［原著］Hemoglobin as an important prognostic factor in concurrent chemoradiotherapy for locally advanced carcinoma of the cervix

Hemoglobin as an important prognostic factor in concurrent chemoradiotherapy for locally advanced carcinoma of the cervix

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ABSTRACT

Objective: To examine a possible association of hemoglobin with clinical outcome in patients with locally advanced squamous cell carcinoma of the cervix who were treated with concurrent chemoradiotherapy (CCRT).
Methods: Seventy-five patients with Stage IB to IVA disease who were treated with CCRT were reviewed retrospectively. The mean age was 49.8 years. In the treatment, standard radiotherapy was performed accompanied by concomitant chemotherapy using cisplatin. Pre-treatment hemoglobin was defined as the earliest hemoglobin level prior to the initiation of treatment. Weekly nadir hemoglobin levels throughout treatment were averaged and used as average weekly nadir hemoglobin during treatment (AWNHg). The mean follow-up time was 28.6 months.
Results: The mean pre-treatment hemoglobin of 11.6 g/dL was significantly reduced to the mean AWNHg of 9.9 g/dL. The levels of pre-treatment hemoglobin and AWNHg were significantly associated with tumor response to treatment. The 5-year cumulative disease-free survival and overall survival rates for all 75 patients were 67.8% and 75.3%, respectively. Multivariate statistical analysis revealed that AWNHg (>=9.0 versus <9.0 g/dL) was an independent prognostic factor for overall survival (p=0.038), but pre-treatment hemoglobin was not a significant factor.
Conclusion: AWNHg was one of the most powerful independent predictors of overall survival in patients undergoing CCRT for locally advanced squamous cell carcinoma of the cervix. *Ryukyu Med. J., 24(1) 1～10, 2005*

Key words: cervical carcinoma, concurrent chemoradiotherapy, hemoglobin, prognosis

INTRODUCTION

The majority of invasive carcinomas of the cervix are treated with radiotherapy, composed of radical external-beam irradiation plus intracavitary brachytherapy. It is well known that anemia before and/or during irradiation for cervical carcinoma has negative effects on local disease control and patient survival[1-3]. Many believe that uncorrected anemia compromises tumor radiation response by increasing the hypoxic tumor cell fraction and inducing a lower radiosensitivity.

Within the last decade, conventional radiotherapy as a single treatment modality has been replaced by concurrent chemoradiotherapy (CCRT) that can have significantly more favorable therapeutic effects than radiotherapy alone on advanced but localized cervical carcinoma[2,4-12]. In this context, anemia might have more adverse prognostic significance in CCRT than in radiotherapy alone, because anticancer drugs used in the treatment have a myelo-suppressive effect. Until recently, only few reports have addressed the clinical significance of anemia in patients undergoing CCRT for cervical carcinoma[9,12-18]. Also, the eligibility criteria of patients for CCRT treatment vary among these stud-

ies. In addition, lack of standardization in the contents or protocol details of treatment are found in each of the studies of which more than half were analyses on the data from different institutions. Therefore, it is important to provide some data obtained by analyzing patients with a more homogeneous clinical and therapeutic background who were treated at a single institution.

The purpose of the present study is to investigate the medical records of patients with cervical squamous cell carcinoma treated with the unified protocol of CCRT at our department, with special reference to a possible association of hemoglobin levels before and during treatment with tumor response to treatment and patient outcome.

MATERIALS AND METHODS

Patients

Between July 1997 and December 2002, 82 patients were treated with CCRT for locally advanced carcinoma of the cervix at the University of Ryukyus Hospital. The patient inclusion criteria for CCRT were: (1) Stage IB to IVA diseases, (2) histologically proven squamous cell carcinoma, (3) a cervical tumor of >4 cm in a diameter and/or a significant regional node swelling with no paraaortic node swelling, (4) no previous treatment, (5) age of <=70 years, and (6) full informed consent for treatment. Seven cases were excluded because of unaccomplished treatment due to rapid disease progression or severe adverse effects (n=4), and incomplete follow-up investigations or failure of follow-up (n=3). Thus, a total of 75 cases with a mean age of 49.8 years (range, 25～69 years) were included in this analysis. We did not request the institutional review board's approval for this study because of its retrospective nature.

The histology of squamous cell carcinoma was confirmed by reexamining hematoxylin and eosin-stained slides according to the World Health Organization criteria[19]. Patient age was <50 years in 35 cases and ≧50 years in 40 cases. Cervical disease was staged IB2 in 2 cases, IIA in 1 case, IIB in 37 cases, IIIB in 34 cases, and IVA in 1 case according to the International Federation of Gynecology and Obstetrics staging system[20]. Pelvic examination combined with magnetic resonance imaging (MRI) showed that the size of the cervical tumor was ≦4 cm in 5 cases and >4 cm in the remaining 70 cases. Parametrial involvement of disease was noted in 72 cases. A significant pelvic node swelling, which was defined as an enlargement of >10 mm in the shortest dimension by computerized tomography (CT)[21], was observed in 27 cases. The performance status was zero in 52 cases and 1 or 2 in 23 cases according to the Eastern Cooperative Oncology Group criteria[22].

CCRT

All patients underwent primary standard radiotherapy and a simultaneous combination of cisplatin chemotherapy. External-beam radiation was delivered using an 18 MV photon beam with central shielding through anteroposterior-opposed portals (4 cm width at the midline) for 5 days each week, to the whole pelvic region and, if needed, to the paraaortic region. Boost external-beam irradiation, if needed, was delivered to enlarged nodes and/or infiltrated parametrium. The total dose of external-beam radiation to the parametrium ranged from 50 to 60 Gy (mean dose; 53.7±4.7 Gy). External-beam irradiation was followed by a high dose-rate intracavitary brachytherapy using a remotely controlled afterloading system with an iridium-192 source. One to 4 fractions were administered once a week with a dose of 6.0 Gy at point A, with a total dose ranged from 6 to 30 Gy (mean dose; 17.9±3.7 Gy). The median overall treatment time was 48.3±5.7 days (range, 35～64 days). For all patients, cisplatin chemotherapy was combined concurrently with radiotherapy. The first cycle of chemotherapy was initiated on day 1 of external-beam radiation and performed as follows: a 2-hour continuous intravenous infusion of 20 mg of cisplatin/m^2 body-surface area on days 1 to 5 of radiotherapy[23, 24]. Chemotherapy was repeated at 3-week intervals. Total cycle given ranged from 1 to 3 cycles (mean; 2.3±0.7 cycles).

Evaluation of tumor response and follow-up after treatment

The response to treatment was evaluated by pelvic examination, MRI, CT, cytology and histology until 6 weeks after completion of treatment. A complete response (CR) was registered when no clinical or histological evidence of disease existed. All other cases with evidence of disease persistence were registered as non-complete response (non-CR).

The subsequent follow-up after treatment was conducted usually every 3 months for the first 2

Table 1 Association of clinical characteristics with hemoglobin level

Item	No. of patients	Pre-treatment hemoglobin (g/dL)	*p* value[b]	AWNHg (g/dL)	*p* value[b]
Age					
＜50 years	35	11.2±1.8 (6.9~14.2)[a]	0.039	9.6±1.3 (5.9~11.5)	0.13
≧50 years	40	12.1±1.9 (6.4~15.7)		10.1±1.5 (6.0~12.6)	
Stage					
IB+II	40	12.1±1.7 (8.0~15.1)	0.022	10.3±1.1 (7.6~12.6)	0.0054
III+IVA	35	11.1±2.0 (6.4~15.7)		9.4±1.6 (5.9~11.5)	
Tumor size					
≦4 cm	5	12.8±0.8 (11.5~13.5)	0.17	10.2±0.8 (9.4~10.8)	0.66
＞4 cm	70	11.6±1.9 (6.4~15.7)		9.9±1.5 (5.9~12.6)	
Parametrium					
Not involved	3	13.2±0.3 (13.0~13.5)	0.15	10.9±0.7 (10.4~11.7)	0.21
Involved	72	11.6±1.9 (6.4~15.7)		9.8±1.5 (5.9~12.6)	
Node swelling					
Negative	48	12.0±1.7 (6.9~15.7)	0.025	10.2±1.4 (5.9~12.6)	0.0090
Positive	27	11.0±2.0 (6.4~15.1)		9.3±1.4 (6.0~11.5)	
Performance status					
0	52	12.1±1.7 (7.8~15.7)	0.0022	10.3±1.1 (7.6~12.6)	0.0002
1~2	23	10.7±1.9 (6.4~13.5)		9.0±1.7 (5.9~11.5)	

AWNHg; average weekly nadir hemoglobin during treatment. a; mean±standard deviation and range shown in parenthesis. b; Student's *t*-test.

years and every 6 months thereafter. Follow-up examination included physical and pelvic examination, routine blood count and chemistry profile, urinalysis, chest radiography, imaging studies, and cytology and histology. Recurrence included both pelvic recurrence and distant extrapelvic recurrence in patients who were registered as CR at the end of radiotherapy. The mean follow-up time was 28.6±17.1 months (range, 6～77 months).

Determination of hemoglobin levels

Hematological data before and during treatment were collected to characterize the time course of anemia and blood transfusion practice. A full blood count was determined before treatment and at least once a week during treatment. The normal level for hemoglobin is ≧11.3 g/dL and anemia is defined as hemoglobin of <11.3 g/dL at the University of Ryukyus Hospital. Usually, patients were recommended to receive blood transfusion when their hemoglobin levels were less than 8.0 g/dL. Thirteen patients received blood transfusion; 9 cases before, 2 cases during, and 2 cases both before and during treatment. The mean amount of blood transfused was 6.1±2.4 units (range, 4～10 units), with a mean trigger hemoglobin of 5.6±1.5 g/dL (range, 2.8～7.5 g/dL). No patients received erythropoietin administration in this study.

Pre-treatment hemoglobin was defined as the earliest hemoglobin level recorded in relation to disease prior to the initiation of treatment. Weekly nadir hemoglobin levels throughout treatment were also recorded and the average was used as an estimate of hemoglobin level; an average weekly nadir hemoglobin during treatment (AWNHg) described by Grogan *et al*[2].

Statistics

Differences among patient groups for clinical characteristics, hemoglobin level, and radiation response were evaluated by the Student's *t*-test and the χ^2 or Fisher's exact test where appropriate. Disease-free survival (DFS) and overall survival (OAS) curves were calculated according to the Kaplan-Meier method using the date of initiation of treatment as the starting point, and differences between patient groups were tested by the log-rank test. Patients who failed to achieve CR were scored as recurrence at time zero.

In the absence of a standardized hemoglobin cut-off level for study of anemia in cervical carcinoma, we performed preliminary calculations on survival rates for patient groups stratified for hemoglobin level. The nearest survival rate to the mean survival rate for all patients was yielded from the groups with hemoglobin of 13.5 to 11.5 g/dL and of 11.5 to 9.5 g/dL for pre-treatment hemoglobin and from the groups with hemoglobin of 7.0 to 9.0 g/dL and of 9.0 to 11.0 g/dL for AWNHg. Therefore, the threshold hemoglobin levels of 11.5 g/dL

Table 2 Correlation between clinical characteristics and tumor response to treatment

Item	No. of patients	Tumor response		*p*-value[a]
		CR [n=55]	Non-CR/Rec [n=20]	
Age				
<50 years	35	24 (68.6%)	11 (31.4%)	0.38
>=50 years	40	31 (77.5%)	9 (22.5%)	
Stage				
IB+II	40	32 (80.0%)	8 (20.0%)	0.16
III+IVA	35	23 (65.7%)	12 (34.3%)	
Tumor size				
<=4 cm	5	5 (100.0%)	0	0.16
>4 cm	70	50 (71.4%)	20 (28.6%)	
Parametrium				
Not involved	3	3 (100.0%)	0	0.29
Involved	72	52 (72.2%)	20 (27.8%)	
Node swelling				
Negative	48	39 (81.3%)	9 (18.8%)	0.039
Positive	27	16 (59.3%)	11 (40.7%)	
Performance status				
0	52	39 (75.0%)	13 (25.0%)	0.62
1~2	23	16 (69.6%)	7 (30.4%)	
Pre-treatment hemoglobin				
>=11.5 g/dL	47	40 (85.1%)	7 (14.9%)	0.0028
<11.5 g/dL	28	15 (53.6%)	13 (46.4%)	
AWNHg				
>=9.0 g/dL	58	49 (84.5%)	9 (15.5%)	<0.0001
<9.0 g/dL	17	6 (35.3%)	11 (64.7%)	

AWNHg; average weekly nadir hemoglobin during treatment. CR; complete response with no recurrence. Rec; recurrence after complete response.
a; χ^2 or Fisher's exact test.

for pre-treatment hemoglobin and of 9.0 g/dL for AWNHg were chosen for further analyses.

Univariate and multivariate analyses were performed using the Cox proportional hazards model of regression analysis.

$P<0.05$ was considered significant for all statistical analyses.

RESULTS

Association of patient characteristics with hemoglobin level

For all 75 patients, the mean pre-treatment hemoglobin was 11.6±1.9 g/dL. Anemia defined as a hemoglobin level of <11.3 g/dL was observed in 26 patients (34.7%). This mean pre-treatment hemoglobin was significantly reduced by 1.7 g/dL to the mean AWNHg of 9.9±1.4 g/dL ($p<0.0001$) and 73 anemic patients (97.3%) were observed during treatment.

The pre-treatment hemoglobin level was significantly associated with age, stage, node swelling, and performance status ($p=0.039\sim0.0022$). In regard to the AWNHg level, a significant difference was noted for stage, node swelling, and performance status ($p=0.0090\sim0.0002$) (Table 1).

Tumor response to treatment by patient characteristics including hemoglobin

Seventy-three of the 75 patients (96.1%) achieved CR at the end of treatment. However, in post-treatment follow-up, 17 of these 73 patients (23.3%) developed pelvic and/or distant recurrent disease. The mean pre-treatment hemoglobin and AWNHg in the CR without recurrence group (n=55) and in the non-CR or recurrence group (n=20) were 12.1±1.4 g/dL (range, 8.2~15.7 g/dL) and 10.3±2.3 g/dL (range, 6.4~15.7 g/dL), and 10.3±1.1 g/dL (range, 7.4~12.6 g/dL) and 8.8±1.8 g/dL (range, 5.9~11.3 g/dL), respectively. There were significant differences for both mean hemoglobin levels between the two patient groups ($p=0.0039$ and $p=0.0028$).

Concerning tumor response to treatment according to patient characteristics, including pre-treatment hemoglobin and AWNHg (>=11.5 versus <11.5 g/dL and >=9.0 versus <9.0 g/dL), a significant difference was found for node swelling status, pre-treatment hemoglobin, and AWNHg ($p=0.039$, $p=0.0028$, and $p<0.0001$, respectively) (Table 2).

Table 3 Univariate analysis of prognostic variables for DFS and OAS

Variables	No. of patients	DFS		OAS	
		5-year rate	*p* value	5-year rate	*p* value
Age					
<50 years	35	67.7%	0.27	63.7%	0.029
>=50 years	40	69.9%		85.6%	
Stage					
IB+II	40	52.0 %	0.21	86.3%	0.022
III+IVA	35	65.5%		64.8%	
Tumor size					
<=4 cm	5	100.0%		100.0%	
>4 cm	70	65.9%		73.4%	
Parametrium					
Not involved	3	100.0%		100.0%	
Involved	72	66.6%		74.1%	
Node swelling					
Negative	48	79.3%	0.055	80.7%	0.75
Positive	27	49.5%		66.0%	
Performance status					
0	52	59.2%	0.69	77.2%	0.19
1~2	23	69.6%		69.1%	
Pre-treatment hemoglobin					
>=11.5 g/dL	47	78.1%	0.0008	90.6%	<0.0001
<11.5 g/dL	28	52.4%		50.2%	
AWNHg					
>=9.0 g/dL	58	77.4%	<0.0001	88.8%	<0.0001
<9.0 g/dL	17	34.3%		33.1%	

AWNHg; average weekly nadir hemoglobin during treatment.

Table 4 Multivariate analysis of prognostic variables for DFS and OAS

Variables	DFS			OAS		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age						
<50 years vs. >=50 years	0.606	0.243-1.510	0.28	0.267	0.089-0.808	0.019
Stage						
IB+II vs. III+IVA	0.777	0.298-2.026	0.61	0.318	0.099-1.024	0.055
Pre-treatment hemoglobin						
>=11.5 g/dL vs. <11.5 g/dL	0.761	0.153-3.780	0.74	0.478	0.077-2.968	0.43
AWNHg						
>=9.0 g/dL vs. <9.0 g/dL	0.230	0.049-1.083	0.063	0.197	0.042-0.917	0.038

AWNHg; average weekly nadir hemoglobin during treatment. HR; hazard ratio. 95% CI; 95% confidence interval.

Prognostic factors and DFS and OAS

The 5-year cumulative DFS and OAS rates for all 75 patients were 67.8% and 75.3%, respectively. Univariate statistical analysis showed that a significant difference was found in the DFS for pre-treatment hemoglobin and AWNHg (p=0.0008 and p<0.0001, respectively) and in the OAS for patient age, stage, pre-treatment hemoglobin, and AWNHg (p=0.0290~<0.0001) (Table 3). Only patients with pre-treatment hemoglobin of >=11.5 g/dL or AWNHg of >=9.0 g/dL had a 5-year OAS rate of approximately 90%. The DFS and OAS curves for 75 patients stratified for pre-treatment hemoglobin and AWNHg are depicted in Figures 1 and 2. Both survivals were significantly worse in patients with pre-treatment hemoglobin of <11.5 g/dL or with AWNHg of <9.0 g/dL, compared to patients with pre-treatment hemoglobin of >=11.5 g/dL or with AWNHg of >=9.0 g/dL (p=0.0008~<0.0001).

Multivariate statistical analysis showed that AWNHg was a significant independent prognostic factor, next to patient age, for OAS (p=0.038), but

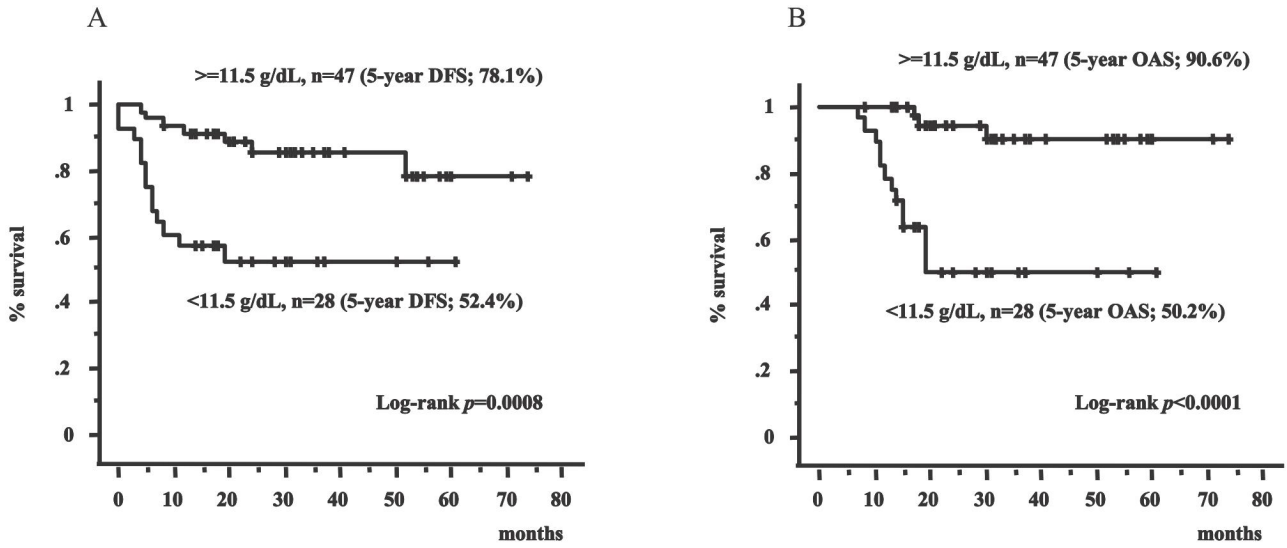

Fig. 1 DFS (A) and OAS (B) curve calculated with the Kaplan-Meier method for 75 patients treated with CCRT stratified for pre-treatment hemoglobin level

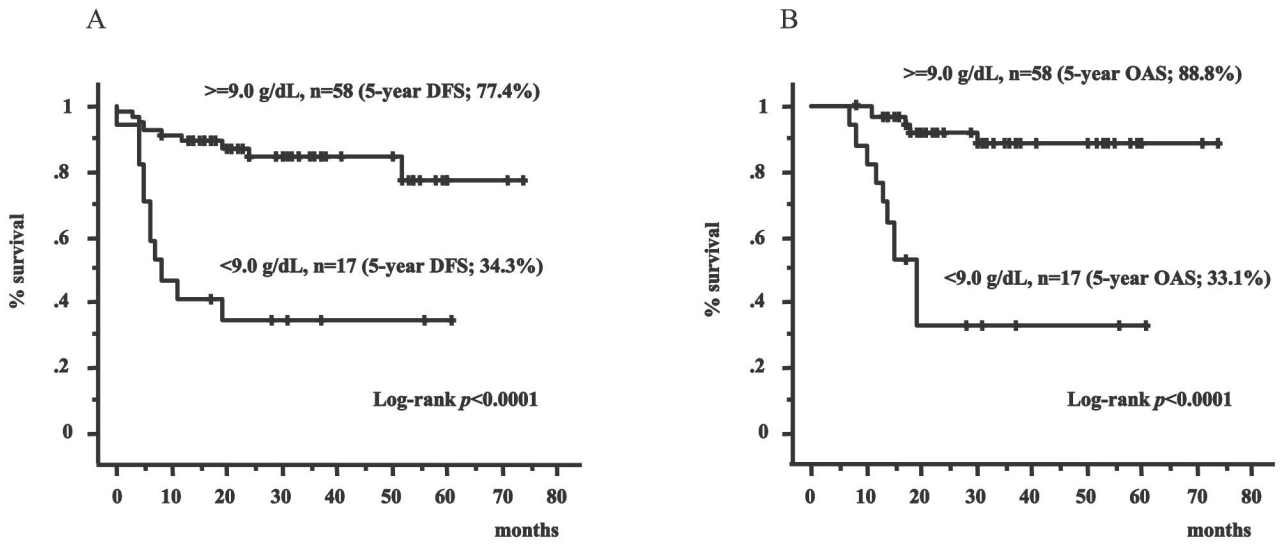

Fig. 2 DFS (A) and OAS (B) curve calculated with the Kaplan-Meier method for 75 patients treated with CCRT stratified for AWNHg level during treatment

pre-treatment hemoglobin was not (Table 4).

DISCUSSION

The main findings in the present study of CCRT are as follows: (1) the mean pre-treatment hemoglobin declined significantly to the mean AWNHg during treatment, (2) the levels of pre-treatment hemoglobin and AWNHg were significantly associated with tumor response to treatment, and (3) AWNHg and age were significant independent prognostic factors for patient survival, but pre-treatment hemoglobin was not.

CCRT is a new standard treatment for cervical carcinoma. The treatment modality might induce more serious anemia than does radiotherapy alone, since anticancer drugs with a myelo-toxic action are given concomitantly with irradiation. In Table 5, we list the data about anemia presented in literature describing CCRT for carcinoma of the cervix. In our study, the mean pre-treatment hemoglobin of 11.6 g/dL was significantly reduced by 1.7 g/dL to the mean AWNHg in CCRT using cisplatin. In

Table 5 Literature review of anemia in CCRT using cisplatin alone or cisplatin-combined regimens for carcinoma of the cervix

Authors	No. of patients	Stage	CCRT		Anemia/Hg
			Radiotherapy	Chemotherapy	
Wong et al[13]	39/25[a]	IIB, IIIB	EBRT, LDR	CDDP	Anemia (WHO grade 2-3); 23% (p<0.05 for 0% in RT)
Tseng et al[14]	60/62[a]	IIB, IIIB	EBRT, HDR	CDDP, VCR, BLM	Anemia (GOG grade 3-4); 23% (p<0.05 for 8% in RT)
Peters III et al[19]	127/116[a, b]	IA~IIA	EBRT	CDDP, 5-FU	Anemia (NCI grade 2-4); 25% (p<0.05 for 12% in RT)
Pearcey et al[12]	127/126[a]	IB~IVA	EBRT, L/M/HDR	CDDP	Hg fall of >=1.5 g/dL; 31% (p<0.05 for 20% in RT)
Strauss et al[15]	27[c]	IB~IVA	EBRT, HDR	CDDP	Anemia (NCI-CTG grade 2); 22%
Obermair et al[17]	60	IB~IVA	EBRT, LDR	CDDP, VBL, 5-FU	Pre-Hg fell by 2.2 g/dL to Hg during treatment
Winter III et al[18]	494	IIB~IVA	EBRT, LDR	CDDP, 5-FU, HU	Pre-Hg fell by 1.0 g/dL to AWNHg
Present study	76	IB~IVA	EBRT, HDR	CDDP	Pre-Hg fell by 1.7 g/dL to AWNHg

EBRT; External-beam radiotherapy. L/M/HDR; Low, medium, or high dose-rate intracavitary brachytherapy. CDDP; Cisplatin. VCR; Vincristine. BLM; Bleomycin. 5-FU; 5-fluorouracil. VBL; Vinblastine. HU; Hydroxyurea. RT; Radiotherapy. Hg; Hemoglobin. AWNHg; Average weekly nadir hemoglobin during treatment. a; Number of patients who underwent CCRT/radiotherapy alone. b; All cases underwent CCRT or radiotherapy postoperatively. c; Fourteen cases underwent CCRT postoperatively.

previous studies by Obermair *et al*[17] and Winter III *et al*[18], the mean pre-treatment hemoglobin was reduced to the mean nadir hemoglobin during treatment by 2.2 g/dL and 1.0 g/dL respectively, in CCRTs using cisplatin and other drugs. Furthermore, a randomized trial by Pearcey *et al*[12] showed that 31% of patients treated with CCRT using cisplatin experienced a hemoglobin decrease of more than 1.5 g/dL, which was significantly higher compared with 20% in the radiotherapy only treatment. Similar incidence of anemia, ranging from 22 to 25% in the CCRT treatment, which is significantly higher than that in the control treatment of radiation alone, have been found in several previous studies[9, 13-15]. These findings, together with ours, indicate that CCRT could induce more severe anemia and more anemic patients than radiotherapy alone.

Our study demonstrated that patient hemoglobin, especially AWNHg, was highly predictive of tumor response to treatment. In a huge tumor of the cervix, the likelihood of sterilizing it with radiation decreases, because of an increased anemic or hypoxic radioresistant tumor cell population due to poor blood supply or ischemia. While drugs given in CCRT are elucidated to exert a radiation-sensitizing effect upon those hypoxic tumor cells[25-27], the drugs are assumed to worsen the existing patient anemia and tumor cell hypoxia. The way that anemia compromises tumor response is relatively unknown in CCRT, although it is well known in conventional radiotherapy. To date, only one study by Obermair *et al*[16] is available for examining an association between patient hemoglobin and tumor response in CCRT. They described that nadir hemoglobin during treatment was the only significant factor predicting tumor response (treatment failure or complete response of local disease), although pre-treatment hemoglobin was not. Together with the aforementioned studies, these findings strongly suggest that the lower hemoglobin level induced in CCRT has more serious negative influence on tumor response to treatment than does the low hemoglobin level in radiotherapy alone.

A large-scale retrospective study on 605 patients by Grogan *et al*[2] qualified for the first time the particular importance of a decreasing AWNHg for the prognosis of patients with carcinoma of the cervix. However, their data gave little information on CCRT, since only 11% of the cases were treated by CCRT while the vast majority were treated by radiation therapy alone. Our study demonstrated that AWNHg, but not pre-treatment hemoglobin, was a significant independent prognostic factor for patient survival in CCRT. Obermair *et al*[16,17] through two retrospective studies on 60 and 57 patients treated with CCRT at two radiation centers, reported that the lowest hemoglobin level during treatment was highly predictive of shortened progression-free survival whereas hemoglobin level at presentation was not significant. More

recently, Winter III *et al*[18] by analyzing the prognostic effects of anemia in a large population of 494 patients treated with CCRT at more than 50 institutions, reported that hemoglobin during treatment was an independent predictor of patient outcome but pre-treatment hemoglobin was not. In their 3 analyses, Stage IB or IIB to IVA cervical tumors included non-squamous cell carcinoma histologies in 5 to 12% of the cases. Their patients who were multi-racial or multi-ethnical, underwent radiotherapy with administration of cisplatin alone, cisplatin combined with vinblastine, 5-fluorouracil, or hydroxyurea. External-beam irradiation was followed mainly by low dose-rate and in part by high dose-rate intracavitary brachytherapies. In addition, they and other investigators mentioned a racial disparity with respect to low hemoglobin levels in cervical carcinoma patients[28]. In our study, all 75 patients were Japanese and treated for locally advanced cervical squamous cell carcinoma of Stage IB2 to IVA by the strictly unified protocol of CCRT involving standard radiotherapy of external-beam irradiation followed by high dose-rate intracavitary brachytherapy and chemotherapy of cisplatin at a single institution. To our knowledge, this is the first report about a possible association between hemoglobin and patient outcome in CCRT using radiotherapy with high dose-rate intracavitary brachytherapy[29]. Thus, the finding of this study that AWNHg was significantly correlated with tumor response to treatment and was consequently one of the most powerful independent predictors for patient survival, is more convincing than the findings of other studies, because this study was conducted on patients with a more homogeneous clinical and therapeutic background.

The more severe and/or frequent anemia observed in CCRT compared with radiotherapy alone is theoretically postulated to be due to the additive superimposition or the synergistic potentiation of bone marrow suppression by both radiotherapy and chemotherapy. It appears that the regimens of cisplatin alone or cisplatin-containing chemotherapies that were used in the majority of clinical trials of CCRT need to be reevaluated, focusing on chemotherapy-induced anemia. The magnitude of impaired local disease-control rate and/or survival rate for those anemic patients might mask the therapeutic gains achieved with the potential synergistic effects of CCRT. Specific alternative chemotherapeutic regimens less toxic on erythropoiesis without losing their anti-tumor and/or radio-sensitization effects, should be sought for clinical practice of CCRT.

In conclusion, AWNHg during treatment was one of the most powerful independent predictors of OAS in patients undergoing CCRT for advanced but localized squamous cell carcinoma of the cervix. In this treatment modality, hemoglobin during treatment should be more seriously appreciated as a prognostic factor since the treatment could cause anemia at a higher rate and/or grade than does conventional radiotherapy.

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