Leukemia Research 42 (2016) 88–92

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Elevated absolute monocyte count predicts unfavorable outcomes in patients with angioimmunoblastic T-cell lymphoma

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ARTICLE INFO

Article history:
Received 2 September 2015
Received in revised form
12 November 2015
Accepted 20 December 2015
Available online 24 December 2015

Keywords:
Angioimmunoblastic T-cell lymphoma
Absolute monocyte count
Prognosis

ABSTRACT

This study was aimed at investigating the prognostic significance of the absolute monocyte count (AMC) in peripheral blood in patients with newly diagnosed angioimmunoblastic T cell lymphoma (AITL). AMC was performed in 73 therapy-naive patients with AITL in 2 institutions during 2008–2015, and higher AMC was observed in those with extranodal sites >1, bone marrow involvement, high lactate dehydrogenase level, the EBV infection, no response to treatment and high IPI, PIT, PIAI score group. The best AMC cut-off level at diagnosis was 0.8×10^9/L and the 3-year overall survival (OS) was 64% for patients with low AMC group ($\leq 0.8 \times 10^9$/L) compared to 10% in high AMC group ($>0.8 \times 10^9$/L) ($P < 0.001$). Multivariate analysis showed that elevated AMC remained an adverse prognostic parameter. Our results suggest that AMC is an independent prognostic parameter for OS in patients with AITL, and AMC $>0.8 \times 10^9$/L can routinely be used to identify high-risk patients with unfavorable survival.

1. Introduction

Angioimmunoblastic T-cell lymphoma (AITL) represents a distinct clinicopathological entity, accounting for approximately 18.5% of peripheral T-cell lymphoma (PTCL) [1]. This disease is characterized by aggressive clinical course with a median survival lower than 3 years in most studies, regardless of therapy options, including anthracycline-containing regimen [2,3]. So far, limited data are available on prognostic factors in patients with AITL. International prognostic index (IPI), as a classic model for risk stratification of patients with aggressive non-Hodgkin's lymphomas (NHL) [4], had limited predictive value for AITL [5]. Similarly, Prognostic Index for PTCL (PIT), originally reported prognostic model for PTCL unspecified (PTCL-U) [6], fails to estimate survival in AITL either [5]. Prognostic index for AITL (PIAI), first described by Federico et al. in 2012, may serve as a surrogate model for predicting outcomes in AITL [7].

In recent years there is growing attention to the role of absolute monocyte count (AMC) for estimation of outcomes in patients with lymphoma. It has been shown that AMC in peripheral blood at diagnosis has prognostic significance and elevated AMC is associated with inferior overall survival (OS) [8–12]. These results agree with some current studies that monocytes may be actively recruited to the tumor microenvironment and promote the proliferation of malignant lymphoma cells, so as to influence the survival in patients with lymphoma [10,13]. However, few reports are available to assess the prognostic impact of AMC in AITL patients.

The current study was undertaken to investigate the prognostic influence of AMC at diagnosis in patients with AITL, and examine whether AMC could be served as an independent prognostic parameter for OS through comparing this parameter with more clinical ones and conventional predictive models, including the IPI, PIT and PIAI scores.

2. Materials and methods

2.1. Patients

This retrospective study included 73 consecutive patients with newly diagnosed AITL between March 2008 and May 2015 at the First Affiliated Hospital of Nanjing Medical University and the

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http://dx.doi.org/10.1016/j.leukres.2015.12.010
0145-2126/

First Affiliated Hospital of Wannan Medical University. All patients were provided with informed consent in accordance with requirements of the Declaration of Helsinki, and the research project was approved by the Institutional Review Boards of the university. All cases were pathologically confirmed as AITL according to 2008 World Health Organization (WHO) classification [14]. The histological features of AITL were as follows: classical morphology with effacement of normal lymph node architecture and marked proliferation of arborizing high endothelial venules (HEV). Characteristically, the neoplastic T cells are positive for CD2, CD3, CD4, CD10, PD1 and CXCL-13 [15,16]. Moreover, scattered large immunoblastic cells frequently are CD20 positive, and often Epstein Barr Virus (EBV)-encoded RNA (EBER) positive. Stains for follicular dendritic cells (FDC) such as CD21, CD23 and CD35 typically show meshworks of FDC outside of the follicles and usually surrounding the high HEV. Complete blood count (CBC), including AMC, absolute lymphocyte count (ALC), hemoglobin (Hb) and platelet (PLT) were assessed in 73 AITL patients upon diagnosis. Visual examination of blood smear was required in the case of abnormal automated counts. Baseline clinical characteristics were totally available, including age, gender, Ann Arbor stage, B symptoms, Eastern Cooperative Oncology Group performance status (ECOG PS), extranodal sites (ENSs), lactate dehydrogenase (LDH), beta-2 microglobulin (β2-MG), bone marrow involvement (BMI) and EBV-DNA. The IPI, PIT and PIAI scores were done as previously described [4,6,7]. Treatment response was evaluated according to the revised response criteria for NHL [17].

2.2. Statistical analysis

OS was defined as the time from diagnosis to death as a result of any cause or to the last follow-up. All calculations were performed using SPSS for Windows (version 20.0; IBM Corporation, Armonk, NY, USA). The normal distribution of data was presented as mean ± SD. Differences of AMC as continuous parameter in different groups were compared using independent *t*-test. The optimal cut-off points of AMC were identified based on receiver operating characteristic (ROC) curves. Survival curves were estimated by the Kaplan–Meier method and log-rank test. The prognostic influence of different parameters on survival was established using the Cox proportional hazards model in both univariate and multivariate analysis. *P* value of less than 0.05 was considered to be statistically significant.

3. Results

3.1. Patient characteristics

The baseline characteristics of all 73 patients with AITL are shown in Table 1. The median age of patients at diagnosis was 62 years (range: 22–90) and 53% of them were more than 60 years old. There was a male predominance (45 men and 28 women). Almost all patients (99%) had advanced disease (Ann Arbor stage: III–IV), and 42% had more than 1 extranodal sites. B symptoms were observed in 78%. Twenty-one patients (38%) had an ECOG PS equal to or more than 2, and 57 patients (78%) had elevated LDH prior to treatment. BMI was found in 20 patients (27%). The IPI score was more than 1 in 92% of patients, PIT more than 1 in 66% and PIAI more than 1 in 75%. There were 68 patients whose EBV-DNA in whole blood was detected at presentation and EBV-DNA positive was found in 27 (40%) of the 68 patients. CBC at diagnosis indicated that the median AMC was 0.46×10^9/L (range: 0.01–1.87×10^9/L) and the median ALC was 1.02×10^9/L (range: 0.20–19.26×10^9/L).

Table 1
Clinical characteristics of the 73 AITL patients at diagnosis.

Characteristic	Patients, *n* (%)
Gender, male	45(62)
Age (years) > 60	39 (53)
ECOG PS ≥ 2	28 (38)
B-symptoms present	57 (78)
ENSs > 1	31 (42)
BMI present	20 (27)
LDH > normal	57 (78)
β2-MG (*n* = 68)	
>normal	55 (81)
EBV-DNA (*n* = 68)	
>5000 copies/mL	27 (40)
Ann Arbor stage	
II	1 (1)
III–IV	72 (99)
IPI	
0–1	6 (8)
2	15 (21)
3	28 (38)
4–5	24 (33)
PIT	
0–1	25 (34)
2	23 (32)
3–4	25 (34)
PIAI	
0–1	18 (25)
2–5	55 (75)
	Median (range)
AMC ($\times 10^9$/L)	0.46 (0.01–1.87)
ALC ($\times 10^9$/L)	1.02 (0.20–19.26)
Hb (g/L)	107 (34–160)
PLT ($\times 10^9$/L)	160 (38–424)

AITL, angioimmunoblastic T-cell lymphoma; ALC, absolute lymphocyte count; AMC, absolute monocyte count; β2-MG, serum beta-2 microglobulin level; BMI, bone marrow involvement; EBV, Epstein Barr virus; ECOG PS, Eastern Cooperative Oncology Group performance status; ENSs, extranodal sites; Hb, hemoglobin; IPI, international prognostic index; LDH, serum lactate dehydrogenase level; PIT, prognostic index for T-cell lymphomas; PIAI, prognostic index for angioimmunoblastic T-cell lymphoma; PLT, platelet.

3.2. Correlations between the AMC and the other factors

Patients' clinical parameters were analyzed for possible interactions with the level of AMC (Table 2), and indicated that the level of AMC at diagnosis in patients with ENSs >1 group was significantly higher than those patients with ENSs ≤ 1 (mean AMC level 0.76×10^9/L vs 0.46×10^9/L; $P = 0.035$), in BMI positive than BMI negative group (0.85×10^9/L vs 0.49×10^9/L; $P = 0.001$), in high LDH level than normal LDH level group (0.66×10^9/L vs 0.34×10^9/L; $P = 0.005$), in EBV-DNA positive than EBV-DNA negative group (0.77×10^9/L vs 0.44×10^9/L; $P<0.001$), in high IPI score (IPI ≥ 3) than low IPI score group (0.65×10^9/L vs 0.43×10^9/L; $P = 0.038$), in high PIT score (PIT ≥ 2) than low PIT score group (0.70×10^9/L vs 0.41×10^9/L; $P = 0.007$), and in high PIAI score (PIAI ≥ 3) than low PIAI score group (0.69×10^9/L vs 0.48×10^9/L; $P = 0.011$). We further analyzed the correlation between the AMC and therapy response. A total of 53 patients (73%) responded to the therapy, including complete remission (CR) or complete remission unconfirmed (CRu) in 25 and partial remission (PR) in 28. Fourteen patients had no response to treatment including stable disease (SD) in 1 and progressive disease (PD) in 19. And the higher level of AMC was observed in patients with no response to treatment group than response to therapy (0.88×10^9/L vs 0.49×10^9/L; $P = 0.002$).

3.3. Clinical outcome and prognostic paramaters

All patients were treated with anthracycline-containing chemotherapy as first-line treatment. A total of 53 received combination chemotherapy containing dose-adjusted etoposide,