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Prognostic Performance of the Derived Neutrophil-to-Lymphocyte Ratio in Stage IV Melanoma Patients Treated with Immune Checkpoint Inhibitors

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Abstract: The purpose was to evaluate the prognostic performance of the derived neutrophil–to-lymphocyte ratio (dNLR) in patients with metastatic cutaneous melanoma (CM) treated with immune checkpoint inhibitors (ICI). We retrospectively investigated 41 CM patients with stage IV disease who had the indication for treatment with ICI. dNLR as well as NLR were routinely determined prior to the start of ICI treatment. The dNLR and NLR were calculated as follows: dNLR = absolute neutrophil counts (ANC)/white blood cell count −ANC and NRL = ANC/absolute lymphocyte counts, respectively. Follow-up of the patients was performed in line with current guidelines. In univariate analysis, dNLR ($p = 0.027$ and $p = 0.032$) as well as NLR ($p = 0.0023$ and $p = 0.0036$) were the only parameters which were significantly associated with the best overall response (BOR) and disease control rate (DCR) on ROC curve analyses. NLR negatively correlated with CM-specific survival ($r = -0.32$, $p = 0.043$). CM-specific deaths were significantly associated with the absence of immune-related adverse events ($p = 0.043$), elevated S100 calcium-binding protein B (S100B) at baseline ($p = 0.0006$), and dNLR ($p = 0.024$). In multivariate analyses, NLR was the only significant independent predictor for BOR ($p = 0.014$; odds ratio: 1.7; and 95% CI 1.11 to 2.61) and DCR ($p = 0.019$; odds ratio: 1.5; and 95% CI 1.07 to 2.19). Regarding CM-specific death, however, normal baseline S100B was the only significant independent predictor ($p = 0.0020$; odds ratio: 0.074; and 95% CI 0.014 to 0.38) for survival. Our data demonstrate that baseline NLR seems to be superior to dNLR in the prediction of ICI response in CM patients.

Keywords: cutaneous melanoma; immune checkpoint inhibitors; ipilimumab; pembrolizumab; nivolumab; neutrophil-to-lymphocyte ratio; neurtophil/lymphocyte ratio; systemic inflammation

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1. Introduction

In Caucasians, incidences of cutaneous melanoma (CM) are increasing worldwide, with estimated continuous case increases for the next decades. The highest incidence is found in Queensland, Australia (about 70 cases/100,000/year). In the USA, an increasing incidence from 14 to 22/100,000 person-years has been observed across all primary tumor thicknesses. Similarly, the incidence of invasive CM increases in Europe, which is mostly attributed to the increasing incidence of thin melanomas [1]. Importantly, more than 55,000 deaths per year can be attributed to CM worldwide. Immune checkpoint inhibitors (ICI), including programmed death protein 1 (PD-1, pembrolizumab, and nivolumab), and cytotoxic T lymphocyte-associated protein 4 (CTLA-4 and ipilimumab), recently turned out to be effective in melanoma treatment. Unfortunately, approximately 50% of patients do not respond to ICI and it is still difficult to predict who will respond to these agents. Thus, there is high need for potent and practicable biomarkers predicting the treatment outcome to ICI, in particular, considering ICI-mediated adverse events and the high cost [1–3].

There is growing evidence that systemic inflammatory responses represent significant determinants of tumor progression and survival in many malignancies. Hence, several immune-based prognostic scores, such as neutrophil count, lymphocyte count, and neutrophil/lymphocyte ratio (NLR), have been developed to predict the prognosis in several cancers, including CM [4–17]. The derived NLR (dNLR), composed of white cell counts (WBC) and absolute neutrophil counts (ANC), has been proposed as a simple alternative to NLR for those studies in which only WBC and ANC have been recorded. Indeed, the absolute lymphocyte count has not been determined in some studies [18–25]. In the present study, we aimed to evaluate the prognostic performance of the dNLR in patients with metastatic CM treated with immune checkpoint inhibitors (ICI).

2. Materials and Methods

2.1. Patients

This retrospective study was performed at the Skin Cancer Center of the Ruhr-University Bochum (Bochum, Germany). We exclusively studied CM patients in unresectable stage IV with an indication for ICI therapy. Treatment and staging procedures were carried out in line with national guidelines for the management of CM and interdisciplinary tumor board decisions [3]. ICI regimens, including nivolumab-mono, pembrolizumab-mono, ipilimumabmono, and ipilimumab plus nivolumab, were administered in label. Complete work-up was regularly performed, including lymph node ultrasound, thoracic and/or abdominal computed tomography (CT) or positron emission tomography in combination with computer tomography (PET-CT), and cranial magnetic resonance tomography [3,26]. The criteria for treatment response were used in accordance with RECIST 1.1. We determined the best overall response rate (BOR; the presence of at least one confirmed complete remission or confirmed partial remission) and the disease control rate (DCR; the presence of at least one confirmed complete remission or confirmed partial remission, or confirmed stable disease) [27]. In most cases, BOR and DCR was determined on the basis of the 3-month imaging studies mentioned above. In order to rule out pseudoprogress, imaging was repeated after 6 to 8 weeks. Before and during therapy, the patients were clinically monitored as recently recommended in national position papers and S3 guidelines. Dependent on the ICI agent used, the patients were treated and monitored every 2 to 6 weeks, whereby blood collections were performed before every cycle. At this time, the patients had clinical assessments and were also asked to report on any adverse symptoms [28].

2.2. Laboratory Parameters

Prior to the initiation of ICI treatment, clinical data (white blood cell (WBC) count, absolute lymphocyte count (ALC), absolute neutrophil count (ANC), serum lactate dehydrogenase (LDH), serum C-reactive protein (CRP), and serum S100 calcium-binding protein B (S100B)) and other clinical data, including BRAF status, were collected. The DNLR and NLR were calculated as follows: DNLR = ANC/(WBC − ANC) and NRL = ANC/ALC, respectively [25].

2.3. Statistics

The MedCalc (Ostende, Belgium) software version 20.009 was used for statistical analysis. Progression-free survival (PFS) was determined from first treatment to disease progression or death (event), or last follow-up (censored). CM-specific survival (CMSS) was calculated from first ICI treatment to death (event) or last follow-up (censored). Analysis of the data distribution was performed by the D'Agostino–Pearson test. Univariate analyses were performed using the Chi^2 test and Spearman's rank correlation procedure. Moreover, receiver operating characteristic (ROC) analyses, including the area under the curve (AUC), were performed in order to determine optimal cut-off values for dNLR and NLR. Multivariate analysis was performed using a logistic regression model including the continuous dNRL and NLR data prior to ICI initiation. All parameters with a p-value < 0.1

following univariate testing were included in the multivariate regression model. $p < 0.05$ was considered significant.

3. Results

The study population consisted of 41 patients with stage IV CM according to the AJCC 8th edition, including 15/41 (36.6%) women and 26/41 (63.4%) men at the median age of 67 years (35–84 years) at ICI therapy initiation (Table 1). In 12/41 (29.3%) patients, a BRAF mutation was found. ICI treatment was initiated with anti-PD1 agents in 26/41 (63.4%) patients, ipilimumab-mono in seven/41 (17.1%) patients, and ipilimumab plus nivolumab in eight/41 (19.5%) patients. The patients received a median of 11.3 cycles ICI (range: 1–64 cycles). BOR was observed in 20/41 (48.8%) patients. DCR was observed in 23/41 (56.1%) patients. The median PFS was 5 months (range: 3–50 months), corresponding to 32/41 (78%) disease relapses. A median CMSS of 22 months (range: 3–76 months) was observed, corresponding to 25/41 (61%) CM-specific death events. Immune-related adverse events of any grade were observed in 20/41 (48.8%) patients. Permanent ICI discontinuation during treatment initiation was observed in 3/41 (7.3%) patients.

Table 1. Clinical characteristics of patients with metastatic melanoma (n = 41) prior to the initiation of treatment with immune checkpoint inhibitors (ICI). Data of the derived neutrophil-to-lymphocyte ratio (dNLR) and NLR are shown.

Parameters	Data
Age prior to ICI	67 years (35–84)
Sex f/m	 26/15 (63.4%/36.6%)
Localization of primary CM Head/neck Upper extremities Lower extremities Trunk (Unknown primary)	 6 (14.6%) 5 (12.2%) 17 (41.5%) 9 (22%) 4 (9.8%)
Tumor thickness of primary CM Median (range) <2 mm/≥2 mm	 3.1 mm (0.8–16) 13/28 (31.7%/68.3%)
Primary CM subtypes Superficial spreading melanoma Nodular melanoma Acrolentiginous melanoma Lentigo maligna melanoma (Unknown primary)	 17 (41.5%) 11 (26.8%) 6 (14.6%) 3 (7.3%) 4 (9.8%)
Ulceration of primary tumor No/yes	 26/15 (63.4%/36.6%)
Lactate dehydrogenase Median (range; 135–14 U/L) Normal/elevated	 201 (118–480) 24/17 (58.5%/41.5%)
Serum S100B Median (range; <0.105 µg/L) Normal/elevated	 17/24 (41.5%/58.5%)
C-reactive protein Normal/elevated	 18/23 (43.9%/56.1%)
BRAF mutation No/yes	 29/12 (70.7%/29.3%)
M-tumor stage prior to ICI (AJCC 2018) M1a M1b M1c M1d	 6 (14.6%) 12 (29.3%) 22 (53.7%) 1 (2.4%)

In the univariate analysis, dNLR ($p = 0.027$, AUC 0.69 and $p = 0.032$, AUC 0.68) as well as NLR ($p = 0.0023$, AUC 0.74 and $p = 0.0036$, AUC 0.73) were the only parameters which were significantly associated with BOR and DCR (Table 2).

Table 2. Clinical outcome of patients with metastatic melanoma ($n = 41$) treated with immune checkpoint inhibitors (ICI). ROC curve analyses of the derived neutrophil-to-lymphocyte ratio (dNLR) and NLR are shown as well.

Outcome	
BOR	48.8% (20/41)
DCR	56.1% (23/41)
Adverse events (all grades, no/yes)	21/20 (51.2%/48.8%)
Progressive disease	78% (32/41)
PFS (months)	5 (3–50)
Melanoma deaths	61% (25/41)
CMSS (months)	22 (3–75)
Significant ROC curve analyses for response to ICI	
dNLR	
Median (range) dNLR *	1.97 (0.43–6.50)
BOR **	AUC: 0.69 (95% CI: 0.53 to 0.83); $p = 0.022$; criterion: <1.93
DCR **	AUC: 0.68 (95% CI: 0.52 to 0.82); $p = 0.032$; J = criterion: <1.36
NLR	
Median (range) NLR *	3.18 (1–9.65)
BOR **	AUC: 0.74 (95% CI: 0.58 to 0.86); $p = 0.023$; criterion: <5.02
DCR **	AUC: 0.73 (95% CI: 0.57 to 0.86); $p = 0.0036$; criterion: <5.02

*, prior to start of ICI; **, continuous values for ROC analysis; BOR, best overall response rate; DCR, disease control rate; PFS, progression-free survival; and CMSS, cutaneous melanoma-specific survival.

Next, we examined the ROC curve analyses. There was a trend for a statistically significant association between elevated S100B at baseline and BOR ($p = 0.089$). Moreover, there was a trend for a statistical significant negative correlation between dNLR and CMSS ($r = -0.29$, $p = 0.066$), and NLR and PFS ($r = -26$, $p = 0.099$). However, NLR negatively correlated with CMSS ($r = -0.32$, $p = 0.043$). Moreover, CM-specific deaths were significantly associated with the absence of immune-related adverse events ($p = 0.043$), elevated S100B at baseline ($p = 0.0006$), and dNLR ($p = 0.024$, AUC 0.69, associated criterion > 2.34).

In the multivariate analyses, NLR was the only independent predictor for BOR ($p = 0.014$; odds ratio: 1.7; and 95% CI 1.11 to 2.61) and DCR ($p = 0.019$; odds ratio: 1.5; and 95% CI 1.07 to 2.19), remaining significant in the logistic regression model. None of the parameters included in the regression model were significantly associated with disease progression. Regarding melanoma-specific death, however, normal baseline S100B was a significant independent predictor ($p = 0.0020$; odds ratio: 0.074; and 95% CI 0.014 to 0.38) for staying alive, whereas high dNLR (>2.34) only showed a trend for statistical significance in the logistic regression model ($p = 0.071$; odds ratio: 2.69; and 95% CI 0.92 to 7.87).

4. Discussion

It is well-known that systemic inflammation plays a crucial role in tumor development, progression, and metastasis [29]. Pro-tumorigenic cytokines secreted by neutrophils and platelets, including the vascular endothelial growth factor, tumor necrosis factor-α, and interleukin-10, can contribute to cancer progression. Furthermore, monocytes as well as lymphocytes have antitumoral effects by increasing immune responses against the tumor [30]. By contrast, a wealth of clinical evidence assessing NLR mostly supports the notion that neutrophil granulocytes may promote cancer progression. Hence, the NLR has been considered an attractive biomarker for the risk stratification of patients with malignancies and to guide treatment decisions. NLR can easily and cost-effectively be assessed using standard blood analyses. Recently, more complex systemic immune-inflammation prognosis scores, including the pan-immune inflammation value (PIV) and

systemic immune-inflammation index (SII), have been reported to be of prognostic value in many malignancies including CM [8,9,16,31]. For example, Ludwig et al. [11] studied SII in patients with uveal melanoma and found that, among other factors, low baseline SII was a significant independent predictor for prolonged overall survival [11]. Similarly, the predictive power of SII has been reported for patients with high-risk acral melanoma under high-dose interferon therapy, i.e., a low SII (<615 $\times$ 10^9/L) was associated with a longer relapse-free and overall survival [7]. In our recent study on CM patients, however, we did not observe a significant association of SII and PIV with survival parameters or ICI-response rates. In a retrospective analysis of metastatic CM patients treated with first-line ICI or targeted therapy, Fucà et al. [16] recently showed that a high baseline PIV was independently associated with poor PFS and overall survival. Moreover, Fucà et al. [16] also observed that a high PIV was associated with primary resistance to both ICI and targeted therapy.

We could confirm the data of many previous studies on CM and other solid cancers that NLR is a potent independent predictor for response to ICI in metastatic CM patients. In line with the present work focusing on the impact of dNLR in stage IV melanoma, Chriscitiello et al. [23] recently demonstrated that dNLR may be more accurate in predicting poor outcome than NLR for patients with solid cancers treated with ICI in the context of phase I trials. Moreover, Ferrucci et al. [25] reported for the first time similar prospective data for 720 patients under ipilimumab treatment. Higher baseline dNLR was significantly associated with worse PFS and overall survival. Notably, when these factors were included in a multivariate analysis (e.g., including LDH and brain metastases), the dNLR had the strongest prognostic power. Indeed, our data only tend to support the notion that dNLR might be a more powerful predictor for survival outcome in CM patients than NLR. Even though NLR and dNLR may appear similar at a glance, the dNLR may be more informative than NLR, because it includes monocytes as well as other granulocyte subpopulations, such as eosinophils. Recent observational investigations indicated that eosinophil counts and serum levels of the eosinophil cationic protein are significantly associated with prolonged survival in metastatic CM [32]. Finally, we acknowledge that our study presents two major limitations: (1) it is a retrospective study without a validation or control cohort and (2) the sample size included in this study was comprised of a small number of CM patients, possibly resulting in statistically insignificant results which could have likely been avoided using a larger study population.

5. Conclusions

Our data demonstrate that baseline NLR appears to be superior to dNLR in the prediction of response to ICI in CM patients. However, this must be substantiated in studies including larger sample sizes.

Author Contributions: T.G. and L.S. contributed to the study conception and design. Material preparation, data collection, analysis, and interpretation were predominantly performed by R.M., C.H.S., S.S., L.S., N.A.R. and T.G. The first draft of the manuscript was written by T.G. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Derived data supporting the findings of this study are available from the corresponding author upon reasonable request.

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