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Change in the lymphocyte-to-monocyte ratio is an early surrogate marker of the efficacy of nivolumab monotherapy in advanced non-small-cell lung cancer

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ABSTRACT

Objectives: Nivolumab, an anti-programmed cell death protein 1 (PD-1) monoclonal antibody, has been shown to yield a durable response and significant prolongation of the survival in some patients with non-small-cell lung cancer (NSCLC). However, identification of patients who are likely to respond to nivolumab remains difficult at present.

Materials and methods: We conducted a retrospective analysis of the clinical data of 87 consecutive patients with advanced NSCLC seen in clinical practice who received nivolumab monotherapy at the National Cancer Center Hospital in Japan between January 2016 and July 2016 (discovery cohort). In addition, we also collected the clinical data of 75 patients who were administered nivolumab monotherapy between August 2016 and March 2017 (validation cohort). For this study, we focused on the changes in the lymphocyte-to-monocyte ratio (LMR) observed after nivolumab monotherapy.

Results: In the discovery cohort, increase (≥10%) of the LMR at 4 weeks after the start of nivolumab monotherapy relative to the pretreatment LMR was positively correlated with an objective response (objective response rate (ORR); 39.4% vs 11.8%, $p = 0.0065$). When this cutoff value of ≥10% was used, increase of the LMR was significantly associated with a prolonged progression-free survival (PFS) (median PFS [mPFS]; 7.3 months vs 2.5 months, $p = 0.0049$) and overall survival (OS) (median survival time; 15.6 months vs 8.9 months, $p = 0.014$). In the validation cohort also, increase of the LMR was significantly associated with higher ORR (50.0% vs 20.0%, $p = 0.015$) and prolonged PFS (mPFS; not reached vs 3.1 months, $p = 0.0092$). On the other hand, no such correlation was observed among patients treated with docetaxel.

Conclusion: A rapid increase of the LMR was significantly associated with the effects of nivolumab monotherapy in our study cohort. Therefore, early change of the LMR may be used as a novel effective surrogate marker to decide on continuation of anti-PD-1 therapy.

1. Introduction

Treatment with nivolumab, a programmed cell death-1 (PD-1) checkpoint inhibitor, has been shown to be associated with a significantly improved overall survival (OS) as compared to standard second-line docetaxel treatment in previously treated patients with advanced non-small-cell lung cancer (NSCLC) [1,2]. Treatment with pembrolizumab, another PD-1 checkpoint inhibitor, not only provided similar results in pretreated patients with NSCLC [3], but also significantly improved the progression-free survival (PFS) and OS, as compared to standard platinum-doublet chemotherapy, in previously untreated patients with NSCLC showing a tumor cell expression level of

Abbreviations: PD-1, programed cell death-1; PD-L1, programmed cell death ligand 1; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; irAEs, immune-related adverse events; RECIST, response evaluation criteria in solid tumors; ROC, receiver operating characteristic; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; BI, Brinkman index; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; LCNEC, large cell neuroendocrine carcinoma; Sq, squamous cell carcinoma; non-Sq, non squamous cell carcinoma

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programmed cell death ligand 1 (PD-L1) of ≥50% [4].

These PD-1 inhibitors have been shown to yield marked and durable responses in about 20% (second-line [1–3]) to 40% (first-line [4]) of the treated patients. However, no predictive biomarker for the response has been established yet. Immunohistochemistry for PD-L1 has been approved as a companion diagnostic test for pembrolizumab, and a correlation between increased PD-L1 expression levels in the tumor and improved outcomes has been reported [5]. For the case of nivolumab, however, the role of PD-L1 expression remains controversial. While a correlation has been demonstrated between increased tumor cell expression of PD-L1 and improved survival in NSCLC patients with a non-squamous cell carcinoma, [2], no such correlation has been shown in NSCLC patients with a squamous cell carcinoma [1]. In addition, among patients with a non-squamous cell carcinoma, while some patients failed to respond to nivolumab treatment despite showing a high tumor cell expression level of PD-L1, others responded to treatment despite a PD-L1-negative status of the tumor [2]. Therefore, the role of PD-L1 as a predictive biomarker remains controversial. Previous studies have reported several kinds of biomarkers to predict the treatment response, such as the expression of MHC-II molecule in the tumor cells [6], a high tumor mutational load [7–9], neoantigens [10], $CD8^+$ tumor-infiltrating lymphocytes (TILs) in the tumor microenvironment [11], the absence of an increase in peripheral-blood regulatory T cells or the absence of a decrease in antigen specific T cells [12], and specific inflammation and INF-γ-related mRNA-based signatures [13]. However, studies on biomarkers are still in the experimental stage, and none of the markers listed above has been used yet in actual clinical practice.

Several studies have shown the existence of a correlation between the lymphocyte-to-monocyte ratio (LMR) or the neutrophil-to-lymphocyte ratio (NLR) in the peripheral blood with the outcomes of treatment against several malignant tumors, including lung cancer [14–19]. Since anti-PD-1 therapy is known to systemically activate immune-related cells, we hypothesized that nivolumab monotherapy might be associated with activation of some subsets of leukocytes, which might lead to changes in the peripheral blood cell fractions after the start of therapy. To examine this hypothesis, we collected clinical data from patients administered nivolumab monotherapy and analyzed the data to determine whether changes in the routine laboratory data, such as the LMR or NLR, might be associated with the treatment outcomes.

2. Patients and methods

2.1. Patients

We retrospectively analyzed the data of consecutive patients with advanced NSCLC in clinical practice at the National Cancer Center Hospital, Tokyo, Japan, who had received nivolumab monotherapy (3 mg/kg intravenously every two weeks) between January 2016 and July 2016 (Cohort 1, discovery cohort) or between August 2016 and March 2017 (Cohort 2, validation cohort). The eligibility criteria included histologically or cytologically confirmed unresectable or postoperative recurrent stage III and IV NSCLC. Patients were excluded from our analyses if they had received nivolumab or other immune checkpoint inhibitors as part of a clinical trial, if they had received nivolumab at a previous hospital and continued the treatment in our hospital, or if nivolumab monotherapy was stopped during the first cycle because of disease progression or adverse events. We also retrospectively analyzed consecutive patients with advanced NSCLC who received docetaxel monotherapy (60 mg/m^2 intravenously every three weeks) between January 2015 and December 2015.

2.2. Data collection

The collected data included each patient's age, sex, ECOG performance status (PS), disease stage, smoking history (light smoker, Brinkman index [BI] < 400; heavy smoker, BI ≥ 400), previous treatment history, tumor histology, results of molecular profiling for the *EGFR*, *ALK* and PD-L1 statuses, if available; complete blood counts (including absolute neutrophil count [ANC], absolute lymphocyte count [ALC], and absolute monocyte count [AMC]) at the baseline (before the initiation of nivolumab treatment) and at 2 and 4 weeks after the start of treatment, incidence and types of immune-related adverse events (irAEs), signs of infection (such as sudden onset of cough, sputum, and fever) during the first 4 weeks after the start of treatment, response status and date of progression as determined according to the RECIST criteria, version 1.1, and the date of death or last follow-up. The data cutoff date was November 30, 2017, for the nivolumab treatment groups and March 31, 2017, for the docetaxel treatment group. The tumor PD-L1 protein expression level was examined in archived biopsy samples of the tumors using the PD-L1 immunohistochemistry (IHC) 28-8 pharmDx (Dako) kit (Agilent Technology), in accordance with the manufacturer's protocol. The stained slides were independently scored by two observers (K.S. and N.M.), including a well-trained certified pathologist (N.M.), and in cases with discordant scores, the two reviewers arrived at a consensus by reviewing the slides together under a multi-headed microscope. According to the kit manufacturer's criteria, cases with positive membranous staining of 1% or more of the tumor cells are defined as positive. In addition, we subdivided the positive group into the high (50% or more) and low (1%–49%) expression categories.

Table 1
Patient Characteristics.

Characteristic		Cohort 1 (N = 87) N (%)	Cohort 2 (N = 75) N (%)
Age in years, median (range)		62 (34–83)	65 (37–83)
Gender	Male	54 (62.1)	50 (66.7)
	Female	33 (37.9)	25 (33.3)
Smoking history	Never	24 (27.6)	17 (22.7)
	Light	13 (14.9)	10 (13.3)
	Heavy	50 (57.5)	48 (64.0)
ECOG PS	0	18 (20.7)	23 (30.7)
	1	59 (67.8)	44 (58.7)
	2	10 (11.5)	7 (9.3)
	3	0 (0)	1 (1.3)
No. of prior systemic therapy	0	2 (2.3)	1 (1.3)
	1	23 (26.4)	49 (65.3)
	2	34 (39.1)	12 (16.0)
	≥3	28 (32.2)	13 (17.3)
Histology	Adenocarcinoma	64 (73.6)	51 (68.0)
	with *EGFR* mutation	21 (24.1)	8 (10.7)
	with *ALK* translocation	0 (0)	2 (2.7)
	Squamous cell carcinoma	10 (11.5)	19 (25.3)
	Other	13 (14.9)[a]	5 (6.7)[b]
PD-L1 expression	Negative (< 1%)	18 (20.6)	
	Low (≥1%, < 50%)	12 (13.8)	
	High (≥50%)	18 (20.6)	
	Not examined	39 (44.8)	75 (100)

[a] Five cases of NSCLC-NOS, three cases of LCNEC, two cases of adenosquamous carcinoma, one case of pleomorphic carcinoma, one case of sarcomatoid carcinoma, and one case of typical carcinoid.

[b] Two cases of NSCLC-NOS, two cases of LCNEC, and one case of lymphoepithelioma-like carcinoma.

2.3. Tumor evaluation

The objective response rate (ORR) was calculated as the percentage of complete or partial responses among all the treated patients with target lesions. Progression-free survival (PFS) was defined as the period from the date of the first administration of nivolumab until the date of documentation of disease progression or death from any cause