Early changes in lymphocyte/monocyte ratio on-treatment as a prognostic marker to predict overall survival in patients with advanced cancer treated with immune checkpoint inhibitors

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Abstract

Background

A low absolute lymphocyte/monocyte ratio (LMR) in the peripheral blood is associated with poor prognosis in various cancers; however, its role as a predictive biomarker has not been well defined in the era of treatment with immune checkpoint inhibitors (ICI).

Methods

We queried a database of advanced cancer patients treated with at least one dose of ICI from 2011 to 2017 to study the association of LMR with overall survival (OS). We calculated LMR at baseline and a median of 21 days after the first cycle of ICI (on-treatment LMR), and defined low if $< 2$ and high if $\geq 2$. OS was calculated from the initiation of ICI to date of death or censored at last follow-up.

Results

1077 patients met the criteria for this study. Patients with low baseline LMR had a shorter median OS compared to patients with a high baseline LMR (8.5 vs 18.1 months, $p < 0.01$). In patients with a low baseline LMR, who on-treatment LMR increased to high had longer median OS compared to those whose on-treatment LMR remained low (16.8 vs 7.8 months, $p < 0.001$). Patients with a high baseline LMR and in whom on-treatment LMR remained high had longer median OS compared to patients with low on-treatment LMR (23.9 vs 9.2 months, $p < 0.001$). In multivariate analysis, high on-treatment LMR was most strongly associated with longer survival compared to low on-treatment LMR, regardless of baseline LMR.

Conclusions

Higher baseline and early changes in on-treatment LMR are associated with improved OS in cancer patients receiving ICI.

Introduction

The use of immune checkpoint inhibitors (ICI) targeting negative regulators of T-cell function such as cytotoxic T-lymphocyte associated protein 4 (CTLA4), programmed cell death-1 (PD-1), and its ligand 1 (PD-L1) has improved outcomes for patients with many types of cancer (1). However only a subset of patients achieve durable response, and the majority of patients eventually develop resistance or fail to respond (2). ICI which can be given alone or in combination with other therapies, are expensive and can cause life threatening immune related adverse events (IrAEs) such a pneumonitis, myocarditis, and encephalitis (3, 4). Biomarkers to predict whether a patient is likely to respond to these treatments could guide appropriate clinical management, including identifying patients least likely to benefit from ICI alone.
who may require multi-modality therapeutic approaches. Recognized clinical biomarkers that may inform response include PD-L1 expression, microsatellite instability (MSI), and tumor mutational burden (TMB) (5). These markers have significant limitations such as lack of assay standardization, cost, need for invasive biopsies, identification of optimal cutoff points, and slow turnaround times which restrict the use during routine practice (2).

ICIs modulate the interaction between T lymphocytes and tumor cells, which leads to re-induction of the “natural” function of T lymphocytes in the tumor microenvironment (TME). In the TME, high levels of regulatory T (TReg) cells [immune suppressive] have been associated with a worsened survival while a high density of cytotoxic CD8+ T lymphocyte has been associated with improved survival (6). Peripheral T lymphocyte activity is closely correlated with T lymphocyte function in the tumor microenvironment (7). Monocyte recruitment into tumors appears to be negatively associated with infiltration of cytotoxic CD8+ T cells, and monocyte-derived cells secrete factors such as CCL5 that recruit immunosuppressive Treg cells (8). Monocytes are recruited into tumors where they alter the TME and can promote cancer progression through local immunosuppression and angiogenesis (9).

Peripheral lymphopenia, in patients with metastatic solid tumors is strongly associated with a worse progression-free and overall survival (10). Peripheral monocytosis is also associated with worsened overall survival (11, 12). Peripheral blood lymphocyte-to-monocyte ratio (LMR) may reflect the interaction between host immune cells and immune suppressive cells in TME, which could be represented by circulating lymphocytes, and monocytes. Techniques such as mass cytometry (13), are also available to further interrogate the types of T lymphocytes and monocytes in peripheral blood, but these assays are not yet widely utilized in clinical practice and are associated with significant cost. In contrast, peripheral blood count can be quickly and inexpensively determined by a standard automated complete blood count machine. Recent studies have indicated that a low LMR, as a simple biomarker of the host immune system, is associated with a poor prognosis in various cancers but its role has not been well defined in the era of ICI therapy, and is not routinely clinically implemented (14). Because the white blood cell differential is routinely tested and available in cancer patients, we conducted this study to evaluate the association of overall survival (OS) with baseline and early changes in LMR during treatment with ICI.

**Methods**

We conducted a retrospective study of patients with advanced cancer treated with at least one dose of ICI either alone or in combination from 2011 to 2017 at the Ohio State University Comprehensive Cancer Center. Patients received ICI as standard of care or as part of a clinical trial. This study was approved by the institutional review board at The Ohio State University (#2016C0070).

**Data collection**

Clinically relevant data were collected in REDCap after retrospective review of electronic medical records (15). These included (1) baseline complete blood count (CBC) with differential was collected on the day
before receiving ICI or within 7 days prior to initiation of ICI; (2) on-treatment CBC collected at the next blood draw after the first dose of ICI - if on-treatment CBC was less than 7 days from the initiation of ICI, a CBC closest to 14 days post-initiation of ICI was used; (3) clinical characteristics - age at ICI initiation, gender, cancer type and stage, performance status (ECOG) at time of ICI initiation, smoking status, BMI, type of ICIs, IrAEs and survival status.

**Statistical analysis**

Descriptive statistics were obtained to summarize the study population including medians and ranges for the continuous variables and frequencies for the categorical variables. LMR was calculated as a ratio of absolute lymphocyte/monocyte counts. We utilized a cut off value of 2, based on prior studies (16, 17). The baseline and on-treatment LMR were grouped into categories: low LMR (< 2) and high LMR (≥ 2), and a derived LMR variable was created by baseline and on-treatment LMR groups (low baseline LMR, low on-treatment LMR; low baseline LMR, high on-treatment LMR; high baseline LMR, low on-treatment LMR; and high baseline LMR, high on-treatment LMR). Survival curves were plotted by LMR groups using Kaplan-Meier (KM) method. Median OS with 95% confidence intervals were estimated, and Log rank test was used for group comparisons. Cox Proportional Hazards Survival Models were used to examine the association between the derived LMR variable with OS, controlling for age, performance status (ECOG), smoking, body mass index (BMI), type of cancer, type of ICIs, and IrAEs. All analyses were conducted using SAS (9.4).

**Results**

**Patient Characteristics**

A total of 1077 patients treated with ICI from 2011 to 2017 were included in this retrospective study. Detailed patient demographics and treatment characteristics are summarized in Table 1. The median age at the time of treatment was 61 (range 54–69), and there were 640 (59.4%) male and 437 (40.6%) female patients. The most common cancer types were melanoma (N = 335 (31.1%)), non-small cell lung cancer (NSCLC, N = 199 (18.5%)), and renal cell carcinoma (RCC, N = 119 (11%)). Most common ICIs were anti-PD-1/PD-L1 (N = 769 (71.40%)), anti-CTLA4 (N = 193 (17.9%)), and the combination PD-1/CTLA-4 (N = 80 (7.4%)). There were 558 patients with baseline LMR < 2 (51.8%) and 519 patients with baseline LMR ≥ 2 (48.2%). We further divided patients into four different categories based on their baseline LMR as well as on treatment LMR (Table 3). 105 patients’ lab values in the on-treatment LMR < 2 group and 92 patients’ lab values in the on-treatment LMR ≥ 2 group were missing. Median OS of all patients was 11.8 months (95% CI, 10.5 to 13.8). One fifth of the patients with missing data (235 (21.8%)) were not included in the Cox regression models: 117 patients (10.9%) were missing ECOG, 10 patients (0.1%) were missing smoking status and 178 patients (16.5%) were missing IrAEs data. All other variables included in the Cox regression model were available for all subjects.
| Characteristic                        | Total (n = 1077) |
|--------------------------------------|------------------|
| **Age**                              |                  |
| < 65                                 | 655 (60.8%)      |
| ≥ 65                                 | 422 (39.2%)      |
| **Gender**                           |                  |
| Female                               | 437 (40.6%)      |
| Male                                 | 640 (59.4%)      |
| **Performance Status (ECOG)**        |                  |
| 0–1                                  | 780 (72.4%)      |
| 2                                    | 148 (3.7%)       |
| > 2                                  | 32 (3.0%)        |
| Missing                              | 117 (10.9%)      |
| **Smoking History**                  |                  |
| Yes                                  | 623 (57.7%)      |
| No                                   | 444 (41.2%)      |
| Missing                              | 10 (0.1%)        |
| **BMI**                              |                  |
| Median                               | 27.5 [23.5, 31.5]|
|                                     | (13.4, 70.2)     |
| **Cancer Type**                      |                  |
| Melanoma                             | 335 (31.1%)      |
| NSCLC                                | 199 (18.5%)      |
| RCC                                  | 119 (11%)        |
| Head and neck                        | 84 (7.8%)        |
| Sarcoma                              | 56 (5.2%)        |
| Bladder                              | 43 (4%)          |
| Other                                | 241 (22.4%)      |
| **Immunotherapy Type**               |                  |
| PD-1/L-1                             | 769 (71.4%)      |
| CTLA-4                               | 193 (17.9%)      |
| PD1 + CTLA4                          | 80 (7.4%)        |
| Other                                | 35 (3.2%)        |
| **Immunotherapy related adverse events** |              |
| No                                   | 581 (53.9%)      |
| Yes                                  | 318 (29.6%)      |
| Missing                              | 178 (16.5%)      |
Table 3
Multivariate analysis with baseline LMR and on-treatment LMR Controlling for age, ECOG, smoking, BMI, type of cancer, type of ICI, IrAEs (N = 742)

| Hazard Ratio | 95% Hazard Ratio Confidence | P value |
|--------------|----------------------------|---------|
| LMR baseline < 2, LMR on-treatment < 2 | Ref | - |
| LMR baseline < 2, LMR on-treatment ≥ 2 | 0.657 | 0.486–0.888 | 0.006 |
| LMR baseline ≥ 2, LMR on-treatment < 2 | 0.921 | 0.708–1.199 | 0.542 |
| LMR baseline ≥ 2, LMR on-treatment ≥ 2 | 0.524 | 0.423–0.650 | < .001 |

Baseline LMR and Survival

In univariate analysis, the Kaplan-Meier estimate of median OS in patients with high baseline LMR was significantly longer than patients with low baseline LMR. (18.1 months [95% CI, 15.8 to 21.6] vs 8.5 months [95% CI, 7.3 to 9.6] months; p < 0.001). (Table 2, Fig. 1).

Table 2
Overall survival according to baseline LMR and on-treatment LMR

| LMR ratio (Baseline) | LMR ratio (On Treatment: After first cycle of ICI) | Number of Patients | Median Overall Survival (Month) | P value |
|----------------------|-----------------------------------------------|-------------------|-------------------------------|---------|
| High (≥ 2)           | All                                           | 519               | 18.1 (15.8–21.6)              | < 0.001 |
| Low (< 2)            | All                                           | 558               | 8.5 (7.3–9.6)                 | < 0.001 |
| High (≥ 2)           | High (≥ 2)                                    | 315               | 23.9 (20.1–29.5)              | < 0.001 |
| High (≥ 2)           | Low (< 2)                                     | 112               | 9.2 (6.7–11) *                | < 0.001 |
| Low (< 2)            | High (≥ 2)                                    | 93                | 16.8 (10-24.4)                |         |
| Low (< 2)            | Low (< 2)                                     | 360               | 7.8 (6.1–9.1) †               |         |

* p-value < 0.001 for comparison between high LMR on treatment vs low LMR on treatment for patients with high LMR at baseline.

† p-value < 0.001 for comparison between high LMR on treatment vs low LMR on treatment for patients with low LMR at baseline.
Change in on-Treatment LMR and Survival

In the group of patients with high baseline LMR, the Kaplan-Meier estimate of the median OS was significantly prolonged in patients who had remained high on-treatment LMR compared to those who had on-treatment LMR decreases (23.9 months [95% CI, 20.1 to 29.5] versus 9.2 months [95% CI, 6.7 to 11]; p < 0.001). In the group of patients with low baseline LMR, the Kaplan-Meier estimate of the median OS was significantly longer in patients who had increased to high on-treatment LMR compared to those who remained low for on-treatment LMR (16.8 months [95% CI, 10-24.4] versus 7.8 months [95% CI, 6.1–9.1; p < 0.001). In univariate analysis, change to high on-treatment LMR after the first cycle of ICI was associated with longer OS compared to low on-treatment LMR regardless of baseline LMR. (Table 2, Fig. 2)

Multivariate Analysis and Survival

A multivariate analysis of baseline LMR and on-treatment LMR after controlling for age, performance status (ECOG), smoking, body mass index (BMI), type of cancer, type of ICIs, and IrAEs, showed that patients with low baseline LMR and high on-treatment LMR; and patients with high baseline LMR and high on-treatment LMR had a 34% and 48% lower risk of death, respectively, compared to low baseline and low on-treatment LMR; p < 0.001. In addition, patients with high baseline LMR but low on-treatment LMR, did not have a statistically significant difference in survival compared to patients with low baseline and low on-treatment LMR, p = 0.542. (Table 3)

Discussion

This is one of the largest retrospective studies evaluating the changes in LMR and association with OS in patients with different malignancies treated with ICI. Patients with high baseline LMR had 9.6 months longer median OS than patients with low baseline LMR (p < 0.001). Furthermore, patients with on-treatment change to high LMR, even with low baseline LMR, had 14.7 months longer OS than patients with persistent low LMR after the first dose of ICIs (p < 0.001). Patients with on-treatment change to low LMR, even with high baseline LMR, had 9 months shorter OS than patients with persistent high LMR after the first dose of ICIs (p < 0.001). Patients with low baseline LMR but high on-treatment LMR had 34% lower risk of death than those with low baseline LMR and low on-treatment LMR (p < 0.001). Patients with high baseline LMR and high on-treatment LMR had 48% lower risk of death than those with low baseline LMR and low on-treatment LMR, after controlling for age, ECOG, smoking, BMI, type of cancer, type of ICI, and IrAEs. Patients with a high baseline LMR and low on-treatment LMR had 8 % lower risk of death those with low baseline LMR and low on treatment LMR. The changes in LMR after the first dose of ICI treatment can predict longer OS in cancer patients. Hence, LMR is a potential potent predictive biomarker for ICI effectiveness.

ICI therapy has led to a new era of cancer therapy with sustained response and significant survival advantages observed in multiple tumors, particularly in metastatic and advanced stage cancers. A subset
of patients receive long term benefits, but many patients will recur. A comprehensive understanding and identification of predictive ICI-related biomarkers is important for predictive purpose. PD-L1 expression, MSI and TMB biomarkers have limitations to routine use during treatment. PD-L1 protein expression on tumor or immune cells has emerged as an accepted predictive biomarker for sensitivity to ICIs. It has shown great promise as a predictive marker, but variability of PD L1 expression observed during testing - type of tissue tested (fresh vs. archival), type of PD-L1 assay, PD-L1 expression cutoffs: 1, 5, and 50%, and type of cells (tumor vs. immune vs. both) tested for PD-L1 expression limit the predictability of response to ICI (18). In 2017, the FDA granted accelerated approval to pembrolizumab for pediatric and adult patients with MSI-high (MSI-H) or mismatch repair–deficient solid tumors, which is the first FDA approval for a cancer treatment based on a common biomarker rather than an organ-based approach (19). However, MSI-H is found only in limited types of cancer (20). Similar to PD-L1 analysis MSI status can only be determined from tissue samples. In 2020, the FDA granted accelerated approval of pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic TMB-high (TMB-H) [≥ 10 mutations/megabase (mut/Mb)] solid tumors (21). TMB has been shown to be a promising predictive biomarker for the stratification of ICI response. However, the requirement of significant amount of tumor material and absence of standardization between the different tests to define low and high TMB currently limits its use in routine practice (22). PD-L1 expression, MSI-H and TMB analyses require invasive biopsies to obtain tissue samples, which are not practical to use for frequent biomarker monitoring, and they are expensive tests (23).

Peripheral blood is a noninvasive source to explore potential biomarkers for ICIs. The immune system plays a key role in cancer as it can destroy cancer cells but also interacts with the TME that facilitates cancer cell proliferation. Monocytes are direct precursors of hematopoietic stem cell-derived macrophages. After their recruitment into the tumor tissue, they can differentiate into tumor-associated macrophages (TAM). TAMs play a role in multiple stages of tumor metastasis, from promoting tumor cell escape from the primary site to facilitating tumor cell arrival and establishment at distant sites (24). A low lymphocyte count has been found to be associated with poor OS in patients with various types of cancer (25). A high monocyte count has been reported to be a poor prognostic factor in patients with solid tumors (26–28). LMR, as a simple biomarker of host immune system, has been able to predict improved long-term prognosis of patients with various malignancies,(29, 30) but its role has not been well defined in the era of ICIs and is not routinely clinically implemented.

Strengths of this study are a large cancer patient population as well as the inclusion of clinically relevant variables that impact survival, such as age, performance status, smoking, BMI, type of cancer, type of ICIs, and IrAEs. While this is one of the largest studies to date evaluating baseline LMR and changes in LMR after the first dose of ICI in diverse cancer patient population, the limitations of this study include most notably its retrospective nature. We were not able to evaluate variables with known predictive power in this context, including line of therapy, mutation status, and predictive biomarkers (PD-L1, TMB and MSI-H). We were also not able to evaluate the relationship with LMR with single agent ICI vs combination therapies which could be subject for further study. Routine complete blood count tests to calculate LMR are inexpensive, non-invasive and readily available compared to PD-L1, MSI and TMB biomarker testing,
especially in developing countries. We suggest using LMR in prospective clinical trials to confirm its validity.

**Conclusion**

We found that both baseline high LMR and changes to high LMR after the first dose of ICI are associated with longer OS in advanced cancer patients. LMR changes after the first dose of ICI may serve as a predictive marker for survival. In multivariate analysis, combination of baseline LMR and on-treatment LMR was most highly associated with improved outcome in patients with cancer treated with ICI. Prospective studies are needed to confirm these findings.

**Abbreviations**

Lymphocyte/Monocyte Ratio (LMR); Immune Checkpoint Inhibitor (ICI); Immune-related Adverse Events (IrAEs); Overall survival (OS); Tumor Microenvironment (TME)

**Declarations**

**Ethics approval and consent to participate:** Data from this work were collected under an IRB-approved retrospective study (OSU- 2016C0070).

**Consent for publication:** Not Applicable

**Availability of data and material:** In accordance with local and/or U.S. Government laws and regulations, any materials and de-identified data that are reasonably requested by others will be made available in a timely fashion.

**Code availability:** All analyses were conducted using the SAS system, version 9.4 (SAS Institute Inc., Cary, NC). No custom codes were used.

**Competing interests:** The authors report no conflicts or competing interests. This study was not funded by any private entity. Financial disclosures not directly relevant to the current work are listed at end of manuscript in compliance with ethical standards.

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**Authors' contributions:** Sandip Patel, Songzhu Zhao, Lai Wei and Dwight Owen contributed to the study conception and design. Material preparation, data collection and analysis were performed by all authors. First draft of the manuscript was written by Sandip Patel and Dwight Owen, and all authors commented
on previous versions of the manuscript. All authors read the manuscript, revised it critically, and approve of the final manuscript.

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Figures
Figure 1

Kaplan–Meier curves for OS according to baseline LMR. Overall survival was 9.6 months longer in patients with high baseline LMR (≥2) compared to patients with low baseline LMR (<2), p<0.001.

Logrank p < .0001

Figure 2

Kaplan–Meier curves for OS according to baseline and on-treatment LMR. Overall survival was 14.7 months longer in patients with high on treatment LMR (≥2) compared to patients with low on-treatment LMR (<2) in patients with high baseline LMR (≥2), p<0.001. Overall survival was 9 months longer in patients with high on-treatment LMR (≥2) compared to patients with low on-treatment LMR (<2) in patient with low baseline LMR (<2), p<0.001.