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Pre-Treatment Peripheral Blood Parameters as Prognostic Biomarkers in Cancer Patients Receiving Immune Checkpoint Inhibitors

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ABSTRACT

Background: Immune checkpoint inhibitors have significantly improved outcomes in select cancers; however, not all patients respond to these therapies, and the duration of the response varies among responders. Markers predictive of the response to immunotherapy, such as PD-L1 expression determined by immunohistochemical staining of tumor sections and microsatellite status, have been identified. Some of these are used in companion diagnostics approved for clinical practice. Additional easy-to-use biomarkers may help clinicians to predict the efficacy of these drugs in individual patients.

Materials and Methods: A retrospective review of the medical records of patients with metastatic cancer treated with immune checkpoint inhibitors in our cancer center was performed to identify the clinical and hematologic parameters associated with survival outcomes.

Results: Among the 163 patients included in the study, most had lung cancer, followed by kidney cancer, melanoma, and bladder cancer. Most patients (61.3%) were male and had good performance status. Nivolumab and pembrolizumab were immune checkpoint inhibitors utilized in 85.9% of cases. Age, sex, and primary cancer type were not associated with survival outcomes. Among the peripheral blood parameters evaluated, lymphocytopenia was the strongest predictor of adverse survival outcomes in univariate analysis and the only clinical or hematologic biomarker that retained significance for overall survival (OS) prediction in multivariate analysis.

Conclusion: Among the clinical and hematologic parameters routinely used in the clinic, a lymphocyte count below 1 x 10^9/ L was predictive of adverse OS in patients with metastatic cancers receiving immune checkpoint inhibitors.

Keywords: Immunotherapy; Biomarkers; Hematologic parameters; Complete blood count; Lymphocytopenia

INTRODUCTION

Immunotherapy with checkpoint inhibitors, monoclonal antibodies that interrupt the interaction of inhibitory ligand/receptor pairs of the immune system, has changed the landscape of clinical oncology and improved the outcomes of patients with various types of cancers[1]. These drugs block either the programmed cell death ligand 1 (PD-L1)/ programmed cell death 1 (PD-1) ligand/receptor pair or the receptor cytotoxic T lymphocyte antigen 4 (CTLA-4), activating the immune cells that express these surface proteins. Inhibitors of the PD-L1/PD-1 pair currently in clinical use include nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab, dostarlimab, and cemiplimab, whereas inhibitors of the CTLA-4 receptor include ipilimumab and tremelimumab[2]. The clinical utility of these checkpoint inhibitors has been demonstrated in a

broad spectrum of malignancies, including lung cancer, melanoma, and urothelial and renal cell carcinomas[3-7]. Benefits were observed in the palliative and adjuvant settings, and a subset of patients with metastasis showed durable responses[8]. Immunotherapy may be used as a monotherapy or in combinations of two immunotherapeutic drugs (PD-1 inhibitors plus CTLA-4 inhibitor); however, for several indications, these drugs are combined with classic chemotherapy .

Despite improvements in the outcomes of patients with various primary cancers and cancer stages, a significant percentage of patients do not respond optimally to immune checkpoint inhibitors. Predictive biomarkers of response have been identified and incorporated into clinical practice. Validated biomarkers include microsatellite instability (MSI), mismatch repair status (MMR), tumor mutation burden (TMB), and, for PD-1/ PD-L1 inhibitors, PD-L1 staining in the tumor microenvironment [9]. These biomarkers are useful in distinguishing patients with a higher probability of response to immunotherapy from those with a lower probability of response. MSI high/deficient MMR status has also become the first biomarker for immunotherapy against primary tumor types[10]. Patients with defects in MMR proteins and associated MSI develop high TMB levels and tend to respond to checkpoint inhibitors. However, responses are variable even in these patients, as well as in patients with positive PD-L1 staining of the tumor, which is an established biomarker[11]. In addition, PD-L1 staining as a biomarker of response to PD-L1/ PD-1 inhibitors is not predictive for all patients, and its use suffers from a lack of consensus regarding the optimal cutoff for positivity, which varies in different primary sites and histologic types. Moreover, although cut-offs are useful for defining treatment indications, PD-L1 staining is a continuous variable, and benefits from treatment may decrease below certain cut-offs; however, some patients with tumors below the cut-off may benefit from treatment.

Given these considerations, additional practical biomarkers of response to immune checkpoint inhibitors to supplement the existing markers would be valuable. As a general rule, these could be of particular interest for patients with microsatellite stable/MMR-proficient tumors, who have a lower probability of response. A subset of patients with microsatellite- stable tumors may respond to immunotherapy, with or without concomitant chemotherapy. A minority of patients with cancers that have no MMR defects possess pathogenic mutations in one of the proofreading polymerases epsilon and delta (POLE and POLD1), which are associated with proofreading polymerase-associated polyposis (PPAP) syndrome[12]. Some additional responding cancers without MMR or proofreading polymerase defects may display a high TMB owing to alternative molecular alterations [13]. Circulating blood cells such as platelets, leukocytes, and their subsets, as well as other hematological and biochemical measurements routinely obtained in clinical practice, have been studied as prognostic biomarkers of outcomes in various cancers. The prognostic role of leukocyte subsets and platelets is observed either when used as stand-alone tests or in combination in common cancers, such as lung, breast, ovarian, and colorectal[14-16]. Therefore, the current study sought to investigate routine peripheral blood parameters as potential predictive biomarkers of response to immune checkpoint inhibitors.

MATERIALS AND METHODS

The medical records of patients with metastatic cancer who had received any immune checkpoint inhibitor therapy over a 6-year period were retrieved and reviewed. All patients who underwent immune checkpoint inhibitor therapy for any metastatic or locally advanced inoperable cancer and had a complete blood count available before the start of treatment were eligible for inclusion in the study. Patients with localized diseases were excluded from the study. Other exclusion criteria were a lack of records on peripheral blood parameters of interest before the start of therapy and incomplete follow-up data to calculate survival outcomes. The demographic and disease characteristics of the included patients were extracted from their electronic medical charts and recorded anonymously in the study flowchart for further analysis. Data

recorded included patient age, sex, Eastern Cooperative Oncology Group Performance Status (ECOG PS), type of cancer, whether the cancer had progressed from a localized disease or was diagnosed de novo as metastatic, and previous adjuvant therapy.

The outcomes of interest included overall survival (OS) and Progression free survival (PFS). OS was defined as the interval from the date of the start of immunotherapy treatment to the date of the patient's death or censored at the date of last contact. PFS was defined as the interval from the date of the start of immunotherapy until the date of disease progression or censored at the date of last contact without evidence of progression.

The x^2 test or the Fisher's exact test was used to evaluate differences in categorical clinical characteristics and in peripheral blood parameters of the groups. Student's t-test was used for the statistical comparison of continuous variables. Survival plots were constructed using the Kaplan–Meier method. The OS and PFS of the groups of interest were compared using log-rank tests. Variables of interest confirmed to be significant in the univariate analysis were included in the multivariate analyses of PFS and OS. Multivariate analysis was performed using the Cox proportional hazards survival regression model. Calculations were performed online using publicly available statistical tools (graphpad.com, socscistatistics.com, merser.shinyapps.io/Survival, and statpages.info/prophaz). All p-values less than 0.05 were considered statistically significant.

The study protocol was approved by the hospital's Institutional Review Board.

RESULT

A review of the medical records revealed that 163 patients received immunotherapy with checkpoint inhibitors as part of their treatment. The mean age of the cohort was 65.4 years-old, and 61.3% of the patients were male (Table 1). Most patients (57.1%) had lung cancer, 17.8% had renal cell carcinoma, 12.2% had melanoma, and 8.6% had bladder carcinoma. A few patients had other cancer diagnoses (head and neck, colorectal, brain, and breast cancers; Table 1). Most patients (92%) had a good performance status (ECOG PS of 0 or 1). PD-L1 expression was available in only 67 tumors and was positive in 49 cases (73.1%), with strong positivity (score >50%) in 38.8% of the cases with available data. Most patients (85.9%) received nivolumab (with or without ipilimumab) or pembrolizumab, whereas the remainder received atezolizumab or durvalumab. Immune checkpoint inhibitors were used as standalone therapy in 86.5% of the patients in the series. Chemotherapy concomitant with immunotherapy was used in 13.5% of the patients. Most patients (91.4%) had not previously received adjuvant therapy because they had already been diagnosed at the metastatic stage. Regarding hematologic parameters, 74 patients (45.4%) in the cohort had lymphocytopenia (absolute lymphocyte count < 1 x 10^9/ L), 27 (16.7%) had anemia with a hemoglobin level < 100 g/L, and 37 (22.7%) had thrombocytosis (platelet count >350 x 10^9/L) (Table 2).

After a mean follow-up of 12.6 months, 110 patients had died. The mean follow-up period of the surviving patients was 22.1 months. OS and PFS were not significantly different according to patient age (older or younger than age 65 years) or sex (Table 3). Similarly, no differences in survival outcomes were observed according to the expression of PD-L1 in the tumors and the primary type (lung cancer versus other types of primary tumors). Patients with lymphocytopenia before the initiation of immunotherapy had significantly worse PFS (log-rank test, p= 0.02; Figure 1A and Table 3) and OS (log-rank test, p< 0.0001; Figure 1B and Table 3). Patients with anemia and hemoglobin level < 100 g/L also had worse PFS (log-rank test, p= 0.01; Figure 2A and Table 3) and OS (log-rank test, p= 0.002; Figure 2B and Table 3). In contrast, neutrophil counts with a cut-off of 7.5 x 10^9/ L were not predictive of PFS (log-rank test p= 0.1) or OS (log-rank test p= 0.4, Table 3), and thrombocytosis was only predictive of worse PFS (log-rank test p= 0.03) but not OS (log-rank test p= 0.1). In a multivariate analysis for PFS with adjustment for the three variables that were significant predictors in the univariate analysis (lymphocytes, hemoglobin and platelet counts), no variable retained statistical significance, and only lymphocyte counts approached significance with a

risk ratio of 1.47 (95% confidence interval: 0.97-2.23, p= 0.06). In addition, the multivariate analysis for OS disclosed that lymphocytopenia was the only statistically significant parameter for worse OS with a risk ratio of 1.83 (95% confidence interval: 1.24-2.71, p= 0.002, Table 3). Patients with lymphocytopenia showed no significant differences in mean age, sex, or ECOG PS compared with the group of patients without lymphocytopenia (Table 1). The two groups also showed no significant differences in the prevalence of thrombocytosis, elevated neutrophils, elevated monocytes (above 0.6 x 10^9/ L), anemia, or elevated LDH (Table 2). Lung cancer was more prevalent in patients with lymphocytopenia (67.5% vs. 48.3% in the group without lymphocytopenia), and patients without lymphocytopenia were more often treated with pembrolizumab or nivolumab with or without ipilimumab (91%) compared with patients with lymphocytopenia (79.7%; Fisher's exact test p= 0.01, Table 1).

Table 1: Clinical parameters and treatments of the whole cohort of patients included in the study and in the groups with lymphocytopenia (lymphocyte counts <1 x 10^9/ L) and without lymphocytopenia (lymphocyte count ≥1 x 10^9/ L).

Parameter	Total Population (n=163)(%)	No Lymphocytopenia (n= 89) (%)	Lymphocytopenia (n=74) (%)	P
Age				
Mean (±SD)	65.4± 10.2	66.1± 10.7	64.5± 9.6	0.32
≤65	84 (51.5)	41 (46.1)	43 (58.1)	0.15
>65	79 (48.5)	48 (53.9)	31 (41.9)	
Sex				
Male	100 (61.3)	58 (65.2)	42 (56.8)	0.33
Female	63 (38.7)	31 (34.8)	32 (43.2)	
Cancer type				
Lung	93 (57.1)	43 (48.3)	50 (67.6)	0.01
Kidney	29 (17.8)	21 (23.6)	8 (10.8)	
Melanoma	20 (12.2)	16 (18)	4 (5.4)	
Bladder	14 (8.6)	6 (6.7)	8 (10.8)	
Other	7 (4.3)	3 (3.4)	4 (5.4)	
ECOG PS				
0-1	150 (92)	82 (92.1)	68 (91.9)	1
2-3	13 (8)	7 (7.9)	6 (8.1)	
PD-L1 expression				
<1%	18 (26.9)	8 (26.6)	10 (27)	0.9
1%- 50%	23 (34.3)	11 (36.7)	12 (32.4)	
>50%	26 (38.8)	11 (36.7)	15 (40.6)	
NA	96	59	37	
Immunotherapy regimen				
nivolumab± ipilimumab	74 (45.4)	49 (55)	25 (33.8)	0.01
pembrolizumab	66 (40.5)	32 (36)	34 (45.9)	
atezolizumab	16 (9.8)	8 (9)	8 (10.8)	
Durvalumab	7 (4.3)	0	7 (9.5)	
Previous adjuvant chemotherapy				
Yes	14 (8.6)	5 (5.6)	9 (12.2)	0.16
No	149 (91.4)	84 (94.4)	65 (87.8)	
Concomitant chemotherapy				
Yes	22 (13.5)	10 (11.2)	12 (16.2)	0.36
No	141 (86.5)	79 (88.8)	62 (83.8)	

Other cancers included head and neck cancer (3 patients), colon cancer (2 patients), brain cancer (1 patient), and breast cancer (1 patient). ECOG PS: Eastern Co-operative Oncology Group Performance Status, NA: Not available.

Table 2: Laboratory parameters of the whole cohort of patients included in the study and in the groups with lymphocytopenia (lymphocyte counts <1 x 10^9/ L) and without lymphocytopenia (lymphocyte count ≥1 x 10^9/ L).

Parameter	Total Population (n=163) (%)	No Lymphocytopenia (n= 89) (%)	Lymphocytopenia (n=74) (%)	P
		Neutrophils		
≤7.5 x 10^9/ L	130 (79.8)	74 (83.1)	56 (75.7)	0.24
>7.5 x 10^9/ L	33 (20.2)	15 (16.9)	18 (24.3)	
		Platelets		
≤350 x 10^9/ L	126 (77.3)	69 (77.5)	57 (77)	1
>350 x 10^9/ L	37 (22.7)	20 (22.5)	17 (23)	
		Monocytes		
≤0.6 x 10^9/ L	79 (48.8)	39 (43.8)	40 (54.8)	0.2
>0.6 x 10^9/ L	83 (51.2)	50 (56.2)	33 (45.2)	
NA	1	0	1	
		Hemoglobin		
≥100 g/ L	135 (83.3)	78 (87.6)	57 (78.1)	0.13
< 100 g/L	27 (16.7)	11 (12.4)	16 (21.9)	
NA	1	0	1	
		LDH		
≤210 U/L	124 (78.5)	70 (81.4)	54 (75)	0.33
>210 U/L	34 (21.5)	16 (18.6)	18 (25)	
NA	5	3	2	

NA: Not available

Table 3: Univariate and multivariate analysis of clinical and laboratory parameters associated with Overall Survival (OS) and Progression Free Survival (PFS) in patients receiving immune checkpoint inhibitor treatments for metastatic cancers.

Parameter	Univariate		Multivariate			
	OS	PFS	OS		PFS	
	p	p	RR (95% CI)	p	RR (95% CI)	p
Age (>65 years-old vs ≤65 years-old)	0.8	0.8	-	-	-	-
Sex	0.9	0.8	-	-	-	-
PD-L1 (<1% vs ≥1%, n= 67)	0.6	0.3	-	-	-	-
Cancer type (lung vs other)	0.1	0.4	-	-	-	-
Lymphocytes (≥1 x 10^9/ L vs ≤1 x 10^9/ L)	<0.0001	0.02	1.83 (1.24-2.71)	0.002	1.47 (0.97-2.23)	0.06
Neutrophils (>7.5 x 10^9/ L vs ≤7.5 x 10^9/ L)	0.4	0.1	-	-	-	-
Platelets (>350 x 10^9/ L vs ≤350 x 10^9/ L)	0.1	0.03	-	-	1.39 (0.87-2.23)	0.16
Monocytes (>0.6 x 10^9/ L vs ≤0.6 x 10^9/ L)	0.7	0.3	-	-	-	-
Hemoglobin (≥100 g/ L vs <100 g/ L, n= 162)	0.002	0.01	1.69 (1.05-2.73)	0.02	1.57 (0.92-2.67)	0.09
LDH (≤210 U/L vs >210 U/L, n=158)	0.04	0.9	1.45 (0.92-2.26)	0.1	-	-

Parameters significant in the univariate analyses were included in the respective multivariate analysis models. RR: Risk Ratio, CI: Confidence Interval, vs: versus.

figure 1A

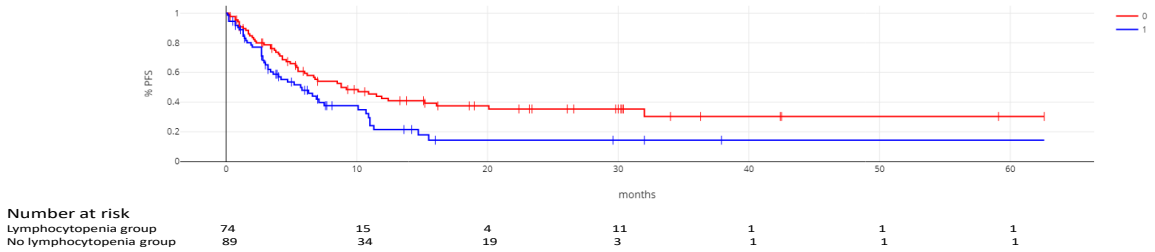


Figure 1A. PFS Kaplan-Meier plot of patients with lymphocytopenia (Blue line) or without lymphocytopenia (Red line) (Log Rank test p= 0.02)

figure 1B

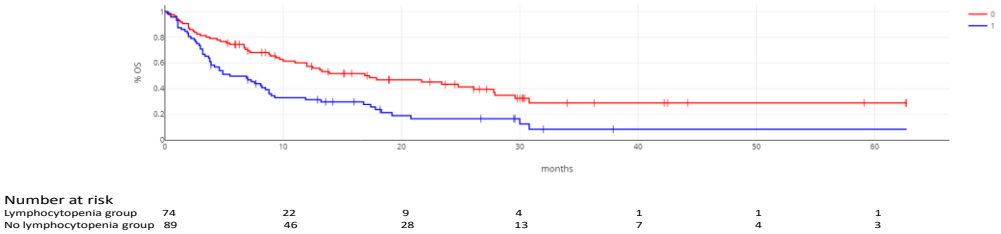


Figure 1B. OS Kaplan-Meier plot of patients with lymphocytopenia (Blue line) or without lymphocytopenia (Red line) (Log Rank test p< 0.0001)

figure 2A

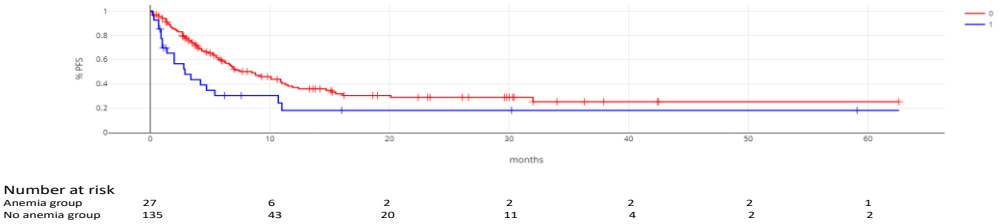
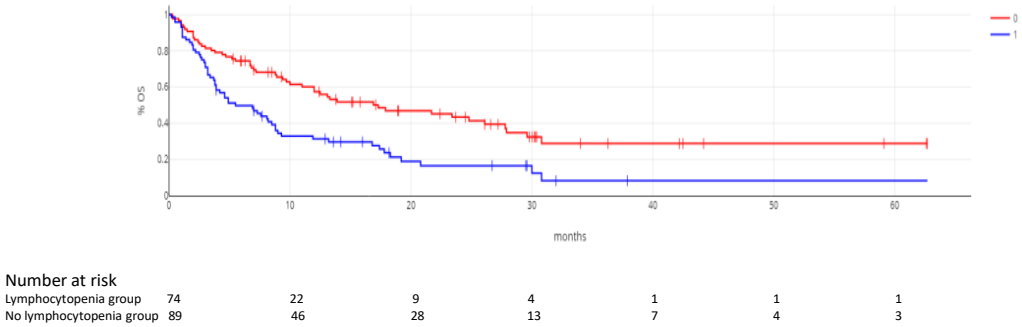


Figure 2A. PFS Kaplan-Meier plot of patients with anemia (hemoglobin below 100 g/ L, blue line) or without anemia (hemoglobin of or above 100 g/ L, red line). (Log Rank test p= 0.01)

figure 1B



Number at risk

Lymphocytopenia group	74	22	9	4	1	1	1
No lymphocytopenia group	89	46	28	13	7	4	3

Figure 2B: OS Kaplan-Meier plot of patients with anemia (hemoglobin below 100 g/ L, blue line) or without anemia (hemoglobin of or above 100 g/ L, red line). (Log Rank test p= 0.002)

DISCUSSION

Immune checkpoint inhibitors have improved the prognosis of patients with a wide variety of cancers[2]. Biomarkers of response to these drugs based on the tumor and tumor microenvironment have been instrumental in identifying patients who are more likely to respond and therefore are more appropriate for treatment. These include patients with MSI-high tumors or deficient MMR, patients with tumors having a high TMB, and patients with cancers that express PD-L1 protein in tumor cells and the tumor microenvironment. These three biomarkers have been used clinically to identify patients who are candidates for immunotherapy and have a high probability of responding[17]. MSI/MMR status and TMB have also become the basis of the first tumor agnostic approvals by the American Food and Drug Administration (FDA) of the PD-1 inhibitor pembrolizumab [18]. The MMR phenotype is produced by mutations or epigenetic downregulation of one of four proteins, MSH2, MSH6, MLH1, or PMS2, that are critical for the repair of mutations created during normal DNA replication owing to the imperfect fidelity of the process[19]. Mutations resulting from defects in the MMR machinery occur more frequently in areas with repetitive sequences of mononucleotides, dinucleotides, or trinucleotides, which are called microsatellites; therefore, defects in mismatch repair proteins produce the phenotype of MSI. MSI can be determined in tumor samples through enzyme restriction PCR using the Amsterdam criteria or other established guidelines[20]. Other genetic lesions, such as hotspot pathogenic mutations in proofreading polymerases epsilon and delta (POLE and POLD1), can also produce high TMB without MSI, resulting in sensitivity to immune checkpoint inhibitors[21]. A high TMB in tumors is the source of neoantigen production, which, if presented to the immune system in the context of major histocompatibility complex molecules, can elicit a cytotoxic response against the bearing cells. In addition to the number of mutations in a tumor, their specific sequence is related to their strength as neoantigens; therefore, different tumor types, which tend to produce different neoantigens due to different underlying genetic lesions, display disparate response rates to immunotherapy[22]. For example, breast cancers and MMR-proficient colorectal cancers have significantly lower responses to immunotherapy with anti-PD-1 or anti-PD-L1 inhibitors than Merkel cell carcinomas or squamous anal carcinomas, despite having similar TMB[22].

Infiltration of the tumor by immune cells, such as tumor-infiltrating lymphocytes (TILs), has also been a biomarker of interest associated with response to

immunotherapies, although the extent of the association varies according to the type of tumor and has not been translated to a clinically validated biomarker at present[23,24]. The quantification and standardization of TILs as biomarkers in immuno-oncology was pioneered by the International Immuno-Oncology Biomarker Working Group on Breast Cancer with the proposal of an Immunoscore for clinical use [25]. TILs and their subsets such as CD8+ and CD4+ cytotoxic and helper lymphocytes are part of the inflamed tumor micro-environment, which is considered a prerequisite for the response to immune checkpoint inhibitors[26,27]. Other lymphocyte subsets, such as CS25+/ FOXP3+ regulatory T cells (Tregs), have immunosuppressive roles as they interfere with the cytotoxicity of CD8+ cells. TILs can be identified and quantified in histological tumor sections using immunohistochemical staining. CD8+ and CD4+ TILs are predictive of OS and PFS in patients with advanced non-small cell lung cancers receiving various immune checkpoint inhibitors as monotherapy[28]. Patients with CD8+ and CD4+ TILs above the median, which were 475 cells/mm^2 for CD8+ lymphocytes and 300.5 cells/mm^2 for CD4+ lymphocytes, had significantly better OS and PFS than patients with TILs below the median. The location of TILs in relation to tumor cells may also be determined in these histological sections. The location of TILs inside the tumor, which favors close contact with their potential target tumor cells or in the periphery of the tumor mass, is also important and has been correlated with the response to therapy [29]. In a study of TILs in colorectal cancer using immunohistochemistry, the type of immune cells, density of immune infiltration, and location inside or in the periphery of the tumor correlated with survival[30]. These elements of the tumor immune microenvironment are more predictive of patient outcomes than standard staging parameters such as tumor infiltration in the colonic wall layers (T stage) and lymph node spread[30].

Circulating lymphocytes, other immune cells, or other markers of activation of the immune system from peripheral blood circulation could correlate with immune antitumor activity; therefore, they could be important as prognosticators of response to immune checkpoint inhibitors[31]. In addition, their quantification is part of established clinical laboratory testing, and their clinical use as predictors does not require analytical validation. In this study, peripheral blood cells and other circulating biomarkers were examined as predictive markers of survival outcomes in patients with metastatic cancers, including lung, kidney and bladder carcinomas and melanomas, who received immune checkpoint inhibitors. Among the tested peripheral blood parameters, lymphocytopenia, defined as a peripheral lymphocyte count lower than 1 x 10^9/L was the most robust predictor of worse OS in univariate and multivariate analyses and of worse PFS in univariate analysis, approaching significance in multivariate analysis. Therefore, this routinely obtainable laboratory test may to a clinically useful degree mirror the immune environment of the tumor and provide a practical and easily obtainable predictive marker for immunotherapy with immune checkpoint inhibitors.

Several other studies have evaluated circulating lymphocyte counts and responses to immune checkpoint inhibitors. A retrospective study of 167 patients with solid tumors (predominantly lung cancer and melanoma) receiving pembrolizumab or nivolumab revealed that patients with lymphocytopenia had a shorter time to progression than those without lymphopenic[32]. In contrast, patients with elevated lymphocyte counts above 2 x10^9/ L were at a higher risk of immune-related adverse effects upon exposure to immunotherapy drugs. In another retrospective evaluation of patients who participated in phase 1 trials of PD-L1 or PD-1 immune checkpoint inhibitors as monotherapy, peripheral lymphocytopenia below 1 x 10^9/L was not associated with a response to treatment[33]. Given that these patients participated in phase 1 trials that used escalating doses of the investigational drug, they may not have received the optimal dose of the immune checkpoint inhibitors. A study that evaluated the presence of baseline lymphocytopenia in a cohort of 100 patients receiving nivolumab for the treatment of head and neck cancer failed to show any predictive value for PFS or OS[34]. Most of these patients received concomitant chemoradiotherapy, and lymphocytopenia might have been induced by these

treatments. In contrast to baseline lymphocytopenia, ongoing lymphocytopenia during immunotherapy was associated with decreased OS. In patients with recurrent or metastatic esophageal cancer treated with immune checkpoint inhibitors, lymphocytopenia, defined as an absolute lymphocyte count below 0.625 x10^9/L in this study, was associated with a significantly worse 1-year OS (median OS of 6 months compared with median OS of 12 months in patients with higher lymphocyte counts)[35]. In an analysis of two randomized studies of patients with melanoma receiving ipilimumab or other treatments (DTIC or gp100 peptide), patients with higher lymphocyte counts (either above the 25th or 75th percentile or above 1 x10^9/ L) receiving ipilimumab had a significantly better OS than patients with lower lymphocyte counts[36]. However, lymphocyte counts were similarly predictive of better OS in the arms of the two trials that did not receive ipilimumab, suggesting that absolute lymphocyte counts are prognostic of OS but not strictly predictive of anti-CTLA-4 immunotherapy benefits.

The current study had some limitations. The retrospective design is prone to bias related to patient selection and disproportionate distribution of characteristics, although this was partially accounted for in the multivariate analysis. Biomarkers known to affect immunotherapy efficacy, including the MMR status and TMB, were unavailable for the current cohort. In addition, PD-L1 status was only available for a subset of the included patients. However, the cancer types included in the cohort had a low prevalence of MMR deficiency. Finally, a matched control group that did not receiving immune checkpoint inhibitors was not included in the analysis. Therefore, it cannot be excluded that the predictive value of the lymphocyte counts represents a broader association with disease prognosis.

CONCLUSION

In conclusion, the current study shows that peripheral blood lymphocyte count is a valuable prognostic factor in patients receiving immune checkpoint inhibitors. Although treatment decisions should not be made based on the baseline levels of lymphocytes in individual patients, these levels may be used to assist in discussions with patients and set expectations for treatment outcomes. Prospective validation of the predictive value of lymphocyte count is required to confirm these retrospective data. In patients with lymphocytopenia, in whom immune checkpoint inhibitors may be less effective, combination with cytokine therapies or immunotherapies may increase efficacy [37]. However, this hypothesis requires confirmation in prospective trials.

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