Perspectives: Neutrophil-to-lymphocyte Ratio as a Potential Biomarker in Immune Checkpoint Inhibitor for Non–Small-Cell Lung Cancer

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Abstract

There is a rising need for optimal biomarkers to better tailor treatments for patients with cancer in the era of immunotherapy. In addition to programmed death-ligand 1 (PD-L1) and tumor mutation burden (TMB), neutrophil-to-lymphocyte (NLR) is regaining interest as a biomarker in immunotherapy for its availability, accessibility, and reproducibility. High NLR, according to different thresholds, is consistently reported to correlate with poor prognosis in different treatments in several cancers. Yet, most data come from retrospective analysis, and proof of mechanism and principle evaluations are limited. Prospective studies or adequately sized retrospective analyses of prospectively collected data are required to best assess its role in clinical practice. Moreover, effective myeloid or neutrophil modulators in tumor microenvironment can potentially contribute as a new therapeutic strategy. This perspective will summarize our current knowledge and will discuss where we stand now and propose future directions.

Clinical Lung Cancer, Vol. 20, No. 3, 143-7

Keywords: Advanced non-small cell lung cancer, Biomarker, Cost-effectiveness, PD-1 inhibitor, Neutrophil-to-lymphocyte ratio

Introduction

Immunotherapy has marked an impressive progress in cancer treatment recently. In certain cancers, immunotherapy has outperformed conventional systemic treatment options like chemotherapy and targeted therapy.[1-4] Unsurprisingly, the indications of immune checkpoint inhibitors like programmed death-1/ligand 1 (PD-1/L1) and cytotoxic T-lymphocyte associated protein 4 as first-line treatment options are expanding rapidly. And emerging lung cancer clinical trial results are continuously reshaping the practice of thoracic oncology.[5-7] Nonetheless, we are still at infancy in selecting the best population who can benefit the most with least toxicity from single or combination immunotherapy. The search of optimal biomarkers remains to be the critical mission in the field.

Neutrophil-to-lymphocyte ratio (NLR) is a simple and convenient measure ubiquitously available in any clinic visit by a simple draw of peripheral blood. It is inexpensive, minimally invasive, and reproducible. The role of NLR has been refocused and reevaluated as immune cells are the main tools that immunotherapy work through to fight cancers. There are numerous reports correlating NLR with different cancer immunotherapy. But the mechanism needs to be answered before we can meaningfully utilize NLR as a biomarker. Deciphering the role of NLR in immunotherapy and identifying potential strategies to modulate certain resistant groups defined by high NLR would provide new opportunities for managing patients with resistant lung cancer with immunotherapy.

Literature on the Role of Neutrophils and Lymphocytes in Cancer

One of the early appearances of neutrophil and lymphocyte measurements in the cancer literature was in 1976, when Russell et al described the major immunologic constituents in tumor foci of mice sarcoma at different time points after inoculation of sarcoma cancer cells in mice.[8] Intratumoral immune cells including neutrophils, T-lymphocytes, and macrophages were analyzed. A higher number of T-lymphocytes were observed in regressing tumors as opposed to in progressing tumors, whereas significantly higher neutrophils were found in progressing sarcomas. In a similar context of human peripheral blood, Liu et al also observed 41 patients with metastatic cancer without evidence of infection had neutrophilia and decreased marrow granulocyte reserve.[9]

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Submitted: May 28, 2018; Revised: Nov 25, 2018; Accepted: Dec 8, 2018; Epub: Dec 19, 2018

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1525-7304/$ - see frontmatter
https://doi.org/10.1016/j.clc.2018.12.003

The ironic antagonistic roles of these 2 major immune cells were also described in a maternofetal model. Valdimarsson et al reported the longitudinal observation of leukocytes and neutrophils in 77 pregnant women to describe the concept of immune tolerance and rejection in these immune compartments.[10] Throughout normal pregnancies of these women, high neutrophil counts continued in contrast to decreasing absolute lymphocyte counts in both B and T lymphocytes until the second trimester, and T cell reactivity was decreased to T cell mitogens. This hypothetical antagonistic interaction was observed among T helper lymphocytes and neutrophils by Zoschke et al as well, where hydrogen peroxide releasing function from activated neutrophils was suppressed by lymphocyte proliferation.[11,12]

Clinically, higher peripheral lymphocyte counts have shown to correlate well with better outcomes of patients with melanoma treated with ipilimumab and pembrolizumab.[13,14] Moreover, a higher number of infiltrating T lymphocytes at tumor foci and at invasive margins from a pathologic analysis called "Immunoscore" has shown to correlate with better prognosis and with lower recurrence rates in patients with resected colon cancer, adding additional value to conventional TNM staging.[15] In contrast, high neutrophil counts are reported to correlate with more advanced cancers and proposedly more inflammation, and therefore poor prognosis in cancers.[13,16-18]

NLR combines the inversed value of peripheral absolute lymphocyte counts and the neutrophil counts to mathematically augment their negative effect in the course of cancer progression. Simply and conveniently, it may represent the balance of myeloid versus lymphoid, innate versus adaptive immunity, chronic inflammation versus acute immune rejection, and protumor versus antitumor immune phenotypes. NLR has been incorporated together in different models in cancer studies to increase their utility. Many of these reports are validated in large scale as well as in meta-analyses.[16,19-22] However, most of these are retrospective analyses.

Preclinical Evidence: The Interplay Between Neutrophils and Lymphocytes in Immunotherapy

Whether NLR reflects merely the mathematical relations between neutrophils and lymphocytes or a more biological relation remains to be further studied. The interplay among these 2 important immune cells has been reported in preclinical studies. Although both neutrophils and lymphocytes are critically important constituents of immunity for the host defense, they have different roles in the spectrum of innate immunity and adaptive immunity. Neutrophils are the most abundant and the first recruited immune cells at the tumor for its attempted role of acute rejection, whereas the lymphocytes are slowly recruited experienced immune cells that essentially become the pillar element of long-term adaptive immunity in cancer immunotherapy.

Myeloid immune compartments have been suggested as contributors for a resistance mechanism to host immune system against cancer. The immunosuppressive function of tumor-associated neutrophils (TANs) along with tumor-associated macrophages and myeloid-derived suppressive cells have been described.[23-25] The plasticity and bipolar functions of these immune cells have been reported to be influenced by different tumor microenvironment (TME). Particularly for TANs, Singhal et al has shown that CD11b+CD15^{hi}CD10-CD16^{low} TANs exhibited more antitumor effect with non-professional antigen-presenting function in the early stage resected lung cancers.[26] On the contrary, higher level of tumor growth factor-beta in advanced lung cancer TME was shown to affect TANs to be more protumoral phenotype so-called "N2".[24] This immunosuppressive TME is suggested to be influenced by chemokine receptor 2 (CXCR2), and interleukin-8 (IL-8) arginase-1, indoleamine 2,3-deoxygenase, and adenosine as well, which are currently being tested as myeloid modulating strategies in cancer immunotherapy.[27]

An interesting hypothesis of granulocyte-macrophage-colony stimulating factor (GM-CSF-PD-L1) axis in the tumor-infiltrating neutrophils in treatment of immunotherapy of gastric cancer has been proposed.[28] Wang et al showed that PD-L1 expression is inducible through Janus Kinase (JAK)-signal transducer and activator of transcription 3 (STAT3) signaling on neutrophils by GM-CSF derived from tumor, which creates immunosuppressive TME and impairs the cytotoxic and proliferation ability of T cell lymphocytes. This T cell immunity was demonstrated reversible by PD-L1 blockade. Besides the induction of PD-L1, the recruitment of neutrophils and myeloid-derived suppressor cells via tumor-derived CSF is suggested to be a resistance mechanism to immunotherapy.[29] Taking advantage of this mechanism reversely is proposed as a novel strategy to overcome the resistance to immunotherapy in cancer. In Glodde et al's study, this is more simplified as neutrophil recruitment as an important resistant mechanism, and the author uses different syngeneic cancer models treated with different immunotherapy modalities not only limited to PD-1/L1 blockade but also 4-1BB (CD137) blockade, adoptive cell therapy, and poly (I:C) + CpG.[30] Utilizing c-MET inhibition was able to reverse the course of neutrophil recruitment, and the resistance of immunotherapy was reversible.

The Prognostic Implications and Predictive Potential of NLR

In a large scale meta-analysis that included 40,559 patients with cancer, the reproducibility of NLR at different cutoffs was tested for the prognostic value. High NLR conferred poor clinical outcome with higher hazard ratio (HR): overall survival using an NLR cutoff of 4 (HR, 1.81; 95% confidence interval [CI], 1.67-1.97; $P <$ .001), progression-free survival using an NLR cutoff of 3 (HR, 1.63; 95% CI, 1.39-1.91; $P <$ .001), and disease-free survival using an NLR cutoff of 5 (HR, 2.27; 95% CI, 1.85-2.79; $P <$ .001).[31] In a retrospective analysis of 801 patients with colon cancer, NLR, as well as other composite ratios and scores reflecting high monocytes, high platelet, low albumin, and high C-reactive protein, were correlated with the poor outcomes.[32] Likewise, in multiple smaller studies, the prognostic value of high NLR correlating with worse clinical outcome are consistently reported in many cancer types including head and neck, lung, gastric, pancreatic, liver, colon, kidney, bladder, melanomas, and cervical cancers at different stages.[33-40]

Predictive biomarkers require precision in identifying the individuals who would benefit and have their disease course impacted by an intervention. The utility of NLR is clearly prognostic in many reports. However, prognostic markers can also be predictive when

Table 1 Biomarker Strategy Using NLR in Immunotherapy[5,16,19,45,46,48-51]

	Ontology	Treatment	Size	Variables	Timing of Measurement	Worse Group Definition	PFS			OS		
							HR	95% CI	*P* Value	HR	95% CI	*P* Value (Difference)
Jung et al	Melanoma	Ipilimumab	104	NLR	Baseline	NLR > 5	2.2		.023	0.99		.944
Cassidy et al	Melanoma	Ipilimumab	197	NLR	Baseline, 3-, 6-, 9-week	NLR > 5 during treatment	1.81	1.33-2.46	< .001	2.03	1.49-2.77	< .001
Lalani et al	RCC	Nivolumab	142	NLR	Baseline and 6 ± 2 weeks posttreatment	NLR increase > 25% baseline	2.6	1.53-4.39	< .001	1.57	0.8-2.99	.004
Bagley et al	NSCLC	Nivolumab	175	NLR	Baseline	NLR > 5	1.43	1.02-2.0	.04	2.07	1.3-3.3	.002
Park et al	NSCLC	Nivolumab	159	(Gender, ECOG, NLR, DNLR)	Baseline and 2-week posttreatment	Baseline NLR > 5 AND posttreatment increase, Male, PS > 2	Poor: 2.8	1.7-3.2	.0001	7.1	3.2-9.3	.0001
Fernucci et al	Melanoma	Ipilimumab	720	dNLR	Baseline	dNLR > 3	4.1	3.08-5.46	.0001	2.46	1.88-3.23	.0001
Mezquita et al	NSCLC	PD-1/L1 i	466	dNLR, LDH	Baseline	dNLR > 3 AND LDH > ULN	Poor: 1.61	1.1-2.34	.01	Poor:1.98	1.27-3.1	.002

Abbreviations: CI = confidence interval; dNLR = delta NLR; ECOG-PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; NLR = neutrophil-to-lymphocyte ratio; NSCLC = non–small-cell lung cancer; PD-1/L1 i = programmed death-1/ligand-1 inhibitors; RCC = renal cell carcinoma; ULN = upper limit of normal; DNLR (delta NLR) = (posttreatment NLR at 2 to 3 weeks)–(baseline NLR); dNLR (derived NLR) = (white blood cell count)–(NLR).

the specific mechanism and precision is proven, the effective intervention is identified, and this is tested in a well-designed prospective manner.[41-44] Efforts are invested to evaluate the predictive value such as evaluating and comparing the different peripheral blood parameters at different time points and from patients treated with different modalities.[19,20,45,46] Because NLR is not a specific qualitative marker such as a specific mutation would be, highly validated evaluation with specific modulator and contrasting control groups at an a priori cutoff is proposed and may serve for predictive potential evaluation.

NLR as a Biomarker in Immunotherapy in NSCLC

Lung cancer remains the leading cause of cancer-related mortality in the world.[47] With recent advances in immunotherapy in this disease, there are many potential biomarkers emerging and tested in larger cohorts of patients. One of the first reports of NLR correlating with NSCLC on PD-1 blockade used the conventional cutoff of 5, and it showed concordance of NLR > 5 correlating with poor prognosis.[48] Our group also built a multivariate model called the iSEND model that reflects baseline NLR and change of NLR (delta NLR [DNLR]) after the first dose of nivolumab in patients with advanced NSCLC in the post-platinum setting, which is now validated in an international cohort.[46,49] Baseline composite multivariate model using derived neutrophil-lymphocyte ratio (dNLR = neutrophil/[leukocyte − neutrophil]) at baseline also showed prognostic value specifically in immunotherapy but not in chemotherapy.[19] Biomarker strategies utilizing NLR or dNLR in cancer immunotherapy are summarized in Table 1.

Although most articles have correlated NLR with outcomes retrospectively, Fukui et al performed a prospective observational study in Japanese patients with advanced NSCLC (n = 52). The article showed the association of PD-L1 expression and NLR in these patients with NSCLC. Despite its small sample size, NLR was able to categorize patients into good or poor groups after adjustment with PD-L1 > 50% as well as bony metastasis. Clinically, the cutoff of PD-L1 > 50% is practical as the United States Food and Drug Association approval of pembrolizumab in first-line for advanced NSCLC uses this cutoff.[3] Also, this study was performed in a unique population where driver mutations are more prevalent, which is known to be a negative marker for resistance to immunotherapy. The advantage of NLR is the accessibility, and its use can complement the predictability of PD-L1 expression when combined to better choose patients with NSCLC who will do better with PD-1/L1 blockade.

Role of NLR in Relation to PD-L1 and TMB

Biomarkers for immunotherapy in NSCLC are emerging rapidly from new positive clinical trials.[5-7] PD-L1, TMB, and microsatellite mismatch instability are the most evaluated markers that may complement each other because the spectrum of PD-L1 expression is not exclusively parallel to the level of tumor mutation burden, and it follows for microsatellite mismatch instability and TMB. Using a single or composite biomarker of them may enhance the predictive value. These biomarkers have made the field of immuno-oncology most tantalizing, but more evaluations are needed for different cutoffs in different treatments. Currently, major biomarker efforts have focused on positive predictive biomarkers for the sensitivity to

immunotherapy, but finding the negative biomarker for resistance would add a high value to the field as single agent PD-1/L1 inhibitors are approved without biomarkers in the second-line and above settings as well as the platinum doublet chemotherapy plus immunotherapy combination, which is also approved in the front-line setting.

PD-L1 immunohistochemistry staining by antibody 22C3, 28-8, and E1L3N except the SP142 were tested to have concordance, and once PD-L1 is positive above 50% on the biopsy tissue in NSCLC, the single agent pembrolizumab is indicated.[3,52] There is also KN189 in a recently published large cohort that a combination of platinum doublet chemotherapy plus immunotherapy upfront, regardless of PD-L1 expression, compared with platinum doublet chemotherapy can achieve a better response rate as well as better overall survival (HR, 0.49; 95% CI, 0.38-0.64) and progression-free survival (median of 8.8 months vs. 4.9 months).[6] However, by default, the conventional clinical trial design can only evaluate patients with good performance status, which is very different from the real-world clinical practice. If the PD-L1 expression is at least greater than 1% by the Keynote 042 study, patients will benefit from single-agent immunotherapy, and especially less physically fit patients can still improve their quality of life tremendously instead of receiving combinational therapies. NLR is what can be easily retrievable practically to identify those who would be still very resistant to single PD-1 blockade and can be tested for combination with myeloid or neutrophil modulators.

In Checkmate 227, the validation of TMB with the cutoff of 10 (mutations per megabase [Mt/Mb]) was tested in advanced NSCLC in which patients with TMB > 10 Mt/Mb irrespective of their PD-L1 expression have shown to benefit more from a nivolumab and ipilimumab combination compared with standard chemotherapy.[7] The response rate of ipilimumab and nivolumab arm was 42.6% compared with 13.2% in the chemotherapy arm. This effect was also seen in patients with PD-L1 < 1%, and they are proposed as another potential first-line option compared with single agent or chemo-immunotherapy if TMB is greater than 10 Mt/Mb. Comparing NLR and its dynamic change in these new trials with combination can better characterize the specificity of NLR. Once these are validated, comparing the performance and cost-effectiveness of each marker and composite modeling are necessary.

Conclusion and Perspectives

Deciphering the precise mechanism of interplay among neutrophils and lymphocytes in immunotherapy in patients with NSCLC and evaluating the concordance of NLR in tumor and in the peripheral blood would be the most important next steps to improve the usage of this biomarker. There is also a need to determine the specific cutoff for NLR in prospective design with endpoints set as a priori. It would also be critical to assess NLR in patients treated not only with immune checkpoint inhibitors, but also chemotherapy and targeted kinase inhibitors. Also, the adaptive dynamic change of NLR while receiving treatment would suggest different but more precise prediction.[46,50] Other possibilities for evaluation include the assessment of NLR as a predictive marker in earlier settings.[20,46,50] Finally, the cost-effectiveness evaluation of NLR as a biomarker would also need to be carried out. We still have a lot of work to do before NLR can become a validated and practical biomarker.

Disclosure

The authors have stated that they have no conflicts of interest.

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