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Prognostic value of pre-treatment circulating monocyte count in patients with cervical cancer: Comparison with SCC-Ag level

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ABSTRACT

Objective. Higher level of circulating monocyte has been reported to be related with higher cancer incidence and mortality. We investigated the role of pre-treatment circulating monocyte count for cancer specific survival in cervical squamous cell carcinoma patients comparing with pre-treatment squamous cell carcinoma-related antigen (SCC-Ag) level.

Methods. We retrospectively enrolled patients with squamous cell carcinoma of the cervix (FIGO stage IB to IVA) who had complete blood cell counts with differential cell count and serum SCC-Ag level within 2 weeks before starting initial treatment and were treated at Samsung Medical Center, Seoul, Korea, from 1996 to 2007.

Results. The 788 patients in our study group had a median follow-up of 53.4 months and a five-year survival rate of 87.8%. The median value for pre-treatment circulating monocyte count was 349/μl (21–1463), and the median concentration of SCC-Ag was 1.6 ng/ml (0.1–362.0). In multivariable analysis, the pre-treatment circulating monocyte count was an independent prognostic factor for progression-free survival and overall survival in locally advanced disease ($P=0.007$ and $P=0.038$) but not in case of SCC-Ag for overall survival. The combined index of monocyte count and SCC-Ag level could enhance the prognostic value of SCC-Ag alone in patients with locally advanced cervical squamous cell carcinoma.

Conclusions. A higher pre-treatment circulating monocyte count is independently associated with poor prognosis in patients with locally advanced cervical squamous cell carcinoma. The pre-treatment circulating monocyte count may be considered as an adjunctive biomarker with SCC-Ag.

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Introduction

Cervical carcinoma is the second most common cancer in women on a global scale and one of the most lethal female malignancies in developing countries [1,2]. Cervical carcinoma has different histological subtypes, of which invasive squamous cell carcinoma (SCC) is the most common, accounting for about 80% of invasive cancer in the cervix [3]. Squamous cell carcinoma-related antigen (SCC-Ag), which is also known as TA-4 (tumor antigen), is the tumor marker of choice for SCC of the cervix; it emerges concurrently with squamous formation of the uterine cervix and increases during the neoplastic transformation of the cervical squamous epithelium [4]. Increasing serum SCC-Ag level can precede the clinical diagnosis of recurrent disease in 46–92% of the cases; however, the clinical relevance in predicting prognosis based on pre-treatment serum SCC-Ag assay is still debated [5,6].

In the human innate immune system, antigen-presenting cells (APCs), such as dendritic cells and macrophages, display antigen complexes which present major histocompatibility complex on their surfaces so that T-cells can recognize the complex using their T-cell receptors [7]. Interestingly these APCs, which play pivotal roles in the initiation, programming, and regulation of tumor-specific immune responses [8], are derived from peripheral monocytes [9,10]. Moreover, it was recently reported that SCC of the head and neck influences monocyte phenotype [11], and the circulating monocyte count can be used to independently predict incident cancer and mortality [12], which suggests an association between cancer prognosis and monocyte.

The purpose of this study is to investigate the prognostic role of pre-treatment circulating monocyte comparing with SCC-Ag level

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and the clinical relevance in prediction prognosis based on the pre-treatment peripheral monocyte count in combination with the level of pre-treatment SCC-Ag in patients with SCC of the cervix.

Materials and methods

Patients

Patients with SCC of the cervix (FIGO stage IB to IVA) who were treated at Samsung Medical Center, Seoul, Korea from 1996 to 2007 were retrospectively enrolled in this study. The patients' clinico-pathological findings as well as laboratory results were collected from electronic medical records with Institutional Review Board approval. We excluded patients with early cervical cancer having microscopic lesions on the cervix including IA1 and IA2; histological subtypes except for SCC and its variants; patients who underwent fertility-saving surgery; patients with concurrent hematologic (myeloproliferative disorders, autoimmune diseases and vasculitis) or infectious diseases (tuberculosis, brucellosis, listeriosis, bacterial endocarditis, syphilis, viral infection, protozoal or rickettsial infection); patients who did not have the results of complete blood cell counts with differential cell count and serum SCC-Ag level within 2 weeks before starting initial treatment; and patients who received neo-adjuvant chemotherapy before surgery.

Treatment

We usually performed surgery-based treatment in patients with early stage cervical cancer (IB1 to IIA), including bulky tumor (IB2) or radiation therapy (RT)-oriented management in patients with locally advanced cervical cancer (IIB to IVA). However, the choice for primary treatment was dependent on the attending physician's preference. Since 2000, concurrent chemotherapy with radiation therapy (CCRT) has been recommended as either the primary [13] or adjuvant treatment [14] in cases with more than one high-risk pathological factor for recurrence after surgery (please see below). Cisplatin-based regimens were used for the concurrent chemotherapy.

Standard surgery consisted of type III radical hysterectomy with bilateral pelvic lymph node (LN) dissection. Bilateral salpingo-oophorectomy and para-arotic LN sampling or dissections were not routine procedures. Adjuvant therapy after surgery was considered based on pathological risk factors. Patients who had one or more high-risk factors (positive pelvic or para-aortic LN, microscopic parametrial invasion, and positive resection margins with tumor) received adjuvant RT or CCRT. Cisplatin-based chemotherapy was administered in all cases of CCRT. Patients with at least two of the three intermediate risk factors (stromal invasion of more than half of the cervix or stromal invasion more than 1 cm, lympho-vascular space invasion, and the largest diameter of 4 cm or greater) received adjuvant RT alone. Radiation protocols were as previously described [15].

Patients had follow-up examinations approximately every 3 months for the first 2 years, every 6 months for the next 3 years, and every year thereafter. During the routine follow-up, imaging studies including computed tomography (CT) or magnetic resonance imaging (MRI), and chest X-ray was performed each year. When tumor recurrence was suspected based on clinical findings or imaging studies, biopsy was performed. We defined progression-free survival as the time from the initial treatment to relapse noted on images or to the final follow-up visit, and overall survival was defined as the time from the initial treatment to death due to cervical carcinoma or to the final follow-up visit.

Quantification of tumor-infiltrating immune cells

To evaluate the clinical significance of tumor-infiltrating histiocytes and association with circulating monocyte count in patients with cervical cancer, we investigated the tumor-infiltrating immune cells of tumor samples in cervical cancer patients who underwent type III radical hysterectomy ($n = 55$). First, each tumor section was evaluated for immune cell infiltration in the tumor stroma. After evaluating the percentage of tumor-infiltrating immune cells in tumor stroma, we investigated the percentage of histiocyte count among these tumor-infiltrating immune cells in 5 representative visual fields selected for the most abundant immune cell distribution under a microscope at 400× magnification. Finally, we calculated tumor-infiltrating histiocyte score by multiplying percentage of tumor-infiltrating immune cells and percentage of tumor-infiltrating histiocyte and then the score divided by 100. Cases were scored blindly with respect to patient history, presentation, and previous scoring by two independent observers.

Statistical analysis

The Wilcoxon rank sum test (Kruskal–Wallis test if there are more than three the groups) or two-sample *t* test (One-way ANOVA if there are more than three the groups) was used to compare the median or mean values, respectively, after checking whether the data had non-normal or normal distributions according to the Shapiro–Wilks test. Spearman correlation analysis was used to investigate the association between pre-treatment monocyte count and SCC-Ag. The overall and progression-free survival curves were calculated according to the Kaplan–Meier method with the log-rank test. Variables shown to be significant or borderline significant ($P<0.2$) in the univariable analysis were selected for the Cox model. WBC subset counts are analyzed as continuous variables and when we analyzed the combine index (the monocyte count and SCC-Ag level, Table 4) as a categorical variable, we divided the patients based on the median values of the monocyte count (408.5/μl, 55–1187) and SCC-Ag level (7.1, 0.1–362.0), respectively. The Cox proportional-hazards model was used for the multivariable analyses. Statistical analyses were performed using SPSS software (version 12.0; SPSS, Chicago, IL, USA). A P-value ≤ 0.05 was considered statistically significant and all P-values were two-sided.

Results

We enrolled 788 patients with SCC of the cervix who had macroscopic lesions at initial diagnosis (IB to IVA). The basal characteristics of these patients are presented in Table 1. The median age of the cohort was 51 years, with a range of 21–85. The median pre-treatment circulating monocyte count was 349/μl (21–1463), and median SCC-Ag level was 1.6 ng/ml (0.1–362.0). More than half of the cohort had early stage disease (628/788, 79.7%). The median follow-up for the patient group was 53.4 months, with a range of 1–181 months, and the five-year progression-free and overall survival rates were 83.9% and 87.8%, respectively. There were 121(15.4%) disease progressions and 88 (11.2%) cancer-related deaths during the study period.

The pre-treatment level of monocyte count was different between stages (Fig. 1). Among patients with stage IB1, conization was performed in 17.1% (79/384) and pre-treatment monocyte count was not different between patients who received conization and who did not (328/μl, 80–895 vs. 328.5/μl, 21–1059, P-value = 0.989). When the cohort was divided according to stage as either early cervical carcinoma (ECC) or locally advanced cervical carcinoma (LACC), patients with LACC had higher pre-treatment neutrophil count, monocyte count, and level of SCC-Ag (Table 2). In correlation analysis with monocyte counts and SCC-Ag, there was no significant correlation for ECC ($R^2 = 0.01$, P-value = 0.810). For LACC, there was a significant positive correlation between these two values, but the correlation coefficient was low ($R^2 = 0.28$, P-value < 0.001).

In the univariable, all of the clinical parameters including age, WBC subset counts, level of SCC-Ag, stage, and type of treatment had prognostic significance for both progression-free survival and overall survival (Table 3). In multivariable analysis, except for mono cyte count and SCC-Ag level in overall survival (*P*-

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