ORIGINAL ARTICLE

Peripheral Blood Biomarkers Associated with Clinical Outcome in Non–Small Cell Lung Cancer Patients Treated with Nivolumab

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ABSTRACT

Objective: The aim of this study was to identify baseline peripheral blood biomarkers associated with clinical outcome in patients with NSCLC treated with nivolumab.

Methods: Univariable and multivariable analyses were performed retrospectively for 134 patients with advanced or recurrent NSCLC treated with nivolumab to evaluate the relationship between survival and peripheral blood parameters measured before treatment initiation, including absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute monocyte count, and absolute eosinophil count (AEC), as well as serum C-reactive protein and lactate dehydrogenase levels. Progression-free survival, overall survival, and response rate were determined.

Results: Among the variables selected by univariable analysis, a low ANC, high ALC, and high AEC were significantly and independently associated with both better progression-free survival ($p = 0.001$, $p = 0.04$, and $p = 0.02$, respectively) and better overall survival ($p = 0.03$, $p = 0.03$, and $p = 0.003$, respectively) in multivariable analysis. Categorization of patients according to the number of favorable factors revealed that those with only one factor had a significantly worse outcome than those with two or three factors. A similar trend was apparent for patients with a programmed death 1 ligand

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Drs. Tanizaki and Haratani equally contributed to this work.

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tumor proportion score less than 50%, whereas all patients with a score of 50% or higher had at least two favorable factors.

Conclusions: A baseline signature of a low ANC, high ALC, and high AEC was associated with a better outcome of nivolumab treatment, with the number of favorable factors identifying subgroups of patients differing in survival and response rate.

Keywords: Non–small cell lung cancer; Nivolumab; Peripheral blood biomarker; Prognostic factor; Predictive factor

Introduction

Targeting of the immune system has been found to confer clinical benefit for patients with some types of advanced solid tumor. Nivolumab, a monoclonal antibody to the immune checkpoint protein programmed death 1 (PD-1), has been approved for the treatment of several solid tumor types including metastatic NSCLC.[1–4] Given that only a limited number of patients experience a durable response whereas all those treated are at risk for specific immune side effects, the identification of individuals who are most likely to benefit from nivolumab and similar agents is an important clinical goal. Given the heterogeneity of the observed association between expression of the PD-1 ligand (PD-L1) on tumor cells and the clinical response to immune checkpoint inhibitors (ICIs), which is likely due in part to the difficulty in defining PD-L1 positivity and limited assay standardization, the establishment of reliable laboratory parameters predictive of the clinical outcome of ICI treatment in daily clinical practice is needed.

Although most immune therapies engage T cells, the immune response to cancer is a multistep process involving multiple cell subsets and soluble mediators that function at different times and at different sites. For instance, several blood-based parameters—including markers of systemic inflammation such as baseline absolute neutrophil count (ANC) and the neutrophil-to-lymphocyte ratio—have been associated with survival in patients with melanoma treated with the ICI ipilimumab.[5–7] However, few studies have examined such potential markers for clinical outcome in patients with lung with cancer treated with ICIs. We have now examined the possible impact of clinical parameters determined in the routine laboratory setting—including peripheral blood cell counts such as ANC, absolute lymphocyte count (ALC), absolute monocyte count (AMC), and absolute eosinophil count (AEC)—on outcome in patients with advanced or recurrent NSCLC treated with nivolumab. Given that the serum concentration of C-reactive protein (CRP), a nonspecific marker of inflammation, has also been identified as an indicator of an immune response to tumor antigens[8] and that the serum level of lactate dehydrogenase (LDH) has been associated with outcome in patients with melanoma treated with the ICI pembrolizumab,[9] we also included CRP and LDH in our analysis. In addition, we investigated the impact of the level of PD-L1 expression in tumors, which has been identified as a biomarker for the response of patients with NSCLC to antibodies specific for PD-1 such as nivolumab and pembrolizumab.[10,11] Our results suggest that a combination of peripheral blood parameters may prove useful for the stratification of patients with NSCLC according to the probability of their receiving benefit from nivolumab treatment.

Patients and Methods

Patients

We reviewed the medical records of all patients with advanced (stage IIIB to IV) or recurrent NSCLC who were treated with nivolumab at Kindai University Hospital, Kishiwada City Hospital, Izumi Municipal Hospital, or National Hospital Organization Osaka Minami Medical Center between December 2015 and August 2016. From this review, we identified a total of 139 patients with advanced NSCLC who were treated with nivolumab and for whom data for differential blood counts and serum levels of CRP and LDH determined within 7 days before the initiation of nivolumab treatment were available. Of these patients, 134 individuals were included in the analysis (see Supplementary Fig. 1). Nivolumab was administered intravenously at a dose of 3 mg/kg every 2 weeks. The end of the follow-up period was December 31, 2016. The study was performed according to protocols approved by the institutional review board of each participating hospital.

Data Collection

Data regarding clinicopathologic features and treatment history were extracted from the medical records review and were updated as of December 31, 2016. Tumor response was assessed by computed tomography every 6 to 8 weeks according to the Response Evaluation Criteria in Solid Tumors, version 1.1,[12] and was evaluable in 133 of the 134 patients enrolled in the study. Progression-free survival (PFS) was measured from the time of treatment initiation to clinical or radiographic progression or death from any cause. Overall survival (OS) was measured from the time of treatment initiation to death from any cause. Patients without documented clinical or radiographic disease progression or who were still alive were censored on the date of last follow-up. If exact dates were not known because the treating physician did not provide the appropriate information, the first day of the pertinent month was estimated as the date of disease progression or censoring. Precise dates related to nivolumab treatment were available for all patients.