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Original article

Prognostic significance of pretreatment total lymphocyte count and neutrophil-to-lymphocyte ratio in extensive-stage small-cell lung cancer

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ABSTRACT

Background: We evaluated pretreatment total lymphocyte count (TLC, marker of immunosuppression), neutrophil-to-lymphocyte ratio (NLR, marker of inflammation), and overall survival (OS) in patients with extensive-stage small-cell lung cancer (ES-SCLC).

Methods: Pretreatment blood characteristics, age, sex, performance status, race, stage (M1a vs. M1b), number and location of metastases, weight loss, smoking status, chemotherapy cycles (<4 vs. ≥4), thoracic radiotherapy dose (<45 vs. ≥45 Gy), and receipt of prophylactic cranial irradiation (PCI) were evaluated in 252 patients with ES-SCLC treated in 1998–2015. Factors significant in univariate analysis were selected as covariates for a multivariate Cox model.

Results: Pretreatment TLC was below normal ($<1.0 \times 10^3/\mu\text{L}$) in 58 patients (23%). Median OS time was 11.0 months and was worse for those with $\text{TLC} \leq 1.5 \times 10^3/\mu\text{L}$ (9.8 vs. 12.0 months) and pretreatment $\text{NLR} > 4.0$ (9.4 vs. 13.9 months). Multivariate analysis identified low TLC (hazard ratio [HR] 0.734, 95% confidence interval [CI] 0.565–0.955, $P = 0.021$) and high NLR (HR 1.521, 95% CI 1.172–1.976, $P = 0.002$) as predicting inferior survival. Age (>63 y), sex (male), performance status (≥2), chemotherapy cycles (<4), radiation dose (<45 Gy), and no PCI also predicted worse OS ($P < 0.05$).

Conclusions: Pretreatment TLC and NLR may be useful for stratifying patients with ES-SCLC for treatment approaches.

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Lung cancer is the second most common type of cancer and the leading cause of death among both women and men in the United States [1]. Although the incidence of small cell lung cancer (SCLC) has declined over the past decades, it still comprises 15% of all lung cancer cases, and 60% of patients present with extensive-stage (ES) disease [2]. SCLC is highly proliferative and prone to widespread metastases. Because of its aggressive nature and its common dissemination at diagnosis, treatment for ES-SCLC tends to be given with palliative intent, as the 5-year survival rate is only 2% and the median survival time only 6.1 months [2].

Chemotherapy was regarded as the mainstay of treatment until the 1980s, when the effectiveness of adding radiotherapy to systemic therapy was revealed [3]. The therapeutic plateau for chemotherapy seems to have been achieved with the introduction of platinum-etoposide doublet therapy [4]. Most of the advances in terms of disease control and survival benefit for SCLC at any stage

during the past two decades have resulted from improvements in radiotherapy, particularly the addition of thoracic radiotherapy (TRT) and prophylactic cranial irradiation (PCI) [5–7]. More recently, the emergence of immunotherapy has brought a paradigm shift for lung cancer treatment [8].

Identifying reliable markers with which to better select patients for both currently available approaches and upcoming approaches such as immunotherapy would greatly aid clinical decision-making. Performance status (PS), age, and sex are well-established predictors in ES-SCLC [9]. However, no other relevant prognostic factors are available at present, especially as we anticipate use of immunologic therapies.

Immune and inflammatory responses in the body are critical for tumor development [10]. In immunocompetent patients, immunosurveillance prevents or inhibits tumor growth; however, immune suppression expressed as lymphopenia has been linked with poor survival in many malignancies such as breast cancer, sarcoma, lymphoma, cervical cancer, glioblastoma, pancreatic cancer, and non-small cell lung cancer (NSCLC) [11–17]. Treatment-related lymphopenia was found to be correlated with poor survival in one study of patients with limited-stage SCLC [18]. However, the

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effect of reduced lymphocyte counts at baseline on outcome for patients with ES-SCLC is still unknown.

In addition to immune suppression, inflammation can affect every aspect of tumor development and progression as well as the response to therapy [10]. Systemic inflammation has been linked with outcome in several types of cancer. Platelets have numerous roles in physiological and pathological pathways, including homeostasis and inflammation [19]. Several groups have reported that increased platelet counts correlated with dismal prognosis in patients with various types of cancer, including lung [19–23]. Other markers of inflammation and immunologic function including the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been linked with prognosis in a variety of malignancies such as cholangiocarcinoma, esophageal, colorectal, ovarian, and head and neck cancers [24–28]. The pertinence of NLR and PLR has also been demonstrated in both NSCLC and SCLC [29,30]; higher NLR generally implies worse outcome, but the implications of PLR have not been consistent in patients with SCLC.

The aim of this study was to investigate the influence of pretreatment immunologic and inflammatory hematologic markers (total lymphocyte count [TLC], platelet count, NLR, and PLR) as a manifestation of immune and systemic inflammation status on overall outcome in patients with ES-SCLC.

Methods

Patients

After review and approval of this study by the appropriate institutional review board, subjects were retrospectively identified from a database of SCLC patients treated at a single tertiary cancer center. Inclusion criteria were as follows: (1) pathologically confirmed SCLC, (2) pathologically or radiologically confirmed ES (i.e., TNM stage IV disease), (3) new diagnosis of ES-SCLC from May 1998 through September 2015, and (4) available data on baseline (pretreatment) complete blood count (CBC) with differentials obtained at our institution. In addition to tissue biopsy and laboratory tests, the initial diagnostic work-up included computed tomography (CT) of the chest and upper abdomen, brain magnetic resonance imaging (MRI) (or brain CT if MRI was contraindicated), bone scan, and positron emission tomography/CT. Patients with abnormal CBC findings underwent bone marrow aspiration. The standard practice at our institution is to administer 4–6 cycles of platinum chemotherapy. Patients who experienced response to this chemotherapy in the chest and at metastatic sites were offered consolidative TRT and PCI. Re-imaging of the brain (with MRI or CT if MRI was contraindicated) was required for patients who were candidates for PCI. Patients with brain metastases could receive whole-brain radiotherapy (WBRT) before or after chemotherapy depending on their symptoms. Patients who were not candidates for chemotherapy or had disease that progressed after chemotherapy were offered palliative TRT.

Data collection

Variables including clinicopathologic and treatment characteristics were extracted from the electronic medical records of patients in our SCLC database. Baseline CBC and blood chemistry findings were collected between the date of diagnosis and the initiation of any treatment (chemotherapy or radiotherapy [TRT or WBRT]). NLR was calculated by dividing the total neutrophil count by the TLC. Similarly, PLR was calculated by dividing the total platelet count by the TLC. Patients were stratified according to the median values of the baseline hematologic markers (albumin [Alb], lactate dehydrogenase [LDH], white blood cell count

[WBC], hemoglobin [Hb], platelets, neutrophils, TLC, NLR, and PLR). Other clinical characteristics were the date of diagnosis (1998–2005, 2006–2010, or 2011–2015), age (<63 or ≥63 years), sex, Eastern Cooperative Oncology Group [ECOG] PS score (0–1 vs. ≥2), race (white vs. non-white), TNM M status (M1a vs. M1b), number of metastases (1 vs. >1), presence of metastases in liver, brain, or bone, weight loss of ≥10%, tobacco smoking history (ever vs. never), current smoking status, number of initial chemotherapy cycles (0 vs. 1–3 vs. ≥4), dose of TRT (<45 Gy vs. ≥45 Gy), and receipt of PCI.

Statistical analysis

Clinicopathologic and treatment characteristics were summarized by using descriptive statistics. Differences between higher- and lower-TLC groups were compared with Chi-square tests or Mann–Whitney *U* tests as appropriate. The primary outcome of interest was overall survival (OS), which was calculated from the date of diagnosis to the date of death or last follow-up. The log-rank test was used to compare Kaplan–Meier estimates of survival between groups. All baseline clinical and treatment variables except for ever-smoking status were evaluated as covariates. A univariate proportional hazard Cox model was used to assess potential associations between these characteristics and OS. To assess whether hematologic markers (including TLC and NLR) were independent predictors of survival, a multivariate Cox model was constructed using all of the other factors having a *P* value of ≤0.25 on univariate analysis, and each factor was eliminated using backwards elimination in a stepwise manner until the most significant variables were identified. The Wald test was used to assess the role of covariates in the model. Because of the strong collinearity between TLC and NLR (Spearman's correlation coefficient 0.738), these factors could not be included simultaneously and were tested in separate models. All analyses were two-sided and significance was set at a *P* value of 0.05. Statistical analyses were done with SPSS Statistics 24 (SPSS Inc., Chicago, IL) and Stata/MP 14.2 statistical software (Stata Corp LP, College Station, TX).

Results

A total of 252 patients met the inclusion criteria and were included in the analysis (Table 1). The median patient age was 63 years [interquartile range (IQR) 56–69]; 53% of the patients were female and 27% had an ECOG score of ≥2. Seventy-five percent of the patients received ≥4 cycles of platinum-based chemotherapy; 45% received TRT to ≥45 Gy for consolidation or palliation; and 19% received PCI. No significant differences in these characteristics were found between patients who had TLC lower or higher than the median value with the following exceptions. More male patients (54%) had low (below-median-value) pretreatment TLC than did female patients (46%) (*P* = 0.026); pretreatment Alb, WBC, Hb, and platelet count were generally lower in patients who had low TLC, and pretreatment LDH and neutrophil levels were generally higher in patients who had low TLC. These values were well within the normal range except for LDH, which slightly exceeded the upper limit of normal [618 U/L] for patients with low TLC (Table 1). Regarding treatment details, 159 patients received TRT (63%), 113 (45%) receiving ≥45 Gy and 46 (18%) receiving <45 Gy; TRT was used for palliation or salvage in 78 patients (5 who were not candidates for chemotherapy, 10 who could not tolerate the full course of chemotherapy, 15 for symptom control before chemotherapy, 37 who experienced disease progression during chemotherapy and 11 with tumor recurrence within the chest after chemotherapy); and 95 patients received no TRT. As for chemotherapy, 12 patients received no chemotherapy, and

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