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Original Article

Prognostic significance of neutropenia during adjuvant concurrent chemoradiotherapy in early cervical cancer

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Objective: To evaluate the prognostic significance of adjuvant concurrent chemoradiotherapy-induced neutropenia with survival in patients with squamous cell carcinoma of the uterine cervix.
Methods: Data from 107 patients with stage IB-IIB cervical cancer were retrospectively analyzed. The median follow-up was 37.5 (4.2-72.7) months. All patients had received radical surgery, including pelvic lymphadenectomy, followed by paclitaxel plus carboplatin-based concurrent chemoradiotherapy. Relative neutropenia, defined as an absolute neutrophil count $<1,000/mm^3$ at the concurrent chemoradiotherapy cycle nadir, correlated to the pathologic findings and survival outcomes.
Results: Sixty-six patients experienced neutropenia at least once during concurrent chemoradiotherapy, and demonstrated marginal improvement in disease-free survival (p=0.055), although not in overall survival. By subgroup analyses, the gain of disease free survival mainly originated from the node metastasis subgroup (p=0.033). Treatment-induced neutropenia proved to be the only significant independent factor for recurrence in cervical cancer (p=0.042) by multivariate analysis.
Conclusion: Concurrent chemoradiotherapy-induced neutropenia may be a prognostic factor of recurrence in patients with cervical cancer. Individualized dose titration of the tolerable myelosuppression might be beneficial.

Key Words: Uterine cervical cancer, Chemoradiotherapy, Neutropenia, Survival

INTRODUCTION

Uterine cervical cancer is the second most frequently diagnosed malignancy in women worldwide, and is the main cause of cancer mortality in developing countries.[1,2] Although surgery is sufficient in most patients with early cervical cancer, adjuvant concurrent chemoradiotherapy (CCRT) has been established as the optimal therapeutic modality after surgery in high-risk early cervical cancers.[3,4] However, hematologic toxicity, especially neutropenia, is the most frequent and significant complication during CCRT.[4]

Until recently, neutropenia was viewed primarily as a toxic side effect of chemotherapy because it is associated with the risk of life-threatening infections, and with chemotherapy dose reductions or delays that may compromise treatment outcomes.[5,6] Conversely, increasing evidence suggests that neutropenia may be a physiologic marker of chemotherapy dose intensity, anti-tumor efficacy and cancer stem cell damage,[7-12] since improved survival is observed in patients who experienced neutropenia during treatment in many cancers, such as breast,[7-9] lung,[10] gastric,[11] and ovarian cancer.[12] However, there have been few studies regarding the prognostic value of CCRT-induced neutropenia in patients with cancers, especially cervical cancer.

Thus, we reviewed our clinical data to assess whether postoperative adjuvant CCRT-induced neutropenia may have a prognostic significance, including recurrence and survival in squamous cell carcinoma of the uterine cervix.

MATERIALS AND METHODS

We identified 114 patients who were evaluated and treated for squamous cell carcinoma of the cervix with paclitaxel + carboplatin-based CCRT between January 2002 and June 2007. This study was approved by the Institutional Review Board of our institution. All patients were clinical FIGO stage IB-IIB, and underwent radical hysterectomy with lymph node dissection, followed by adjuvant CCRT. We excluded those cases that lacked follow-up data or prophylactic granulocyte colony stimulating factor (G-CSF) use, and 107 patients were considered eligible for analysis. The median duration of follow-up was 37.5 months (range, 4.2 to 72.7 months).

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Adjuvant CCRT was recommended in the following cases: pelvic lymph node (LN) metastasis, an involved resection margin (RM), and parametrial invasion (PM). Adjuvant CCRT was also recommended if at least two of the following risk factors were present: a tumor size >4 cm, lymphovascular space invasion (LVSI), and deep stromal invasion (DSI, defined as an invasion into >1/2 of the thickness of the cervical wall). Radiation therapy was delivered at 1.8 Gy per fraction once daily, 5 days per week over 6 weeks. The median dose to the whole pelvis was 50.4 Gy.

Concurrent chemotherapy consisted of intravenous paclitaxel at 135 mg/m^2 administered over 3 hours, followed by carboplatin at a dose giving an area under the time-concentration curve of 5 mg min/ml (Calvert formula). Two courses of chemotherapy were administered at 4-week intervals during radiation therapy as previously reported.[13]

During adjuvant CCRT, a complete blood cell count was performed weekly and serum BUN/creatinine levels, liver function tests, and urinalysis were checked at 4-week intervals. After completion of treatment, patients were followed-up regularly with a pelvic examination, a Papanicolaou smear, tumor marker (SCC-Ag), and image studies, if required. Relative neutropenia was defined as an absolute neutrophil count (ANC) <1,000/mm^3 at the chemotherapy cycle nadir. Disease-free survival (DFS) was calculated as the time in months from the last day of CCRT to date of disease progression or death, or date of last contact. Overall survival (OS) was calculated as the time in months from the last day of CCRT to death, or date of last contact.

Table 1. Characteristics between patients with neutropenia and those who never had neutropenia during treatment

	Neutropenic (N=66; 62%)	Non-neutropenic (N=41; 38%)	p-value
Age			
Median (range)	52 (29-82)	56 (33-74)	0.30
Stage Ib1	30 (45.5%)	13 (31.7%)	0.25
Ib2	13 (19.7%)	6 (14.6%)	
IIa	17 (25.8%)	18 (43.9%)	
IIb	6 (9.1%)	4 (9.8%)	
Leukocytosis at diagnosis			0.52
Median (range)	6,330 (2,920-11,270)	6,500 (4,020-11,220)	
Pre-CCRT hemoglobin			0.43
Median (range)	11.3 (9.4-14.2)	11.2 (8.9-14.1)	
PM invasion	30 (45.5%)	13 (31.7%)	0.22
Involvement of RM	9 (13.6%)	6 (14.6%)	1.00
LN metastasis	38 (57.6%)	18 (43.9%)	0.23
Bulky tumor (>4 cm)	33 (50.0%)	24 (58.5%)	0.43
DSI	54 (81.8%)	39 (95.1%)	0.074
LVSI	52 (78.8%)	25 (61.0%)	0.075

Fisher's exact test, Student *t*-test.
CCRT: concurrent chemoradiation therapy, PM: parametrium, RM: resection margin, LN: lymph node, DSI: deep stromal invasion, LVSI: lymphovascular space invasion.

Statistical analysis was performed by using the Kaplan-Meier method for survival calculation and the Cox proportional hazard model for multivariate analysis. SPSS ver. 15.0 (SPSS Inc., Chicago, IL, USA) was used and p-values <0.05 were considered significant.

RESULTS

Sixty six patients (N=66) experienced relative neutropenia (ANC <1,000/mm^3) at least once during CCRT, while the remaining 41 patients had no episodes of neutropenia. The 66 patients who experienced relative neutopenia had a total of 104 episodes, for an average of 1.58 episodes per patient, and the mean ANC was 520 per episode of neutropenia. Patients with neutropenia during treatment were similar to patients who never had neutropenia with respect to age, clinical FIGO stage, PM invasion, involvement of RM, LN metastasis, large tumor size (>4 cm), DSI, LVSI, leukocytosis at diagnosis, and pre-CCRT hemoglobin level (Table 1).

Both neutropenic and non-neutropenic groups showed good tolerance except for neutrophil count. One patient who experienced grade (Gr) 4 neutropenia suffered from neutropenic fever, and chemoradiotherapy was delayed for about 2 weeks. Other toxicities observed between the two groups (neutropenic group: Gr3 anemia 1, Gr3 thrombocytopenia 1, Gr3 nausea 1, and Gr3 urinary frequency 1; non-neutropenic group: Gr3 urinary frequency 1) were all tolerable as previously reported.[13]

Patients who experienced neutropenia showed marginal improvement of DFS (p=0.055) (Table 2, Fig. 1), although not in overall survival. In the subgroup analysis, we observed that improvement of DFS in the neutropenic group originated from the node metastasis subgroup (p=0.033) (Table 2, Fig. 1), and parametrial invasion subgroup (p=0.051) (Table 2).

Table 2. Survival analysis between neutropenic and non-neutropenic groups, with additional sub-group analysis in patients positive to PM involvement or LN metastasis or RM involvement, respectively

	Mean DFS (months)	95% confidence interval	p-value*
Stratified by neutropenia			
Neutropenic group	62.5	(58.1-66.9)	0.055
Non-neutropenic group	57.6	(51.0-67.2)	
Subgroup analysis:			0.051
PM (+) subgroup			
Neutropenic group	54.2	(48.4-60.0)	
Non-neutropenic group	50.0	(32.7-65.2)	
Subgroup analysis:			0.033
LN (+) subgroup			
Neutropenic group	61.5	(55.3-67.7)	
Non-neutropenic group	49.4	(36.0-62.9)	

PM: parametrium, LN: lymph node, RM: resection margin, DFS: disease-free survival.
*Log rank test.

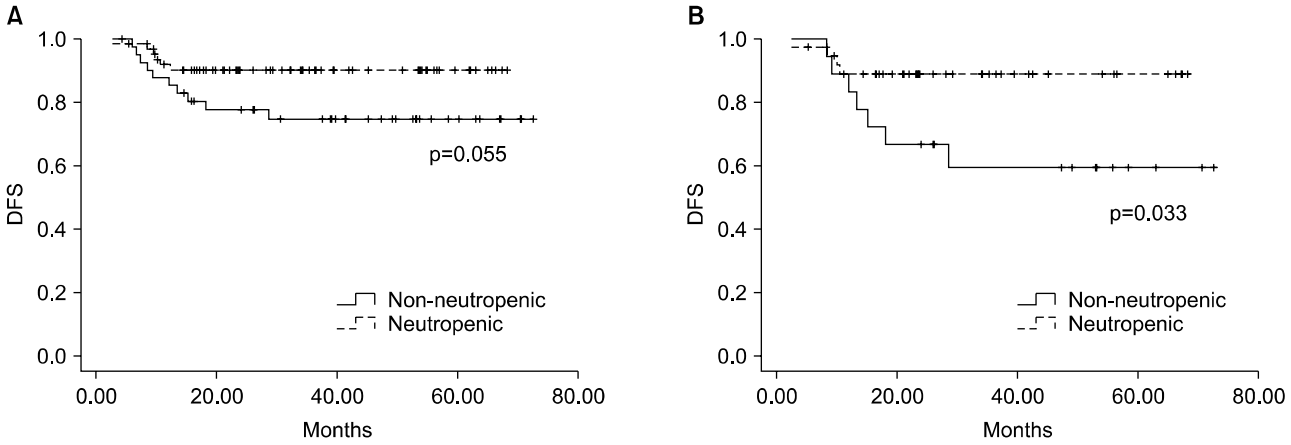

Fig. 1. Kaplan-Meier curve depicting the disease-free survival (DFS) for neutropenic and non-neutropenic patients. (A) DFS (p=0.055), (B) DFS in cases of lymph node metastasis (p=0.033).

Table 3. Risk factor analysis of recurrence in patients treated with adjuvant chemoradiation

Risk factors	DFS	DFS	
	p-value*	Adjusted HR (95% CI)	Adjusted p-value†
Age	0.66	1.0 (0.98, 10.7)	0.34
Stage	0.25	0.88 (0.28, 2.80)	0.83
Bulky tumor (>4 cm)	0.38	0.72 (0.25, 2.01)	0.53
Depth of cervical invasion	0.94	2.37 (0.45, 12.53)	0.31
Lymphovascular apace invaion	0.43	0.44 (0.05, 3.93)	0.46
Parametrial extensions	0.40	0.82 (0.27, 2.44)	0.72
LN metastasis	0.17	0.47 (0.15, 1.48)	0.20
Resection margin	0.38	0.65 (0.18, 2.34)	0.65
Neutropenia	0.055	0.35 (0.13, 0.96)	0.042

DFS: disease-free survival, LN: lymph node, NS: not significant.
* Log Rank Test, †Cox proportional hazard model.

On the contrary, node negative or PM free subgroups had no difference in DFS when stratified by neutropenia (p=0.49 and 0.31, respectively).

The neutropenia was suspected to be the only significant parameter of recurrence in the univariate analysis. We used the Cox proportional hazard model to compensate the confounding effect of other well-known risk factors, including age, stage, PM invasion, involvement of RM and LN metastasis; only neutropenia was determined as a prognostic factor for recurrence with statistical significance (Hazard ratio, 0.35; 95% confidence interval, 0.13 to 0.96; p=0.042) (Table 3).

DISCUSSION

The object of this study was to evaluate the prognostic significance of neutropenia during adjuvant concurrent chemoradiotherapy in early cervical cancer. We demonstrated that DFS was prolonged in patients with CCRT-induced neutropenia.

The prognostic significance of CCRT-induced neutropenia has not determined until now. However, the prognostic value of chemotherapy-induced neutropenia has been investigated in many cancers. As a marker of therapeutic efficacy, chemotherapy-induced neutropenia began to be reported in early breast cancer.[7-9] In these studies, the hematologic toxic effects represented by neutropenia,[9] myelosuppression,[8] and leucocyte nadir[7] had a significant association on survival gain. In advanced lung cancer, the positive correlation between neutropenia and longer survival was demonstrated by analyzing the pooled data from three randomized trials of 1,265 patients with non-small cell lung cancer. Regarding the severity of neutropenia, some studies have suggested that moderate neutropenia was associated with higher drug efficacy and increased survival than no or severe neutropenia, especially in early breast[9] and advanced gastric cancers.[11]

Our findings support the idea that neutropenia may be a surrogate indicator for the biological activity of cytotoxic agents and 'chemoradiation therapy'. Although tumors have another mechanism of acquiring resistance by genetic changes to the specific drug or radiation, the sensitivity of tumor cells reflect the genetic predisposition, which would theoretically be the same in all cells, including hematopoietic cells. Therefore, neutropenia represents adequate exposure of a drug[14] or radiation to the tumor cells and all other cells, including hematopoietic cells in that individual.

In other words, the absence of neutropenia during chemoradiation therapy might be associated with under-dosing. Usually, the dose of cytotoxic agents is determined by biophysical profiles, such as body surface area (BSA) or body weight. However, there has been criticism against the correlation between BSA and the pharmacokinetic variables (e.g., hepatic and renal blood flow and activity of enzymatic systems) of most cytotoxic agents.[15-18] Unrecognized under-dosing has been reported in about 30% or more of patients receiv-

ing a standard regimen.[15] On the contrary, toxicity or response in some tumors are known to be more correlated with pharmacokinetics, yet not completely explaining the variation in drug effect between individuals.[17]

As a recent point of view, one study hypothesized that cancer stem cell[19,20] suppression is correlated with normal stem cell suppression, because stem cells between normal tissue and cancer have a common genetic predisposition. The cancer stem cell suppression is clinically presented as neutropenia; suppression of normal hematopoietic stem cell. Therefore, chemotherapy-induced neutropenia could be a surrogate indicator of cancer stem cell suppression.[12] This concept means that the eradication of cancer stem cells is more likely when neutropenia is observed during chemotherapy. Therefore, treatment-induced neutropenia indicates not only treatment efficacy, but also damage to cancer stem cells, which leads to complete cure.

Interestingly, in our study, the DFS advantage was enhanced significantly in patients with nodal metastasis, and marginally in those with PM invasion. On the contrary, patients without LN metastasis or PM invasion showed no difference in DFS between the neutropenic and non-neutropenic groups. This may be due to the 'residual tumor' effect. Although progressive pathologic findings could be a risk factor of disease recurrence, these could also be translated into an increased possibility of 'residual cancer cells' that responds to chemoradiation therapy, resulting in a therapeutic effect. This phenomenon was also observed in cases of ovarian cancer in which the survival advantage was mainly achieved in the suboptimally debulked patients.[12]

Although improvement of DFS was evident, our study did not show advantages in OS in patients with neutropenia. One possible reason is the limitation of the cases and relatively short follow-up time in our study. The prognosis of early cervical cancer is relatively good; over 80% of 5-year OS rate in Korea.[21] So, larger number of patients should be analyzed to detect the effect of CCRT-induced neutropenia on OS. The second possible reason may be due to the prolonged survival by adjuvant or palliative treatment in recurred patients, which also makes it complicated to analyze OS. The limitation of this study was mainly from the inherent problems of retrospective analyses, although we minimized this weakness by selecting refined data consisting of the same chemoradiation regimen and the dose in a squamous cell type.

To our best knowledge, there have been few reports regarding the effect of CCRT-induced neutropenia on survival. From this study, we conclude that CCRT-induced neutropenia may be a prognostic factor of recurrence. However, whether high-dose CCRT could be beneficial or not is still undetermined, although treatment-related neutropenia is dose-dependent. On the contrary, the feasibility and efficacy of high-dose chemotherapy has been reported in other tumors including germ cell tumors,[22] sarcomas,[23] and breast cancers.[24,25]

In summary, we demonstrated that adjuvant CCRT-induced neutropenia may be a prognostic factor of recurrence in cervical cancer. From this study, we suggest that individualized dose titration of CCRT might be considered under the safe range of myelosuppression, although further systemic studies are required.

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