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Lymphopenia and its association with survival in patients with locally advanced cervical cancer

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HIGHLIGHTS

- Patients with cervical cancer treated with chemoradiation experience severe and sustained lymphopenia.
- Pre- and post-treatment lymphopenia appear to be associated with shorter overall survival in women with advanced cervical cancer.
- Further research is warranted, given that lymphopenia could be a reversible prognostic factor.

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ABSTRACT

Objective. To evaluate the association between lymphopenia and survival in women with cervical cancer treated with primary chemoradiation.

Methods. A single institution, retrospective analysis of patients with stage IB2-IVA cervical cancer who received upfront chemoradiation from 1998 to 2013 was performed. Complete blood counts from pre-treatment to 36 months post-treatment were analyzed. Lymphopenia and known prognostic factors were evaluated for an association with progression-free (PFS) and overall survival (OS).

Results. Seventy-one patients met study criteria for whom 47 (66%) had a documented total lymphocyte count (TLC) two months after initiating chemoradiation. FIGO stage distribution was 6% Stage I, 46% Stage II, 45% Stage III and 3% Stage IV. Pre-treatment TLC was abnormal (<1000 cells/mm^3) in 15% of patients. The mean reduction in TLC was 70% two months after initiating chemoradiation. Severe post-treatment lymphopenia (TLC <500 cells/mm^3) was observed in 53% of patients; they experienced inferior median OS (21.2 vs 45.0 months, P = 0.03) and similar 25th percentile PFS (6.3 vs 7.7 months, P = 0.06) compared to patients without severe lymphopenia. Multivariate analysis demonstrated pre-treatment TLC ≥1000 cells/mm^3 and post-treatment TLC >500 cells/mm^3 had a 77% (HR: 0.23; 95%CI 0.05–1.03; P = 0.053) and 58% decrease in hazards of death (HR: 0.42; 95%CI 0.12–1.46; P = 0.17) respectively.

Conclusion. More than half of cervical cancer patients treated with chemoradiation experienced severe and prolonged lymphopenia. Although statistical significance was not reached, the findings suggest that pre- and post-treatment lymphopenia may be associated with decreased survival. Further research is warranted, given that lymphopenia could be a reversible prognostic factor.

1. Introduction

Multiple biological studies have demonstrated cancer tissue infiltration by white blood cells, particularly lymphocytes. These findings have led to hypotheses such as the cancer immunosurveillance theory, which proposes that lymphocytes act as safeguards against cancer by identifying and destroying malignant cells [1]. Observational studies have also shown that patients with infiltration of cancer tissue by inflammatory cells, particularly lymphocytic cells, have better survival compared to patients without this finding [2–5].

Severe lymphopenia prior to initiating treatment has been correlated with shorter survival in solid tumors such as breast cancer, soft-tissue sarcoma, renal cell carcinoma, colorectal cancer, lung cancer,

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and pancreatic ductal adenocarcinoma [6–13]. Lower pre-treatment lymphocyte count has also been shown to be associated with shorter progression-free survival in locally advanced cervical cancer [14–16].

Radiation therapy itself has historically been associated with post-treatment lymphopenia in a wide range of cancers, including in gynecologic neoplasms [17–20]. Recent studies have identified an association between post-treatment lymphopenia and decreased survival in patients with solid tumors who underwent radiation therapy, irrespective of histology, lymphotoxic chemotherapy regimens and/or corticosteroid administration [21–25]. As a result, studies are currently underway to determine whether lymphopenia in patients with high-grade gliomas can be reversed after radiation-related damage, with the hope of identifying promising new therapies.

The impact of lymphopenia on survival after radiation therapy has not been fully addressed in patients with gynecologic malignancies. This study was therefore undertaken to investigate the association between pre- and post-treatment lymphopenia and survival in women with locally advanced cervical cancer treated with primary chemoradiation.

2. Methods

2.1. Patient selection

After obtaining approval from the Institutional Review Board, women with advanced cervical cancer treated with definitive platinum-based chemoradiation from 1998 through 2013 were identified. Patients who met the following inclusion criteria were selected: 1) biopsy-confirmed cervical cancer, 2) FIGO stage IB2 to IVA, 3) initial treatment administered at our institution (concurrent platinum-based chemotherapy and external radiation therapy, with or without brachytherapy), and 4) pre-treatment TLC available in the medical record. Patients were excluded if they had a hysterectomy or tracheletomy prior to chemoradiation. The standard practice at our institution is to administer four to six cycles of platinum chemotherapy during radiation therapy.

2.2. Data collection

Study variables, including demographic, clinicopathologic, and treatment characteristics, were collected from the electronic medical record and our institutional cancer registry. Vital status was extracted from the electronic medical record, the Social Security Death Index, and Accurint® through January 2014. Data from complete blood counts (CBC) were collected from pre-treatment through up to 36 months after initiating treatment. The most recent CBC from within three months prior to treatment was utilized. Pre-treatment lymphopenia was defined as TLC <1000 cm/mm^3 based on commonly accepted reference values [26]. The total lymphocyte count two months after starting chemoradiation was used to analyze post-treatment lymphopenia. The time interval was based on studies in other solid tumors that found lymphocyte counts at two months to be a prognostic factor for survival [21–25]. If a TLC was not available at two months, the closest value within two weeks was used. The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 threshold for grade III–IV lymphopenia was used to define post-treatment lymphopenia as TLC <500 cm/mm^3. The Charlson Comorbidity Index was calculated for each patient as a proxy for state of health [27,28].

2.3. Statistical analysis

Demographic, clinicopathologic, and treatment characteristics were summarized using descriptive statistics. The Wilcoxon rank-sum and Fisher exact tests were used to compare medians and the proportions between the groups respectively. The primary outcomes of interest were progression free survival (PFS) and overall survival (OS). OS was calculated from the start date of chemoradiation to the date of death and PFS was calculated from the start date of chemoradiation to the date of first radiographic progression or recurrence. Women determined to be progression or recurrence free or alive at the end of this period of observation were administratively censored. If median PFS was not attained, and therefore not measurable, we calculated the 25th percentile PFS in our analysis. Given that clinicians use the absolute change in lymphocyte counts as well as specific thresholds, TLC was evaluated as both continuous and categorical variables. When categorized, the cutoff for the pre-treatment TLC was <1000 cells/mm^3 and for post-treatment TLC was <500 cells/mm^3 [26].

The log-rank tests were used to compare Kaplan–Meier estimates of event rates (time to progression/recurrence and death) between the groups. All demographic and baseline clinical variables in Table 1 were evaluated as covariates. Factors included in the final multivariate stratified Cox regression model were those with a significant unadjusted association with PFS and OS ($p < 0.05$) or those known from the literature as independent prognostic factors for PFS and OS (age, race, FIGO stage, histology, tobacco use, Charlson Comorbidity Index, platelet count). The multivariate Cox model was stratified by grade. HIV status was not analyzed separately, as it was accounted for in the Charlson Comorbidity index where patients with HIV received significantly more points than other patients. However, a sensitivity analysis was performed excluding HIV positive patients.

To account for potential bias and confounding introduced by participants with missing clinicopathologic data, multiple imputation analyses were also performed. Missing-at-random (MAR) assumptions were made and the Markov Chain Monte Carlo approach (chained equations) was used to generate 10 imputed data sets based on age, race, FIGO stage, Charleston score, and the outcome variable. Data were imputed and analyzed using the STATA MI command with STATA version 12. Multivariate analysis results using multiple imputation were similar to those from the complete case series. Thus, only the results from the multivariate analysis using multiple imputation are shown. For all analyses, we used the two-sided level of 0.05 for significance and STATA version 12 (StataCorp) statistical software.

3. Results

Seventy-one patients diagnosed with cervical cancer from 1998 through 2013 met the inclusion criteria and were included in the analysis. A documented total lymphocyte count (TLC) two months after initiating chemoradiation was available for 47 of these patients. Among the patients with a pre-treatment TLC documented ($n = 71$), the median follow-up was 25 months [interquartile range (IQR), 9.2–50.7]. Table 1 shows the demographic, clinicopathologic, and treatment characteristics for the study population. The median age was 49 years (IQR 40–56). Fifty-three patients (75%) had a Charlson Comorbidity Index of 0. Four patients (6%) had stage I disease, 33 (46%) stage II disease, 32 (45%) stage III disease, and two (3%) stage IV disease. On histology, 59 patients (83%) had squamous cell carcinoma. The remaining patients had adenocarcinoma (1%), adenosquamous carcinoma (9%), or other histology (7%). Two patients (3%) had well-differentiated histology, 22 (31%) moderately differentiated histology, 19 (27%) poorly differentiated histology, and 28 (39%) unknown histology. Four patient (6%) were HIV positive.

Prior to initiating treatment, eleven of the patients (15%) had lymphopenia (based on TLC <1000 cells/mm^3 defined in methods above). The median pre-treatment TLC in our study population decreased from 1640 cells/mm^3 to 480 cells/mm^3 two months after initiating chemoradiation ($P < 0.01$). Fig. 1 shows the distributions of lymphocyte count at pre-treatment and through 12 months after initiating treatment. The lymphocyte count nadir occurred two months after initiating chemoradiation, and then slowly increased over time. However, 12 months after treatment initiation, some patients' counts had not