less than 75, (2) Eastern Cooperative Oncology Group performance status equal to or less than 2, (3) evaluable or measurable disease, (4) no prior therapy, (5) adequate bone marrow function (leukocyte count ≥4,000/mm^3, platelet count ≥100,000/mm^3, hemoglobin ≥9.5 g/dl), renal function (serum creatinine ≤ 2.0 mg/dl), hepatic function (AST/ALT ≤ 2.5 times upper limit of normal, serum bilirubin ≤ 1.5 mg/dl), and pulmonary function (arterial blood gases PaO2 ≥70 mmHg), (6) absence of active infection, heart failure, or acute myocardial infarction within 3 months before study entry, no serious medical or psychiatric illness. All patients signed an informed consent form that was approved by each of the institutional review boards. Before entry into the study, all patients underwent an evaluation that consisted of a complete history and physical examination, chest X-ray, chest and upper abdomen (to include the liver and adrenals) computed tomography (CT) scan, brain CT or MRI, and a bone scan.

Chemotherapy

The treatment regimens are outlined in Fig. 1. The study was designed to fix the cisplatin dose at 25 mg/m^2/week and escalate docetaxel dose. The docetaxel and cisplatin administration schedules were: split schedule (SS), 3 out of every 4 weeks (day 1, 8, 15, 29, 36, and 43), continuous schedule (CS), weekly (day 1, 8, 15, 22, 29, 36). Docetaxel was administered as an intravenous (IV) infusion over 30 min and followed by cisplatin given as an IV infusion over 30 min. The participating investigators at each institution were allowed to decide the volume of fluid replacement and the antiemetic therapy to be administered, but adequate amounts of parenteral fluid and diuretics were given in order to prevent the renal toxicity of cisplatin. The patients did not receive steroids due to prevention of a hypersensitivity reaction. The starting dose of docetaxel was 20 mg/m^2/week, and the docetaxel dose was increased by 5 mg/m^2/week. There was no dose escalation in individual patients, and administration of cisplatin and docetaxel was cancelled if the leukocyte count fell below 2,000/mm^3 or any DLTs occurred.

At first, we planed only sequential schedule. However, as we thought that continuous schedule had a stronger radiosensitizing effect compared with sequential schedule, we amended protocol and added continuous schedule. After the MTD and RD of SS had been determined, we treated with CS using the RD of SS.

Thoracic radiation

Thoracic radiation therapy of 60 Gy in 2.0 Gy fractions was given concurrently with weekly docetaxel and

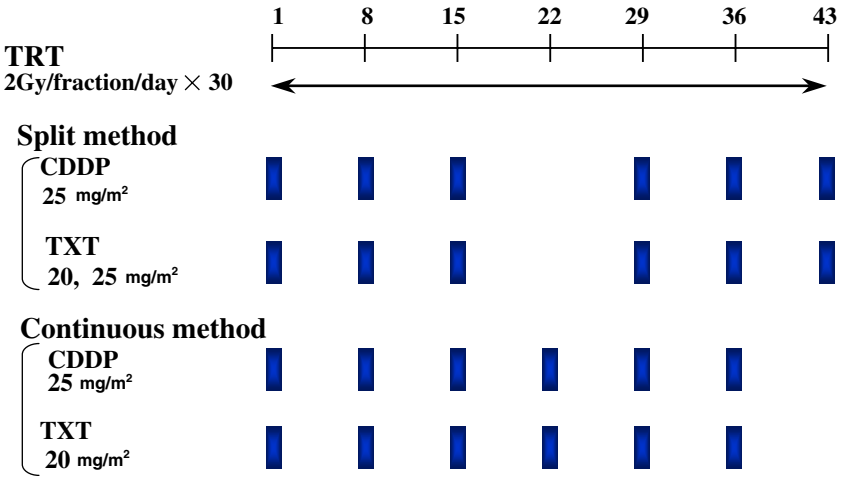

Fig. 1 Treatment regimens for weekly docetaxel and cisplatin concomitant with TRT

cisplatin infusion for 6 weeks. A 6- or 10-MV linear accelerator was used. Two-dimensional treatment planning of TRT was performed by conventional X-ray simulators. Inhomogeneity correction for lung tissues was not done. The initial planning target volume (PTV) consisted of the primary tumor, ipsilateral hilar nodes, and superior mediastinal nodes with 1–1.5 cm margin. If metastasis to supraclavicular nodes were found, they were also included in the initial PTV. This initial large field was treated by parallel-opposed anterior and posterior fields to 40 Gy in 20 fractions. The widths and lengths of the initial fields with appropriate trimming ranged from 10.5 to 16 cm (median; 14 cm) and 10.5–20 cm (median; 16 cm), respectively. After 40 Gy, oblique parallel-opposed fields were used to exclude the spinal cord. The angles of the oblique fields ranged from 15° to 45° with a median of 40°. In the boost fields, the primary tumors and the involved nodes were included with a margin of 0.5–1.5 cm. The total dose to the boost field was 60 Gy in 30 fractions. In the present study, patients were excluded if the initial radiation field exceeded half of the ipsilateral lung. However, no dose constraints on the normal tissues including the percentage of pulmonary volume irradiated to >20 Gy (V20) or esophageal length was determined, as three-dimensional treatment planning using a CT-simulator was not available.

If grade 4 hematologic toxicity occurred during the course of TRT, it was suspended and restarted after recovery to grade 3 or less. If grade 3 or greater esophagitis occurred and the physician decided that the TRT could not be continued, it was suspended and restarted after recovery to grade 2 or less. If PaO_2 fell to 10 torr and a patient had a fever of 38°C or higher, both TRT and chemotherapy were suspended and restarted immediately after recovery.

Definition of MTD, RD and DLT

Maximum-tolerated dose was defined as the dose level at which DLT occurs in more than 50% of the patients treated, and the preceding dose level was defined as RD. At least six patients were entered at each dose level. DLT was defined as grade 4 leukopenia or neutropenia lasting 3 days or more, a platelet count of $\leq 20{,}000/mm^3$, febrile neutropenia and grade 3 or greater non-hematologic toxicities other than nausea and vomiting. Suspension of docetaxel and cisplatin two or more times was also considered as a DLT.

Response evaluation and survival analysis

The criteria for assessing the response to treatment were as follows. Complete response (CR) was defined as total disappearance of all clinically detectable lesions for at least 4 weeks. Partial response (PR) was defined as a reduction of 50% or more in the sum of the products of the cross-sectional diameters of all measurable lesions for at least 4 weeks, without the development of new lesions. Stable disease (SD) was defined as a reduction of less than 50% or an increase of less than 25% in the sum of the products of the cross-sectional diameters of all measurable lesions, with no clear evidence of either regression or progression for at least 6 weeks. Progressive disease (PD) was defined as an increase of 25% or more 25% in the sum of the products of the cross-sectional diameters of all measurable lesions, together with an increase of assessable disease or the appearance of new lesions. Survival time was defined as the interval between the date of the start of treatment and the date of death due to any cause or the most recent follow-up evaluation. The survival curves were estimated by the Kaplan–Meier method.

Statistical analysis

The *T*-test was used to examine the relationship between serum AAG values and the categorical endpoints of major toxicities, such as grade of esophagitis. A *P*-value of 0.05 or less was considered statistically significant.

Results

Patient characteristics

Between April 1999 and April 2000, 21 patients were enrolled in the study, and their characteristics are listed in Table 1. All patients were eligible for evaluation of efficacy, but one who enrolled at a docetaxel dose of 20 mg/m^2/week in SS was excluded from the evaluation of toxicity because chemotherapy was suspended due to exacerbation of a gastric ulcer. That patient experienced no DLT. The 19 men and 2 women enrolled in the study had a median age of 65 (range: 51–75). Most patients had squamous cell carcinoma ($n = 16$: 76%) and stage IIIB disease (n = 17: 81%). Median performance status was 1 (range: 0–2), while only two patients had a performance status of 2.

Dose escalation

The DLTs encountered at each dose level are listed in Table 2. On the SS, six and seven patients were evaluable for toxicity at docetaxel doses of 20 and 25 mg/m^2/week, respectively. Two of the six patients at the 20 mg/m^2/week dose experienced DLTs consisting of grade 3 esophagitis in one patient and cancellation of chemotherapy twice because of grade 3 leukopenia in the other. At the 25 mg/m^2/week dose, four of the seven patients developed DLTs consisting of grade 3 esophagitis in two patients, grade 3 fatigue in one, and febrile neutropenia in one. Accordingly, the MTD and RD on the SS were concluded to be a dose of docetaxel 25 and 20 mg/m^2/week, respectively. The next cohort of patients was treated with a docetaxel dose of 20 mg/m^2/week in CS. However, four of the seven patients developed DLTs, consisting of grade 3 esophagitis in two patients, grade 3 fatigue in one patient, and cancellation of chemotherapy twice because of grade 3 neutropenia in one patient. Finally, we concluded that the dose level 1 in SS was the recommended dose for further study of this therapy.

Table 1 Patient characteristics

Characteristic	Number of patients
Total number of patients	21
Assessable for toxicity	20
Assessable for survival and response	21
Age, years	
Median (range)	65 (51–75)
Sex	
Male	19
Female	2
Performance status	
0	6
1	13
2	2
Histology	
Squamous cell carcinoma	16
Adenocarcinoma	5
Stage	
IIIA	4
IIIB	17

Toxicity

Hematologic and non-hematologic toxicities are summarized in Table. 3 and 4. Twenty patients could be assessed for toxicities. The hematologic toxicities were mild, and there were no grade 4 hematologic toxicities. Grade 3 neutropenia, decrease in hemoglobin, and thrombocytopenia were observed in 6 patients (30%), 6 patients (30%), and 1 patient (5%), respectively. Febrile neutropenia developed in only one patient, and it occurred at the 25 mg/m^2/week dose of docetaxel.

The principal toxicity on this regimen was esophagitis. Grade 2 or higher esophagitis occurred in 12 of the 20 (60%) patients enrolled, and in 5 cases (25%) it was of grade 3 and caused suspension of treatment in 2 patients and permanent discontinuation of treatment in one patient at 52 Gy. Another dose-limiting non-hematologic toxicity was grade 3 fatigue which occurred in one patient each at 25 mg/m^2/week dose of docetaxel on the SS and at the 20 mg/m^2/week dose of docetaxel on the CS. Other non-hematologic toxicities were mild and never greater than grade 2. Grade 2 nausea and pneumonitis occurred in five patients and two patients, respectively. No hypersensitivity reactions occurred. There were no treatment related deaths.

Treatment delivery

A total of 110 chemotherapy cycles were administered to 20 patients at three dose levels. Ten (9%) of the planned doses were omitted. The ratio of actual dose intensity to planned dose intensity of docetaxel and cisplatin at 20 and 25 mg/m^2/week docetaxel dose levels on the SS and at the 20 mg/m^2/week docetaxel dose level on the CS was 0.95, 0.93, and 0.88, respectively. A TRT dose of 60 Gy was administered to 18 of 20 (90 %) patients. TRT at the 25 mg/m^2/week dose of docetaxel on the SS and the 20 mg/m^2/week of docetaxel on the CS each one patient was discontinued at 58 and 52 Gy, respectively, because of grade 3 esophagitis.

Response and survival

Table 5 shows the responses observed at each dose level. All 21 patients enrolled were evaluable for response. CR was observed in 5 of the 21 (24%) patients, PR in 14 (67%) and SD in 1 (5%). The overall response rate was 90% (95% confidence interval: 69.6–98.8%). No significant differences in response were observed between the three dose levels of docetaxel.

Table 2 Dose limiting toxicity

Dose of docetaxel	Assessable patients	Dose limiting toxicitiy
Split schedule		
20 mg/m^2	6	2 1: Grade 3 esophagitis1: 2 times cancellation of chemotherapy due to grade 3 leukopenia
25 mg/m^2	7	4 2: Grade 3 esophagitis1: Grade 3 fatigue1: Febrile neutropenia
Continuous schedule		
20 mg/m^2	7	4 2: Grade 3 esophagitis1: Grade 3 fatigue1: 2 times cancellation of chemotherapy due to grade 3 neutropenia

Table 3 Hematologic toxicity

Dose level of docetaxel	No. of patients	ANC		Febrile neutropenia	Hb		Platelet	
		Grade			Grade		Grade	
		3	4		2	3	2	3
Split schedule								
20 mg/m^2	6	0	0	0	1	2	0	0
25 mg/m^2	7	2	0	1	3	2	1	1
Continuous schedule								
20 mg/m^2	7	4	0	0	2	2	0	0

ANC absolute neutrophil count, *Hb* hemoglobin

Figure 2 shows the overall survival for all 21 patients enrolled in the study; 16 patients (76%) had died at the time of the analysis. All survivors had a follow-up time of 30 months. Based on the Kaplan–Meier method, the 1-, 2-, and 3-year overall estimated survival rates were 71.4, 42.9, and 32.7%, respectively. The median overall survival time was 23.1 months.

Relationship between esophagitis and plasma AAG levels

The principle toxicity on this regimen was esophagitis. Another DLT, grade 3 fatigue occurred in only two patients, and hematologic toxicity was mild. We, therefore, examined the relationship between plasma AAG levels and grade of esophagitis. Plasma AAG was measured in 12 patients prior to the start of the treatment, and the baseline AAG level of the patients who experienced grade 2 or 3 esophagitis was significantly higher ($P = 0.04$) than that of the patients who experienced grade 0 or 1 esophagitis (grade 0/1, mean AAG level = 168 pg/ml vs. grade 2/3, mean AAG level = 83 pg/ml: Fig. 3).

Discussion

We conducted a phase I study of cisplatin and docetaxel administered in weekly infusions concomitant with conventional TRT in patients with unresectable stage IIIA/IIIB NSCLC. This is the first study that examined schedule and dose of weekly docetaxel in combination fixed dose of cisplatin 25 mg/m^2 concomitant with TRT. The recommended dose and schedule were determined to be cisplatin 25 mg/m^2 and docetaxel 20 mg/m^2 on days 1, 8, 15 of every 4 weeks, respectively. Esophagitis and neutropenia were by far the severest toxicities in this

Table 4 Non-hematologic toxicity

Dose level of docetaxel	No. of patients	Esophagitis		Fatigue		Nausea		Pneumonitis	
		Grade		Grade		Grade		Grade	
		2	3	2	3	2	3	2	3
Split schedule									
20 mg/m^2	6	3	1	0	0	2	0	1	0
25 mg/m^2	7	1	2	0	1	1	0	1	0
Continuous schedule									
20 mg/m^2	7	3	2	1	1	2	0	0	0

Table 5 Response at each dose level

Dose level of docetaxel	No. of patients	Response				Response rate
		CR	PR	SD	PD	
Split schedule						
20 mg/m^2	7	2	5	0	0	7/7100%
25 mg/m^2	7	2	5	0	0	7/7100%
Continuous schedule						
20 mg/m^2	7	1	4	1	0	5/771%
Total	21	5	14	1	1	19/2190%

study, while pulmonary toxicity was almost nonexistent. The pulmonary toxicity associated with concurrent chemoradiotherapy using third generation anticancer agents is frequently serious and fatal. When cisplatin and paclitaxel were combined with concurrent TRT, grade 3 or more late lung toxicity in 20%, including grade 5 in 8% was reported [21]. The incidence of grade 3 or more pulmonary toxicity in the studies of cisplatin and docetaxel concomitant with TRT has been low. Grade 3 pneumonitis occurred in 4.8% of patients in the study by Kiura et al. [22], and no grade 3 or more pulmonary toxicity was reported by Wu et al. [23].

Wu et al. [23] conducted a phase I study of weekly docetaxel and cisplatin concomitant with thoracic radiotherapy in stage III NSCLC and reported that the recommended dose was docetaxel 20 mg/m^2 plus cisplatin 20 mg/m^2 weekly. This dose is almost the same as in our study, but the dose intensity of docetaxel at the recommended dose was slightly lower in our study (docetaxel: 14 mg/m^2/week) than in the Wu study (docetaxel: 20 mg/m^2/week). The reason for this difference may be the dose of cisplatin.

Unfortunately, three-dimensional treatment planning and conformal radiotherapy were not available in the present study. Therefore, it was not possible to analyze a relationship between degree and frequency of toxicities and various dose-volume parameters including V20 or the maximum esophageal point dose. The acute toxicities are closely related to the dose-volume parameters of the normal tissues [24–26]. The degree and frequency of toxicities could be reduced by three-dimensional conformal radiation therapy, which can restrict the dose and volume of the normal tissues compared with conventional two-dimensional technique.

The response rate of 90%, median survival time of 23.1 months, and 2-year survival time of 42.9% obtained in our study are very encouraging. One reason for these favorable results may be that the weekly docetaxel and cisplatin not has only radiosensitizing activity but systemic chemotherapeutic activity. Ohe et al. [27] are currently evaluating docetaxel and cisplatin administered in three consecutive weekly infusions as systemic chemotherapy for advanced NSCLC. Thirty-three elderly patients with advanced NSCLC were enrolled in their phase II study of docetaxel 20 mg/m^2 and cisplatin 25 mg/m^2 on days 1, 8, and 15, doses which are similar to the recommended doses and schedule in our study. The overall response rate was 52%, the complete response rate was 6% and the median survival time was 12.4 months. Both response rate and median survival time in their study are promising and the results suggest that a docetaxel dose of 20 mg/m^2/week plus cisplatin dose of 25 mg/m^2/week has an antitumor effect as systemic chemotherapy.

The correlation with AAG was not a primary objective and this was not essential in this study. Thus, we could collect only 12 samples. The baseline AAG

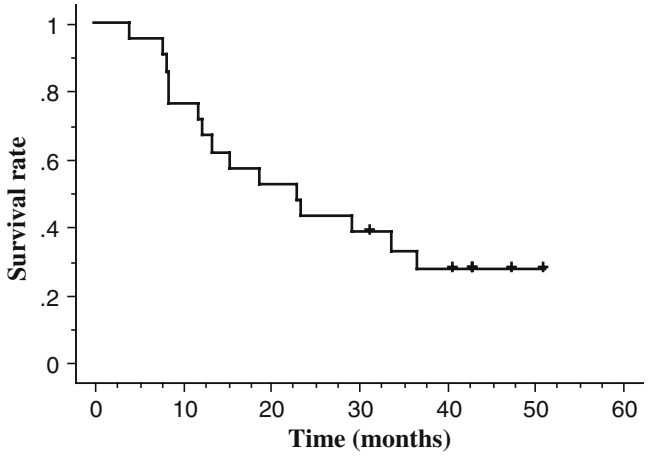

Fig. 2 Overall survival of patients treated with weekly docetaxel and cisplatin concomitant with TRT

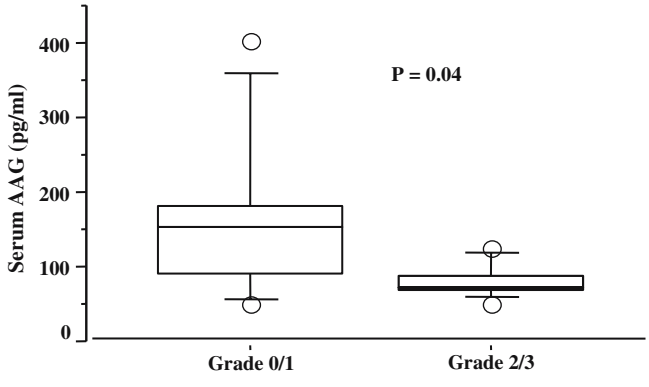

Fig. 3 Relationship between toxicity grade of esophagitis and serum AAG level

levels correlated significantly with the intensity of esophagitis in this study. The plasma AAG level was shown to be a significant predictor of pharmacodynamics in docetaxel treatment of NSCLC by Bruno et al. [20]. Since AAG strongly binds docetaxel, high AAG levels result in a lower free docetaxel fraction, and, therefore, decreased toxicity. The finding that high AAG decreased the grade of esophagitis was not unexpected.

In conclusion, the weekly combination of cisplatin and docetaxel concurrently with TRT is well tolerated and the recommended dose and schedule were determined to be cisplatin 25 mg/m^2 and docetaxel 20 mg/m^2 on days 1, 8, 15 of every 4 weeks, respectively. Because of favorable survival and acceptable toxicity profile, we consider this chemoradiotherapy as a warrant for further evaluation in phase II trials.

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