Radiotherapy and Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Hematologic variables associated with brain failure in patients with small-cell lung cancer

Ryoko Suzuki [1], Xiong Wei, Pamela K. Allen, James W. Welsh, Ritsuko Komaki, Steven H. Lin *

Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, USA

ARTICLE INFO

Article history:
Received 29 January 2018
Received in revised form 23 May 2018
Accepted 24 May 2018
Available online xxxx

Keywords:
Inflammation markers
Immune status markers
Lymphocytes
Platelets
Neutrophils
Brain metastases

ABSTRACT

Background and purpose: We sought factors associated with the development of brain metastases after treatment of small cell lung cancer (SCLC) in patients without brain involvement at diagnosis.
Methods: We analyzed 293 patients with SCLC without brain metastases who received chemotherapy, thoracic radiation therapy (TRT), or both in 2001–2015. Pretreatment hematologic markers (platelet count, neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and lactate dehydrogenase) and other clinical characteristics were evaluated for correlation with brain metastases–free survival (BMFS). Cutoffs were established with receiver operating characteristics curves. Factors significant in univariate analysis were used to build a multivariate Cox model for BMFS.
Results: Median follow-up time was 14.3 months. Brain metastases developed in 115 patients (39%)—32% of those with low pretreatment platelet counts (PPC) ($\leq 270 \times 10^9$/L) and 46% of those with high PPC ($>270 \times 10^9$/L). Median BMFS time for all patients was 27.9 months. Two-year BMFS rates were worse for patients with high PPC (14.6% vs. 22.1% low, $P = 0.009$). High PPC was independently associated with inferior BMFS ($P = 0.038$), as were receipt of TRT <45 Gy and no prophylactic cranial irradiation (both $P < 0.001$).
Conclusions: High PPC was associated with increased rates of brain metastasis in patients with SCLC with no evidence of brain disease at diagnosis.

Introduction

Small-cell lung cancer (SCLC) is highly chemo- and radiosensitive given its propensity for rapid proliferation. Chemotherapy was the mainstay of treatment until the 1990s, when the advantage of adding thoracic radiation therapy (TRT) for patients with limited-stage (LS) SCLC was confirmed in two meta-analyses, which showed an absolute survival benefit of 5.4% at 3 years (from 8.9% with chemotherapy alone to 14.3% with chemotherapy and TRT) [1,2]. The benefit of adding TRT for both disease control and survival has also been confirmed for patients with extensive-stage (ES) SCLC [3].

The therapeutic improvements associated with the inclusion of radiotherapy and the technologic advances in radiotherapy planning and delivery techniques over time undoubtedly contributed to the improvement in 2-year overall survival (OS) rates for patients with LS SCLC from 47% in the Intergroup 0096 study, published in 1999 [4], to 56% in the CONVERT trial, published in 2017 [5]. However, expectations of longer survival should prompt patients and clinicians to prepare for the need to manage disease recurrence, especially in the brain. The brain is considered a sanctuary site for relapse because of the blood–brain barrier, which blocks most chemotherapeutic agents from entry. Autopsy studies have shown that 50% to 65% of patients with SCLC have brain metastases at the time of death [6,7]. Patients who live longer are at higher risk of developing brain metastasis, to a cumulative probability of 80% among patients who live for 2 or more years after treatment [7,8]. The frequency of disease recurrence in the brain led to the advent of prophylactic cranial irradiation (PCI) for patients with SCLC in 1970s. After a meta-analysis revealed that PCI was associated with improvements in both survival and disease control in the brain [9], PCI is generally offered to patients with LS SCLC who respond to initial definitive treatment. Although PCI has not consistently been found to confer a survival benefit, most studies, including trials conducted in Europe and Japan, have shown that PCI improves control of brain disease among patients with ES SCLC [10,11]. Some patients with SCLC who do not receive

* Corresponding author at: Department of Radiation Oncology, Unit 97, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030-4009, USA.
E-mail addresses: szk.mrad@tmd.ac.jp (R. Suzuki), SHLin@mdanderson.org (S.H. Lin).
[1] Present address: Department of Radiation Oncology, Tokyo Medical and Dental University, 1 Chome-5-45 Yushima, Bunkyō, Tokyo 113-8510, Japan.

https://doi.org/10.1016/j.radonc.2018.05.026
0167-8140/

PCI die without brain metastases, but others experience relapse in the brain even after withstanding the physical and financial costs of PCI. Factors associated with the risk of a particular patient's developing brain metastases would be valuable for improving the therapeutic management of SCLC.

Inflammatory and immune responses are integral to tumor development and metastasis [12]. Platelets are known to participate in both homeostasis and inflammation [13], and several studies have linked increased platelet counts with poor prognosis in lung cancer, among others [14–18]. Other inflammation markers that have been linked with prognosis in lung and other forms of cancer include the platelet-to-lymphocyte ratio (PLR) and the neutrophil-to-lymphocyte ratio (NLR) [19–25]. Total lymphocyte count (TLC) is considered an indicator of host immune status, and lymphopenia (i.e., reduced TLC) has also been associated with worse prognosis in lung and other types of cancer [26–33]. Levels of platelets, lymphocytes, and neutrophils are easily measured via routine laboratory testing and can be measured repeatedly, at initial diagnosis as well as during follow-up. However, whether these markers reflect the risk of patients developing brain metastases after the initial treatment of SCLC is unknown.

We sought here to determine whether hematologic markers of inflammation and immune function (platelet count, neutrophil count, TLC, NLR, and PLR), evaluated before definitive treatment and before PCI, could be potential markers of brain metastases in patients with SCLC and no evidence of brain disease at diagnosis.

Methods and materials

Patients and follow-up

After obtaining approval from the appropriate institutional review board, we searched an institutional database for patients with SCLC treated at a single tertiary cancer care center from 2001 through 2015. Inclusion criteria were (1) pathologically proven SCLC, (2) radiographic confirmation of no disease in the brain, and (3) available information from complete blood counts (CBC) with differentials obtained before treatment (chemotherapy, TRT, or both). Patients who had had upfront surgery were excluded. At our institution, SCLC is routinely treated with 4–6 cycles of platinum-based chemotherapy, with concurrent TRT included for patients with LS SCLC or recommended for patients with ES SCLC who either respond well to chemotherapy or experience disease progression during chemotherapy. Patients with either LS or ES SCLC with a favorable response to initial therapy were offered PCI; brain re-imaging (generally with magnetic resonance imaging [MRI] or computed tomography [CT] if MRI was contraindicated) was required to prove the absence of intracranial disease before PCI was begun. PCI typically consisted of 25 Gy delivered in 10 fractions to the whole brain using opposed lateral or bilateral anterior oblique beams and commenced 4–6 weeks after completion of the initial therapy.

Patients generally returned for follow-up every 3 months for the first 2 years, every 6 months from 3 to 5 years, and yearly thereafter; however, this follow-up schedule was not always consistent. Thoracic CT or positron emission tomography/CT (PET/CT) images were commonly obtained at every follow-up visit. Although, variation existed, brain MRI (or brain CT if MRI was contraindicated) was also obtained on every follow-up visit for patients who did not receive PCI. For those patients who received PCI, brain imaging was conducted every 6 months for the first 2 years or upon the appearance of symptoms.

Data collection

Baseline demographic, disease, and treatment characteristics were extracted from the electronic medical records and institutional database. Information on hematologic markers was extracted from laboratory tests done before any therapy was begun; for patients who had several sets of laboratory tests before beginning therapy, values were used from the set obtained closest to the treatment-start date. For patients who had PCI, laboratory findings were assessed at the date closest to the PCI-start date. Hematologic variables included platelet count, neutrophil count, TLC, NLR, PLR, and lactate dehydrogenase (LDH) levels; however, LDH was not investigated in the pre-PCI analysis because this information was missing for most patients at that time. 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. Other variables assessed included age, sex, ethnicity, performance status, TNM disease stage, weight loss, smoking status, number of chemotherapy cycles, TRT dose, and receipt of PCI.

Statistical analyses

The primary outcome of interest was BMFS, which was calculated from the date of diagnosis to the date of brain metastasis detection. Patients alive without brain metastases were censored as of the date of last follow-up. Cutoff values for each hematologic marker in terms of its association with brain metastases were determined by receiver operating characteristics (ROC) curve analysis. Demographic, clinical and treatment characteristics were summarized by descriptive statistics. Differences between patients stratified by the cutoff of platelet count were examined with Chi-square tests, Fisher's exact tests, or Mann-Whitney U tests according to the type of variable. BMFS probabilities were estimated by using the Kaplan–Meier method, with log-rank tests used to compare estimates of event rates. Univariate Cox regression analysis was used to assess potential associations between characteristics and brain metastases. Factors identified as being statistically significant in univariate analysis were selected as covariates to construct a multivariate Cox model for BMFS. All P values were reported as 2-sided, and significance was set at $\leq$0.05. All analyses were done with SPSS Statistics 24 (SPSS Inc., Chicago, IL).

Results

In total, 293 patients met the inclusion criteria and were included in the analyses; patient, disease, and treatment characteristics are shown in Table 1. The median follow-up time was 14.3 months (interquartile range [IQR], 9.3–22.8 months). Median age at diagnosis was 64 years (IQR, 58–71 years). Slightly fewer than half of the study cohort (48%) were men. Most patients (239, or 82%) had good performance status (Eastern Cooperative Oncology Group [ECOG] scores of 0–1); 127 (43%) had TNM stage I–III disease; 249 (85%) had received $\geq$4 cycles of platinum-based chemotherapy as part of initial treatment; 200 (68%) had received TRT to $\geq$45 Gy; and 125 patients (43%) had received PCI.

The median interval between the pretreatment CBC used for this analysis and treatment start was 3 days (IQR, 1–7 days). ROC curve analysis revealed a cutoff value of 270×10^9/L for pretreatment platelet count, with a sensitivity of 62.6% and a specificity of 51.7%. The optimal cutoff values for other pretreatment hematologic markers were $3.9 \times 10^3/\mu$L for neutrophil count, $1.7 \times 10^3/\mu$L for TLC, 1.6 for NLR, 119.4 for PLR, and 543 IU/L for LDH. Based on these cutoff values, patients were stratified into two groups (high vs. low), and BMFS was analyzed within these stratifications.

Over the entire study period, 115 patients (39%) developed brain metastases, 43 (32%) of the 136 patients in the low-platelet-count group ($\leq 270 \times 10^9$/L) and 72 (46%) of the 157 patients in the high-platelet-count group ($>270 \times 10^9$/L). Pretreatment platelet counts were above the upper limit of normal (>440

Please cite this article in press as: Suzuki R et al. Hematologic variables associated with brain failure in patients with small-cell lung cancer. Radiother Oncol (2018), https://doi.org/10.1016/j.radonc.2018.05.026