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ORIGINAL ARTICLE

Absolute monocyte count is a predictor of overall survival and progression-free survival in nodal peripheral T cell lymphoma

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Abstract

Nodal peripheral T cell lymphomas (nPTCL) present aggressive clinical course, and its heterogeneous nature and poor prognosis with current therapeutic strategies make it a target for the development of new prognostic markers. Thus, we investigated tumor-associated macrophages (TAM) according to the number of cells expressing CD68 in biopsies and the absolute monocyte count (AMC) in peripheral blood of 87 patients with nPTCL. The median overall survival (OS) was 3 years (95% CI 1.3–8.4 years) and estimate 5 years OS of 43.3% (95% CI 32.5–53.7%). The median progression-free survival (PFS) was 1.5 years (95% CI 0.8–2.6 years) with estimate 5 years PFS of 29.2% (95% CI 19.7–39.3%). The cutoff for AMC was 1.5×10^9/L and the median OS for patients with AMC $\geq 1.5 \times 10^9$/L was 0.83 years versus 3.7 years for those with AMC $< 1.5 \times 10^9$/L (HR 2.32, 95% CI 1.03–5.22, $p = 0.035$). The median PFS for patients with AMC $\geq 1.5 \times 10^9$/L was 0.50 years versus 1.5 years for those with AMC $< 1.5 \times 10^9$/L (HR 2.25, 95% CI 1.05–4.78, $p = 0.031$). CD68 was evaluated in 26/87 (29.8%) patients with a median expression of 34% and positivity cutoff of 43%. CD68 expression was not associated with OS or PFS either with AMC values. Our findings suggest that the AMC of $\geq 1.5 \times 10^9$/L at diagnosis in peripheral blood is associated with poor prognosis in nPTCL. Further investigations in a larger cohort are required to better validate our results.

Keywords Nodal peripheral T cell lymphoma · Absolute monocyte count · Tumor-associated macrophages · Prognosis

Introduction

Nodal peripheral T cell lymphomas (nPTCL) are a heterogeneous group of lymphoproliferative diseases comprising 15% of non-Hodgkin's lymphomas (NHL). Compared to B cell NHL, nPTCL present aggressive clinical course and poor prognosis with current therapeutic strategies [1]. Indeed, the identification of potential new therapeutic targets and prognostic markers remains a challenge. The influence of the tumor microenvironment on the behavior of neoplasia has been an object of study by several groups. Recent studies have evaluated the contribution of non-neoplastic cells on the promotion of a microenvironment that favors the development and dissemination of the tumor, regulating angiogenesis or establishing immunological dysfunction [2, 3].

A high content of tumor-associated macrophages (TAM), estimated by the number of CD68 positive cells by immunohistochemistry (IHC), has been evaluated as a potential marker of adverse clinical outcomes in different hematological malignancies [4, 5]. The analysis of absolute monocyte count (AMC) in peripheral blood as a simple prognostic parameter and as an alternative biomarker of TAM and host immune homeostasis has become a focus of interest in previous researches [6]. Unfortunately, data of these markers in nPTCL are still scarce and no previous studies in these individuals were conducted in Latin American populations.

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Therefore, we evaluated tumor-associated macrophages in nPTCL using absolute monocyte count in peripheral blood and CD68 antigen expression in biopsies by IHC and their prognostic impact on outcomes namely overall survival and progression-free survival of nPTCL patients treated at the Institute of Cancer of University of Sao Paulo.

Material and methods

Patients

We conducted an observational, retrospective, and unicentric study with previous approval by the Local Ethics Committee. The absolute monocyte count of nPTCL at diagnosis was obtained by reviewing medical records. Archival paraffin blocks were used for IHC staining for CD68 (Abcam, C68/684, 1/100), and a semi-quantitative scoring methodology of 10% was performed by two different and experienced hematopathologists. Only strong expression of CD68 was considered positive (necrotic and fibrotic areas were excluded from analysis).

Bone marrow biopsy as well as neck, chest, abdomen, and pelvis computed tomography (CT) were performed at diagnosis. The patients were stratified in clinical stages I, II, III, and IV according to Ann Arbor criteria. The interim response after the fourth cycle of chemotherapy and the final response at the end of treatment were evaluated using the Cheson 2014 criteria [7]. The International prognostic index (IPI) was calculated for the cohort as described previously [8].

Anaplastic lymphoma kinase (ALK)-positive ALCL patients were treated with six to eight cycles of CHOP-21 (cyclophosphamide 750 mg/sqm IV on day 1, vincristine 1.4 mg/sqm [max 2 mg] IV day 1, doxorubicin 50 mg/sqm IV day 1, and prednisone 100 mg/day PO from day 1 to 5). The majority of ALK-negative ALCL, PTCL-NOS, and AITL patients were treated with six to eight cycles of CHOEP-21 (CHOP plus etoposide 100 mg/sqm IV days 1 to 3). Radiotherapy as consolidation at dose of 3600 cGy was indicated for bulky disease, sinus, bone single lesion, breast, and Waldeyer's ring involvement. Autologous hematopoietic stem cell transplantation (ASCT) was indicated for consolidation in first line for patients in complete remission (CR) or partial remission (PR), except for ALK-positive ALCL and patients above 65 years or with clinical contraindication.

Statistical analysis

Overall survival (OS) was determined as the time from diagnostic date to death or censored at last contact date. Progression-free survival (PFS) was calculated from diagnostic date to progression or death or relapse (whichever comes first) or censored at last contact date. Survival curves were constructed using the Kaplan-Meier method, and the log-rank test was used to assess differences between curves. Proportional hazard assumption was checked graphically by log-minus-log versus log(time) plots.

The 95% confidence intervals (CI) for the survival probabilities were estimated by the complementary log-log transform method. Monocytosis and density of CD68+ cells were dichotomized to find an optimal cutoff value by using the method of Contal and O'Quigley. This method essentially calculates all possible splits and finds the one that maximizes the log-rank statistic. Median follow-up time was computed using the reverse Kaplan-Meier estimator. Unadjusted hazard ratios and their 95% CI were reported.

Correlation between two continuous variables was conducted according to Spearman rank correlation coefficient (rho). The correlation coefficient was interpreted as follows: Very strong linear correlation $|\text{rho}| = 0.9–1.0$, strong $|\text{rho}| = 0.7–0.9$, moderate $|\text{rho}| = 0.4–0.7$, weak $|\text{rho}| = 0.2–0.4$, and very weak $|\text{rho}| = 0.0–0.2$.

Non-normally distributed quantitative variables were presented as median (interquartile range (IQR). Normality was assessed by visual inspection of histogram plots and use of Shapiro-Wilk normality test. All p values were 2-sided. Results were considered significant if $p < 0.05$. All statistical analyses were performed using SAS software version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 87 patients with nPTCL treated with curative intent at our institution from January 2000 to December 2014 were included in this analysis. The clinical laboratory and epidemiological characteristics of this cohort are summarized in Table 1. Fifty-two patients were male (59.8%), and thirty-five were female (40.2%), with a median age of 49 years old (range, 14–84). The distribution by histological subtype was as follows: 34.5% PTCL, not otherwise specified (NOS); 33.3% ALK/negative anaplastic large-cell lymphoma (ALCL/ALK-); 20.7% ALK-positive ALCL (ALCL/ALK+); and 11.5% angioimmunoblastic T cell lymphoma (AITL). The majority of patients had advanced disease (92%), with bulky mass (40.2%) and extranodal involvement (74.7%). Also, 60.2% showed ECOG ≥ 2 and 60.9% were classified as intermediate-high or high-risk according to the International Prognostic Index (IPI).

The median follow-up of the cohort was 7.1 years, with a median OS of 3.1 years (95% CI 1.3–8.4) and estimate 5 years OS of 43.3% (95% CI 32.5–53.7). The median PFS was 1.5 years (95% CI 0.8–2.6 years) and estimate 5 years PFS of 29.2% (95% CI 19.7–39.3). The cutoff point for AMC was 1.5×10^9/L. The median, in days between access to absolute monocyte count before the first treatment, was 19 days

Table 1 Clinical laboratory and epidemiological characteristics of patients

Age	49 (14–84)
LDH	780 (185–3024)
Sex	
Male	52 (59.8%)
Female	35 (40.2%)
Histopathological subtype	
ALCL/ALK+	18 (20.7%)
ALCL/ALK-	29 (33.3%)
PTCL/NOS	30 (34.5%)
AITL	10 (11.5%)
IPI	
Low and intermediate-low	34 (39.1%)
High and intermediate-high	53 (60.9%)
IPI-T	
Low and intermediate-low	34 (39.1%)
High and intermediate-high	53 (60.9%)
ECOG	
< 2	34 (39.1%)
≥ 2	53 (60.9%)
Extranodal sites	
No	22 (25.3%)
Yes	65 (74.7%)
Bulky disease	
No	52 (59.8%)
Yes	35 (40.2%)
Ann Arbor stage	
Early (I and II without X)	07 (8.0%)
Advanced (X, III, and IV)	80 (92.0%)
Radiotherapy	
No	61 (70.1%)
Yes	26 (29.9%)
Auto SCT	
No	57 (65.5%)
Yes	30 (34.5%)

LDH lactate dehydrogenase, *ALCL/ALK+* ALK+ anaplastic large-cell lymphoma, *ALCL/ALK-* ALK- anaplastic large cell lymphoma, *PTCL/NOS* peripheral T-cell lymphoma not otherwise specified, *AITL* angioimmunoblastic T cell lymphoma, *IPI* International Prognostic Index, *IPI-T* International Prognostic Index for T cell Lymphomas

(interquartile range (6; 44), $n = 75$, minimum 0 days and maximum 523 days). The median OS for patients with AMC ≥ 1.5×10^9/L was 0.83 years versus 3.7 years for those with AMC < 1.5×10^9/L (HR 2.32, 95% CI 1.03–5.22, $p = 0.035$). The median PFS for patients with AMC ≥ 1.5×10^9/L was 0.50 years versus 1.5 years for those with AMC < 1.5×10^9/L (HR 2.25, 95% CI 1.05–4.78, $p = 0.031$) (Fig. 1).

We evaluated the associations among absolute monocyte counts (using cutoff of 1.5×10^9/L monocytes), histopathological nodal PTCL subtypes, and patient characteristics such as age and sex. As displayed in Table 2, it was not possible to find statistically significant association between AMC, age, and sex. However, there was statistically significant association among AMC and the different histological subtypes of nodal PTCL, as well as with IPI.

Immunohistochemistry for CD68 was evaluated in 26/87 (29.8%) patients due to technical staining issues and the unavailability of paraffin blocks. All specimens for TAM analysis were obtained from tissue biopsies at the time of diagnosis (biopsies of tissues compromised by neoplasia prior to initiation of primary treatment). The median of CD68 expression was 34% (range, 10–80%; IQR 28–49) with a positivity cutoff of 43%. Eighteen patients expressed CD68+ < 43% and eight patients had CD68+ ≥ 43%. Significant association between CD68 immunoexpression with OS or PFS was not found ($p = 0.13$ and $p = 0.21$, respectively). The correlation between CD68 tissue expression and AMC was also not demonstrated ($p = 0.80$). Figure 2 demonstrates immunohistochemical reactions using anti-CD68 monoclonal antibody to estimate the TAM in 2 distinct cases of PTCL nodal included in our study: (a) high TAM and (b) low TAM.

Discussion

Here, we demonstrate that the assessment of absolute monocyte count in the peripheral blood can represent a potential biomarker for prognosis in nPTCL patients. In the last decade, several independent studies have validated the adverse prognostic impact of AMC on the outcome of patients with different lymphoproliferative diseases, including Hodgkin's lymphoma and non-Hodgkin's lymphoma, such as follicular lymphoma, diffuse large B cell lymphoma, and mantle cell lymphoma [9, 10]. However, few studies have evaluated the impact of AMC on nPTCL, which represents neoplasms with markedly poor prognosis [1, 11–13].

Recent studies conducted by Li et al. and Jia et al. have described the adverse prognostic impact of AMC in PTCL/NOS and ALCL, respectively [6, 11]. Our study corroborates the data reported by these groups and expands the adverse significance of AMC encompassing the four major histopathological subtypes of nPTCL, recognized in the last World Health Organization Classification of Lymphomas [14].

In pathophysiological terms, different studies have shown that circulating monocytes are recruited into the tumor microenvironment and promote the proliferation of malignant lymphoma cells, having a direct influence on the survival of patients with different B and T/NK lymphoproliferative diseases.

Studies published in the last 5 years by different international groups have demonstrated the adverse prognostic impact of a high absolute count of peripheral blood monocytes

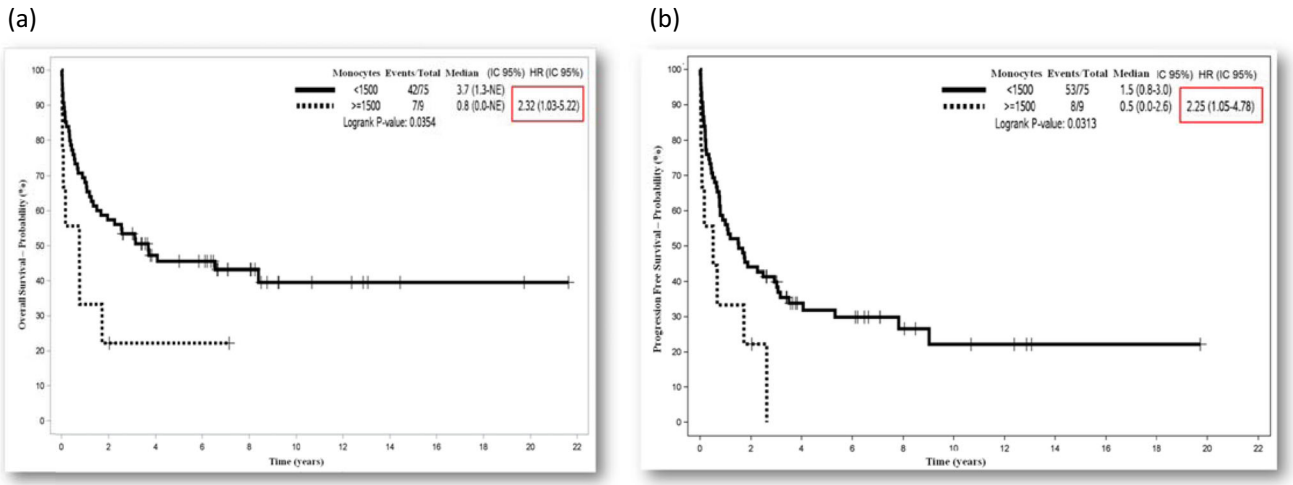

Fig. 1 **a** Overall survival and **b** progression-free survival according to absolute monocyte count in nodal PTCL

on different histological subtypes of PTCL. These studies indicate that a high AMC and a low absolute lymphocyte count/absolute monocyte count ratio (ALC/AMC ratio) indirectly reflect the host's immunity and tumor microenvironment and can interfere in the prognosis of PTCL patients.

Yang et al. [15] were able to demonstrate that high AMC ($> 0.8 \times 10^9$/L) was an independent prognostic parameter associated with worse 3 year-OS (64% versus 10%, $p < 0.001$) in a cohort of 73 AITL patients, using the cutoff for AMC = 0.8×10^9/L. The authors also found correlation among high AMC and adverse prognostic factors, such as involvement of > 1 extranodal site, neoplastic involvement of bone marrow, elevated levels of LDH, active EBV infection, absence of response to treatment, and high IPI. In our study, the cutoff of 0.8×10^9/L monocytes was not able to discriminate prognosis in nodal PTCL, but we found statistical significance for prognostic association with the cutoff value of 1.5×10^9/L monocytes. Although our cutoff point was higher, we must consider that our cohort is more heterogeneous, encompassing four different subtypes of nPTCL, as shown in Table 1. Moreover, there was statistically significant association among AMC and the histopathological variants of nodal PTCL ($p = 0.046$) in our study.

Li Y et al. [16], Jia et al. [6], and Li Q et al. [11] evaluated the prognostic significance of the absolute lymphocyte count/absolute monocyte count (ALC/AMC) ratio in 264 patients with NK/T extranodal lymphoma, nasal type; 29 patients with systemic ALCL; and 58 patients with PTCL/NOS, respectively. They demonstrated that low ALC/AMC ratio, reflecting high AMC, was associated with worse OS and PFS and was

Table 2 Associations among AMC and patients characteristics and histopathological subtypes

Variable	$< 1.50 \times 10^9$/L monocytes (N = 75)	$\geq 1.5 \times 10^9$/L monocytes (*N* = 09)	Total	*P* value
Age (Mean ± SD (*N*))	47.68 ± 18.23 (N = 75)	49.44 ± 16.05 (*N* = 9)		0.78
Gender				1.00
Male	44 (58.7%)	5 (55.6%)	49 (58.3%)	
Female	31 (41.3%)	4 (44.4%)	35 (41.7%)	
Total	75	9	84	
Subtype				0.046
ALCL/ALK+	14 (18.7%)	3 (33.3%)	17 (20.2%)	
ACLL/ALK-	28 (37.3%)	0 (0%)	28 (33.3%)	
PTCL/NOS	25 (33.3%)	4 (44.4%)	29 (34.5%)	
AITL	8 (10.7%)	2 (22.2%)	10 (11.9%)	
Total	75	9	84	
IPI				0.037
Low risk	10 (55.6%)	24 (36.4%)	34 (40.4%)	
High risk	8 (44.4%)	42 (63.6%)	50 (59.6%)	
Total	18	66	84	

ALCL ALK+/− anaplastic large cell lymphoma, anaplastic lymphoma kinase positive/negative, *PTCL/NOS* peripheral T-cell lymphoma, not otherwise specified, *AITL* angioimmunoblastic T cell lymphoma

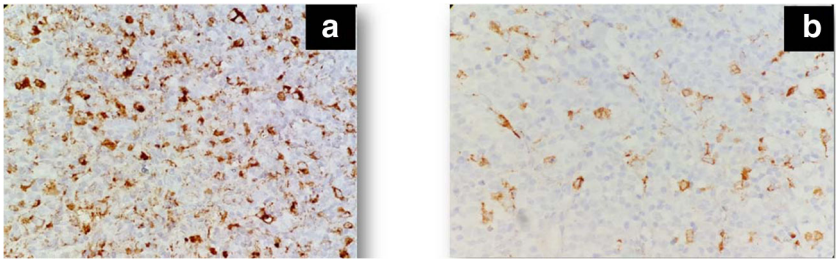

Fig. 2 Anti-CD68 immunohistochemical staining for TAM detection. **a** High macrophagic content in reactive tumor microenvironment. **b** Low macrophagic content in non-neoplastic tumor microenvironment. Granular and cytoplasmic staining pattern

also associated with characteristics indicative of high tumor mass, such as high levels of LDH, poor performance status (ECOG ≥ 2), and high IPI. In our study, we did not test the ALC/AMC ratio, but high AMC reflects low ALC/AMC ratio, as mentioned before. We have also found an association between high AMC and high-intermediate and high-risk IPI ($p = 0.037$) in the pathological subtypes evaluated by such studies, with the exception of the extranodal T/NK lymphoma, nasal type, not contemplated in our analysis.

Wilcox et al. [17] demonstrated that neoplastic lymphoid T cells may recruit circulating monocytes into the tissue via CCL5, enhancing neoplastic cells survival. CCL5 further precludes the differentiation of monocytes into mature dendritic cells, increasing the half-life of tumor cells in a contact-dependent manner.

Circulating monocytes may still respond to tumor proliferation as they synthesize angiogenesis-promoting mediators. It is also speculated that monocytes secrete products that stimulate the proliferation of the Epstein Barr virus directly by increasing the expression of latent membrane protein 1 (LMP-1), which has a direct role in lymphomagenesis. When peripheral monocytes migrate into the tumor tissue, a polarization for a type 2 macrophagic response (M2) may occur, producing IL1, IL4, IL10, and IL13 that accentuate tumor resistance against the suppressive action of TCD8+ cytotoxic cells [17].

Zhang et al. were pioneers in establishing the negative prognostic impact of TAM measured by the pan-macrophage marker CD68 by IHC in PTCL/NOS [18]. Our study was not able to replicate this finding, and we believe that this was due to multiple factors, including the reduced number of samples tested for CD68 staining ($n = 26$) in our cohort, greater histopathological heterogeneity of our samples (including PTCL/NOS, ALCL and AITL), and limitation in the IHC study of associated macrophage subpopulations, as it is well known to have distinct M1 and M2 histiocytic populations related to tumor resistance or tumor progression, respectively [19].

The better understanding of the tumor microenvironment on the maintenance of neoplastic cell survival and growth has clarified many aspects of cancer biology. The rate between macrophages and tumor cells in the neoplastic tissue has been associated to prognosis in peripheral T cell lymphoma and other types of cancer [19]. Likewise, the interaction between tumor-associated macrophages and tumor cells through receptors and cytokines has emerged as an important physiopathology pathway in PTCL.

In addition, many authors have used different methods and monoclonal antibodies to identify TAM in tumor. Therefore, these results are heterogeneous and difficult to compare among themselves. In this context, we highlight that the AMC in the peripheral blood, instead of TAM, could add more homogeneous and comparative information regarding monocyte/macrophage influence in cancer and importantly it is an easier and cost-effective marker.

One limitation of our study is that we were not able to perform a multivariate analysis due to small number of patients. Based on our results, we propose that peripheral blood monocyte should be better studied in larger cohort of patients to verify its biological characteristics, since nPTCL patients with high AMC showed poor prognosis. Moreover, CD68 analysis by IHC showed that positivity interpretation is subjective and observer dependent. Importantly, peripheral blood monocytes are easy to obtain and can be employed for more sensitive and specific techniques, such as flow cytometry.

In conclusion, we demonstrate that absolute monocyte count in peripheral blood $\geq 1.5 \times 10^9$/L at diagnosis is associated with poor prognosis in nPTCL, constituting an easily accessible and potentially useful variable to be incorporated in future prognostic score index if confirmed as an independent prognostic marker in larger cohort of patients.

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Compliance with ethical standards

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study.

Conflict of interest The authors declare that they have no conflict of interest.

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