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Pretreatment neutrophil-to-lymphocyte ratio as a marker of outcomes in nivolumab-treated patients with advanced non-small-cell lung cancer

Stephen J. Bagley[a,*], Shawn Kothari[a], Charu Aggarwal[a], Joshua M. Bauml[a], Evan W. Alley[a], Tracey L. Evans[a], John A. Kosteva[a], Christine A. Ciunci[a], Peter E. Gabriel[a], Jeffrey C. Thompson[b], Susan Stonehouse-Lee[a], Victoria E. Sherry[a], Elizabeth Gilbert[a], Beth Eaby-Sandy[a], Faith Mutale[a], Gloria DiLullo[a], Roger B. Cohen[a], Anil Vachani[a], Corey J. Langer[a]

[a] Division of Hematology/Oncology, Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA
[b] Division of Pulmonary, Allergy and Critical Care Medicine, Thoracic Oncology Group, Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

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ABSTRACT

Objectives: Efficient use of nivolumab in non-small-cell lung cancer (NSCLC) has been limited by the lack of a definitive predictive biomarker. In patients with metastatic melanoma treated with ipilimumab, a pretreatment neutrophil-to-lymphocyte ratio (NLR) < 5 has been associated with improved survival. This retrospective cohort study aimed to determine whether the pretreatment NLR was associated with outcomes in NSCLC patients treated with nivolumab.
Methods: We reviewed the medical records of all patients with previously treated advanced NSCLC who received nivolumab between March 2015 and March 2016 outside of a clinical trial at the University of Pennsylvania. Patients were dichotomized according to pretreatment NLR < 5 vs. ≥5. Multivariable logistic regression and Cox proportional hazards models were used to assess the impact of pretreatment NLR on overall survival (OS), progression-free survival (PFS), and overall response rate (ORR).
Results: 175 patients were treated. Median age was 68 (range, 33–88); 54% were female. Twenty-five percent of patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≥2; 46% had received ≥2 prior systemic therapies. In multivariate analyses, pretreatment neutrophil-to-lymphocyte ratio (NLR) ≥5 was independently associated with inferior OS (median 5.5 vs. 8.4 months; HR 2.07, 95% CI 1.3–3.3; p = 0.002) and inferior PFS (median 1.9 vs. 2.8 months; HR 1.43, 95% CI 1.02–2.0; p = 0.04).
Conclusions: In a cohort of patients with NSCLC treated with nivolumab in routine practice, pretreatment NLR ≥ 5 was associated with inferior outcomes. It is unclear whether this marker is predictive or prognostic. Prospective studies are warranted to determine the utility of NLR in the context of other biomarkers of programmed death-1 (PD-1) therapy.

1. Introduction

Two programmed death-1 (PD-1) checkpoint inhibitors, nivolumab and pembrolizumab, were recently approved by the US Food and Drug Administration (FDA) for previously treated advanced non-small-cell lung cancer (NSCLC). Nivolumab was approved first for squamous-cell NSCLC based on a phase III randomized controlled trial (RCT) demonstrating increased overall survival (OS) compared to standard second-line docetaxel [1], and was subsequently approved for non-squamous NSCLC after a parallel phase III trial yielded a similar OS benefit in this population [2]. Pembrolizumab was initially approved after phase I/II data demonstrated its efficacy in NSCLC patients with ≥ 50% programmed death ligand 1 (PD-L1) expression [3]. A second-line phase III study ultimately confirmed a survival advantage over docetaxel in this same subgroup of patients [4].

In light of the marked and durable responses observed in a subset of NSCLC patients treated with nivolumab, many studies have

* Corresponding author at: Division of Hematology/Oncology, 3400 Civic Center Boulevard, Perelman Center 10th Floor, South Pavilion Extension Philadelphia, PA 19104, USA.
E-mail address: stephen.bagley@uphs.upenn.edu (S.J. Bagley).

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focused on identifying predictors of benefit. Use of PD-L1, the most studied biomarker, has been fraught with challenges. Trials of pembrolizumab demonstrated a correlation between increased PD-L1 expression and improved outcomes [4], with an FDA requirement of PD-L1 expression ≥50% for its use. The role for PD-L1 as a biomarker for nivolumab use, however, is less well defined. Although PD-L1 expression in tumor cells was associated with improved survival with nivolumab compared to docetaxel in patients with non-squamous histology [2], there was no association between PD-L1 expression and outcomes in a trial that enrolled patients with squamous-cell histology [1]. Even in non-squamous patients, responses to nivolumab were observed in patients with no discernible PD-L1 expression, highlighting the challenges with this biomarker.

Given the shortcomings of PD-L1 as a predictive biomarker for use of nivolumab, novel markers of outcomes are needed to define the select patient population who will derive durable benefit from this agent. The pretreatment neutrophil-to-lymphocyte ratio (NLR), a marker of systemic inflammation previously associated with outcomes in a variety of cancers [5–9], was recently shown to be associated with clinical benefit in metastatic melanoma patients treated with ipilimumab [10]. Our primary objective was to determine whether pretreatment NLR was associated with outcomes in patients with NSCLC who received nivolumab in routine clinical practice. Because patients with NSCLC treated off study protocols likely differ considerably from those enrolled in RCTs [11–15], our secondary objective was to describe the clinical and demographic characteristics, as well as effectiveness outcomes and toxicities, of a cohort of NSCLC patients treated with nivolumab outside the context of a clinical trial at an academic U.S. cancer center.

2. Methods

2.1. Patients, data collection, and study design

We conducted a retrospective cohort study of all patients with previously treated advanced NSCLC who initiated nivolumab (3 mg/kg intravenously every 2 weeks) at the Abramson Cancer Center of the University of Pennsylvania between March 4, 2015, the date that nivolumab was approved by the US FDA, and March 1, 2016. We focused exclusively on patients treated with nivolumab (and not other PD-1 inhibitors) given treatment practices at our institution during this time period, and to minimize treatment heterogeneity. Patients were excluded from our analysis if they received nivolumab as part of a clinical trial or if any additional anti-neoplastic therapies were administered concurrently. Electronic medical records and pharmacy databases were used to obtain patient-specific information. Data collected included patient demographics, Eastern Cooperative Oncology Group Performance Status (ECOG PS) at time of initiating nivolumab, smoking history, histology, molecular profiling for *EGFR, ALK,* and *ROS1* when available, PD-L1 status when available, sites of metastatic spread at time of initiating nivolumab, previous treatments, baseline complete blood count [defined as the most recent complete blood count drawn within 2 weeks prior to initiation of nivolumab, including absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) to calculate the neutrophil-lymphocyte ratio (NLR)], number of doses of nivolumab received, response status and date of progression (or last follow-up) as determined by review of clinician progress notes and radiology reports, and date of death or last follow-up. We also collected data on the incidence, timing, severity, and management of nivolumab-related immune-related adverse events (irAEs) (ie, pneumonitis, diarrhea and/or colitis, hepatitis, dermatitis, thyroiditis, arthritis, and others). irAEs were determined by one investigator (S.J.B.) and characterized and graded on the basis of chart review with use of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE; version 4.0).

EGFR, ALK, ROS1, and PD-L1 status were available only if such profiling had been performed as part of routine clinical care. For patients who had tumor tissue tested for PD-L1 expression as part of routine clinical care, the commercially available Dako immunohistochemical assay (Dako; Carpinteria, CA, USA) was utilized in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory and quantified according the Tumor Proportion Score, which is the percentage of viable tumor cells showing partial or complete membrane staining [3].

The primary exposure variable was pretreatment NLR, calculated as the ratio of ANC to ALC [16]. Patients were dichotomized according to a pre-specified cutoff value of NLR ≥ 5 vs. <5, as NLR ≥ 5 has been previously validated as being associated with inferior progression-free survival (PFS) and overall survival (OS) in patients with metastatic melanoma treated with ipilimumab [10]. The primary outcome was OS, defined as the number of months between the first nivolumab treatment and death, or censored at the date of last patient contact. Secondary outcomes were overall response rate (ORR) and PFS. ORR was calculated as the percentage of responses among all treated patients. A response was counted if the clinician or radiologist reported decreased size of lesions. PFS was defined as the number of months between the first nivolumab treatment and death or progression, whichever occurred first (censored at date of last patient contact). Patients were counted as having pseudoprogression if i) the first follow-up scan after initiating therapy demonstrated progressive disease or a mixed response AND ii) either the subsequent (second) scan demonstrated a response to therapy OR both of the two subsequent (second and third) scans demonstrated stable disease. This definition of pseudoprogression did not incorporate formal tumor assessment by immune-related response criteria [17], but instead, aimed to capture nonconventional patterns of benefit as observed and interpreted by treating oncologists in routine practice [18].

The following predetermined covariates were categorized based on clinically meaningful values and evaluated as candidate variables for inclusion in the final logistic regression and Cox proportional hazards models: sex, age (≥75 vs. <75 years), ECOG PS (0–1 vs. ≥2), number of lines of prior systemic therapies (1 vs. ≥2), smoking status [light/never (<10 pack–years) vs. heavy (≥ 10 pack-years)], site of metastases at time of initiation of nivolumab (brain, bone, and/or liver), presence of a targetable oncogenic driver mutation (defined as having *EGFR* mutation, *ALK* translocation, or *ROS1* translocation), and histology (squamous vs. non-squamous).

In an exploratory analysis to determine whether differences in OS according to NLR were attributable mainly to the ALC, ANC, or both, we divided the cohort into quartiles based on NLR, ALC, and ANC and generated survival curves by quartile for each of these values according to the Kaplan-Meier method.

The University of Pennsylvania institutional review board reviewed the project and a waiver of informed consent was obtained.

2.2. Statistical analysis

Statistical analyses were performed using Stata version 14.1 (Stata, College Station, TX). All statistical tests were two-sided, and 5% was set as the level of significance.

Demographic characteristics were described using frequencies and percentages for categorical variables and medians and ranges for quantitative variables. Survival curves were generated according to the Kaplan-Meier method, and crude differences in PFS/OS according to baseline characteristics were assessed using the log-rank test. Multivariate Cox proportional hazards models