Absolute peripheral monocyte count at diagnosis predicts central nervous system relapse in diffuse large B-cell lymphoma

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ABSTRACT

Recently, elevated peripheral blood monocyte counts at diagnosis have been shown to be an independent marker associated with poor prognosis in patients with both non-Hodgkin and Hodgkin lymphoma. In this study, we retrospectively analyzed the data from a total of 550 patients with diffuse large B-cell lymphoma and evaluated the relationship between central nervous system relapse and absolute monocyte counts at diagnosis. Twenty-six patients developed central nervous system relapse. The central nervous system relapse-free survival rate was significantly lower in patients with the absolute monocyte counts ≥0.51x10^9/L (87.8% *versus* 96.4%; P<0.001). This association was independently significant after adjusting for other significant factors, including systemic relapse as a time-dependent covariate by multivariate analysis (hazard ratio 2.46; 95% confidence intervals 1.05-5.75; P=0.039). These results suggest that the absolute monocyte count at diagnosis is an independent significant risk factor for central nervous system relapse in patients with diffuse large B-cell lymphoma.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is characterized as an aggressive lymphoma with heterogeneous clinical behaviors. DLBCL accounts for 25-30% of non-Hodgkin lymphomas among adults in the west, and it is even more prevalent in developing countries.[1] In Japan, it was reported that DLBCL is the most frequent subtype and accounts for over 30% of cases of non-Hodgkin lymphomas among adults.[2] Central nervous system (CNS) involvement is not common in DLBCL, but several risk factors for CNS involvement have been identified, including high International Prognostic Index score, involvement of more than one extranodal site, elevated lactate dehydrogenase level, poor Eastern Cooperative Oncology Group performance status (PS), advanced stage, and involvement of bone marrow, breast, testis, retroperitoneal lymph nodes, orbit, or epidural space.[3,4]

Macrophages are an important component of the tumor microenvironment and the immune response to malignancy. Recently, elevated peripheral blood monocyte counts have been shown to be an independent predictor of poor prognosis in patients with both non-Hodgkin and Hodgkin lymphoma.[5-10] Here, we investigated the relationship between peripheral blood monocytes at diagnosis and prognosis, focusing on CNS relapse in DLBCL.

Methods

Patients' characteristics

In the present study, we reviewed the medical records of patients with DLBCL who were treated at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research from February 2005 to May 2014, and retrospectively analyzed the data of a total of 550 consecutive DLBCL patients, excluding seven patients who had CNS involvement at diagnosis. This study was approved by the Institutional Review Board at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research.

The diagnosis of CNS relapse required at least one of the following conditions: the presence of histologically confirmed CNS involvement, neuroimaging findings compatible with CNS relapse with lymphoma associated with consistent clinical presentation and the absence of any other clinically feasible diagnosis, or positive cerebrospinal fluid involvement.

Systemic and central nervous system prophylaxis

Patients in this study were treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) or R-CHOP-based regimens with minor modifications. CNS prophylaxis was given to 72 patients with DLBCL having "high-risk" features for CNS involvement including an involvement of breast, testis, orbit, or epidural space, and paravertebral body or high tumor burden. The intrathecal injection for CNS prophylaxis consisted of methotrexate 15 mg, cytarabine 40 mg, and predonisone 20 mg at least once in the first course of chemotherapy. Furthermore, two patients with DLBCL with the *MYC* translocation received intravenous high-dose methotrexate and cytarabine chemotherapy and one patient received R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin).

Statistical analysis

Receiver operating characteristics (ROC) curve analysis was used to determine the optimal cutoff points of the absolute monocyte count (AMC) or monocyte percentage of the total white blood cell count at diagnosis.[10] Monocyte percentages were confirmed by visual exami-

 doi:10.3324/haematol.2014.114934
Manuscript received on August 4, 2014. Manuscript accepted on Septemebr 19, 2014.
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nation of blood smears in cases in which the automated counts were abnormal.

CNS relapse-free survival was calculated by cause-specific function, censoring patients who died without CNS relapse, in accordance with previously published studies.[11-14] The starting date of the time-to-event analysis was defined at diagnosis. Univariate and multivariate analyses of estimated risk factors for CNS relapse in DLBCL patients were performed using the log-rank test and Cox proportional hazard regression analysis. *P* values <0.05 were considered statistically significant. Background characteristics of the patients with and without CNS involvement were compared using the Fisher exact test and Student *t*-test. All statistical analyses were performed with EZR[15] (Saitama, Medical Center, Jichi Medical University, Japan).

Results

The incidence of central nervous system relapse and the impact of monocyte count at diagnosis

The clinical features of all 550 DLBCL patients, including 26 patients who eventually developed CNS relapse and those who did not, are summarized in Table 1. The median age, AMC, and the monocyte percentage were 64.5 years, 567.8x10^9/L, and 8.8%, respectively, for patients who developed CNS relapse and 65 years, 378.0x10^9/L, and 6.0%, respectively, for those who did not. The CNS relapse-free survival was 95.6% at 3 years and 94.2% at 5 years. The median duration of follow-up was 44.5 months (range, 1-111 months) for the whole cohort and 52 months (range, 2-111) for surviving patients.

Both AMC and monocyte percentage at diagnosis as continuous variables were significantly associated with CNS relapse-free survival (*P*=0.0054 and *P*=0.0040, respectively). ROC curve analysis revealed that optimal cutoff values, defined as those with the highest sum of sensitivity and specificity, were 0.51x10^9/L) for AMC and 8% for monocyte percentage. The areas under the ROC curves were 0.66 [95% confidence interval (CI) 0.57-0.76] for AMC and 0.64 (95% CI 0.53-0.75) for monocyte percentage. The 5-year CNS relapse-free survival was 96.4% and 90.0% for patients with low and high AMC, respectively, at diagnosis (*P*<0.001, Figure 1) and 96.1% and 90.8% for patients with low and high monocyte percentage (*P*=0.0177), respectively.

In the following analyses we used AMC rather than monocyte percentage, because AMC better discriminated high-risk patients for CNS relapse. The 5-year cumulative incidence of CNS relapse was 3.6% and 10.0% for patients with low and high AMC at diagnosis, respectively. Treating death without relapse as a competing risk, the 5-year cumulative incidence of CNS relapse was 3.3% and 9.3% for patients with low and high AMC at diagnosis, respectively.

Table 1. Patient's characteristics.

Factor	Group	CNS relapse		*P* value
		Absent n (%)	Present n (%)	
Age (years)	<60	343 (65.5)	16 (61.5)	0.678
	≥60	181 (34.5)	10 (38.5)	
Sex	Female	232 (44.3)	7 (26.9)	0.104
	Male	292 (55.7)	19 (73.1)	
Monocyte percentage	Low	334 (63.7)	11 (42.3)	0.037
	High	190 (36.3)	15 (57.7)	
AMC	Low	348 (66.4)	9 (34.6)	0.001
	High	176 (33.6)	17 (65.4)	
Soluble IL-2R	Low	147 (28.1)	2 (7.7)	0.022
	High	377 (71.9)	24 (92.3)	
LDH	Low	292 (55.7)	11 (42.3)	0.226
	High	232 (44.3)	15 (57.7)	
PS	0-1	478 (91.2)	17 (65.4)	<0.001
	2-4	46 (8.8)	9 (34.6)	
Stage	1-2	319 (60.9)	7 (26.9)	0.001
	3-4	205 (39.1)	19 (73.1)	

AMC: absolute monocyte count; soluble IL-2R: soluble interleukin-2 receptor; LDH: lactate dehydrogenase; PS: performance status; CNS: central nervous system.

Multivariate analysis to adjust for other significant factors

To adjust the impact of AMC at diagnosis for other significant factors for CNS relapse, we identified the following risk factors by univariate analysis (Table 2): clinical stage III-IV, PS ≥2, and elevated soluble interluekin-2 receptor levels. We then performed multivariate analyses using all these factors in the Cox proportional hazard model. As shown in Table 3, high AMC [hazard ratio (HR) 2.94, 95% CI 1.28-6.76; *P*=0.011), poor PS (HR 4.01, 95% CI 1.70-9.48; *P*=0.0016), and stage III-IV disease (HR 2.76, 95% CI 1.09-6.99; *P*=0.033) were identified as independent significant prognostic factors for CNS relapse. In multivariate analyses including extra-nodal involvement or the presence of intrathecal treatment as an independent variable, the impact of AMC did not change by adding these variables into the model (HR 2.85, 95% CI 1.24-6.54; *P*=0.013 and HR 2.83, 95% CI 1.23-6.50; *P*=0.014, respectively). The presence of intrathecal treatment was associated with a non-significant increase in CNS relapse (HR 1.92, 95% CI 0.79-4.65; *P*=0.15).

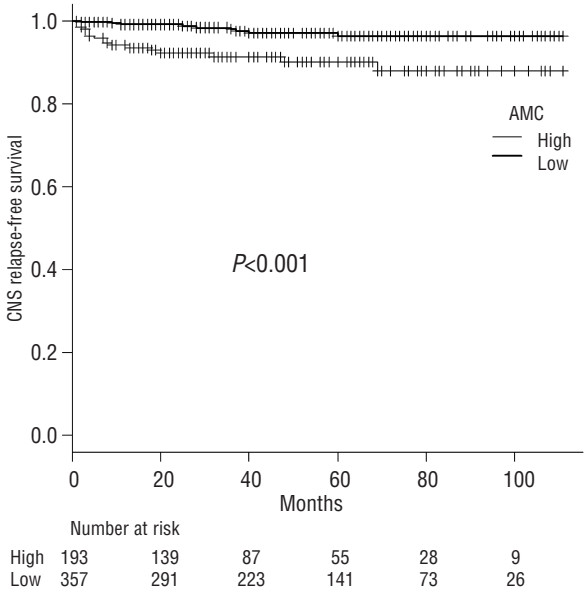

Figure 1. The CNS relapse-free survival curves grouped according to the absolute monocyte count (AMC) at diagnosis. CNS: central nervous system.

Next, we evaluated whether the impact of AMC on CNS relapse is independent of its impact on systemic relapse, as systemic relapse is a strong predictor of CNS relapse, and high monocyte count at diagnosis has been shown to be a significant risk factor for systemic relapse.[5] In fact, in this cohort, systemic progression-free survival was significantly associated with AMC at diagnosis (78.4% *versus* 67.4% at 5 years; *P*=0.0019) (Figure 2).

We, therefore, added systemic relapse as a time-dependent covariate into the Cox proportional hazard model. The impact of AMC was still significant even after adjusting for systemic relapse (HR 2.46, 95% CI 1.04-5.75; *P*=0.039) (Table 3). In addition, among the 130 patients who developed systemic relapse, the incidence of subsequent CNS relapse was higher in patients with high AMC at diagnosis (78.0% *versus* 65.9% at 5 years after systemic relapse; *P*=0.030) (Figure 3). These findings suggest that the impact of AMC on CNS relapse is independent of its impact on systemic relapse.

Discussion

In this study, we retrospectively analyzed the data from a total of 550 DLBCL patients and evaluated the relationship between CNS relapse and AMC at diagnosis. The CNS relapse-free survival was significantly lower in patients with AMC ≥0.51x10^9/L at diagnosis. This association could be explained by the previous findings that systemic relapse is a strong predictor of CNS relapse, and

Table 2. Univariate analysis for CNS relapse.

Factor	Group	CNS relapse-free survival probability	range	*P* value
Age (years)	<60	0.945	(0.909-0.967)	0.82
	≥60	0.938	(0.882-0.968)	
AMC	Low	0.964	(0.930-0.982)	<0.001
	High	0.900	(0.838-0.939)	
Soluble IL-2R	Low	0.972	(0.876-0.994)	0.0226
	High	0.929	(0.894-0.953)	
LDH	Low	0.956	(0.916-0.977)	0.123
	High	0.924	(0.876-0.954)	
PS	0-1	0.957	(0.929-0.974)	<0.001
	2-4	0.790	(0.620-0.890)	
Stage	1-2	0.971	(0.934-0.987)	<0.001
	3-4	0.898	(0.843-0.935)	

AMC: absolute monocyte count; soluble IL-2R: soluble interleukin-2 receptor; LDH: lactate dehydrogenase; PS: performance status; CNS: central nervous system.

Table 3. Multivariate analysis for CNS relapse. Systemic relapse was treated as a time-dependent covariate and was included in the model on the right.

Factor	Group	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
AMC	Low	1.000	0.011	1.000	0.039
	High	2.94 (1.28-6.76)		2.46 (1.05-5.75)	
Soluble IL-2R	Low	1.000	0.47	1.000	0.54
	High	1.76 (0.38-8.20)		1.63 (0.34-7.67)	
PS	0-1	1.000	0.002	1.000	0.0068
	2-4	4.01 (1.70-9.48)		3.58 (1.42-8.99)	
Stage	1-2	1.000	0.033	1.000	0.28
	3-4	2.76 (1.09-6.99)		1.71 (0.65-4.55)	
Systemic relapse	Absent			1.000	<0.001
	Present			14.49 (6.25-33.56)	

95% CI: 95% confidence interval; AMC: absolute monocyte count; soluble IL-2R: soluble interleukin-2 receptor; PS: performance status; CNS: central nervous system.

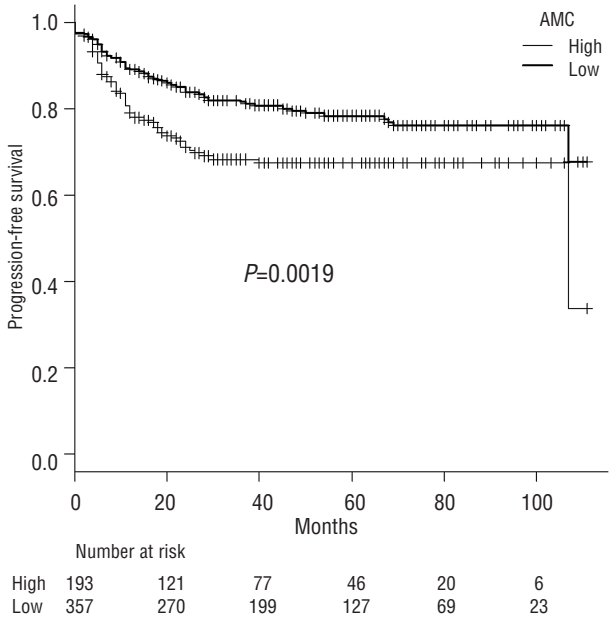

Figure 2. Progression-free survival curves grouped according to the absolute monocyte count (AMC) at diagnosis.

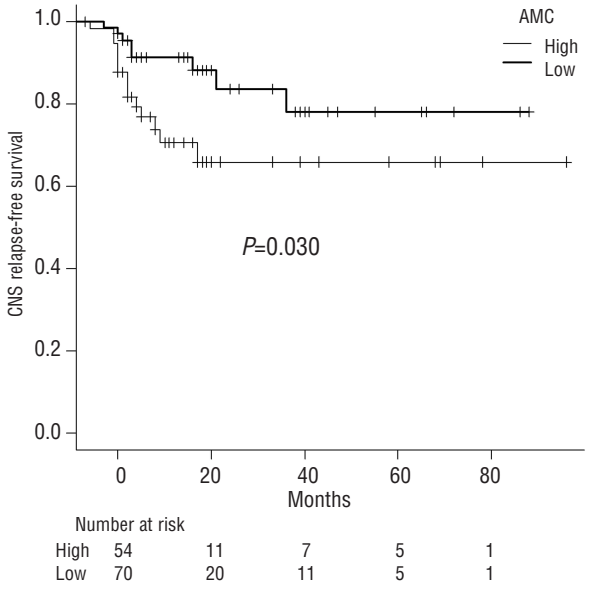

Figure 3. The CNS relapse-free survival curves after systemic relapse, grouped according to the absolute monocyte count (AMC) at diagnosis. CNS, central nervous system.

high monocyte count at diagnosis has been shown to be a significant risk factor for systemic relapse.[5] In fact, in this cohort, systemic progression-free survival was significantly associated with AMC at diagnosis. Tumor-associated macrophages and monocytes can foster cancer progression by promoting proliferation and angiogenesis.[16] It has been reported that an elevated ratio of $CD14^+$ monocytes without HLA expression was significantly related to aggressive clinical behavior in DLBCL.[17] These peripheral blood monocytes suppress host immunity by inhibiting the proliferative ability of interferon-γ, impairing the differentiation ability of dendritic cells.[1]

In this study, however, the impact of AMC was still significant even after adjusting for systemic relapse as a time-dependent covariate. In addition, among patients who developed systemic relapse, the incidence of subsequent CNS relapse was significantly higher in patients with high AMC at diagnosis. AMC at diagnosis does, therefore, have a significant adverse effect on CNS relapse, independently of systemic relapse. Peripheral monocytes, which migrate to cancer tissue and differentiate into tumor-associated macrophages, are increased in a variety of malignancies, including lymphoma.[18] The M2c subtype of monocytes can produce CXCL13 and interleukin-10,[19,20] which are known to be associated with the development of CNS lymphoma.[19] Accordingly, AMC at diagnosis in DLBCL patients may be related to CNS relapse.

Patients with high AMC may require intensified prophylaxis for CNS relapse. Intrathecal prophylaxis has been investigated to determine whether it prevents CNS relapse in high-risk patients, but its efficacy was not proven in studies employing modern regimens.[21] In fact, in the current study, intrathecal prophylaxis was added to patients at high-risk of CNS relapse, but these patients still had a higher incidence of CNS relapse.[22] Therefore, high-dose intravenous methotrexate and/or cytarabine chemotherapy as dose-intensive systemic antimetabolite-containing chemotherapy may be required in high-risk patients.[22]

In conclusion, our findings suggest that the AMC at diagnosis has an independent impact on CNS relapse in patients with DLBCL. Novel strategies to prevent CNS relapse should be explored for patients with high AMC.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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