Absolute monocyte count in follicular lymphoma patients treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone

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ABSTRACT

Elevated absolute monocyte counts (AMCs) have been reported to indicate poor prognosis for patients with lymphoproliferative disease, including those with follicular lymphoma (FL) receiving various treatments. We evaluated the prognostic impact of AMC in 150 consecutive FL patients who received rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) therapy. Progression-free survival (PFS) did not differ significantly according to the AMC level. Univariate and multivariate analyses did not indicate a prognostic significance of AMC for PFS. Thus, the AMC is not a prognostic factor for FL patients treated with R-CHOP. However, immunochemotherapy might influence the prognostic impact of AMC.

1. Introduction

Follicular lymphoma (FL) is an indolent non-Hodgkin lymphoma (NHL), with a variable clinical course that ranges from stable disease to rapid progression with transformation to aggressive NHL. The Follicular Lymphoma International Prognostic Index (FLIPI) [1], which includes parameters such as age, stage, presence of anemia, number of involved nodal regions, and serum lactate dehydrogenase (LDH) levels, is a well-known scoring system for risk stratification of FL patients at the time of diagnosis. The FLIPI is useful for predicting the outcome of newly diagnosed FL patients treated with immunochemotherapy [2] and those experiencing their first relapse [3]. The FLIPI has also been reported to be the most important variable for predicting transformation [4].

The tumor microenvironment, including the non-malignant cells of the tumor, has recently been shown to predict the clinical outcome of FL [5]. Farinha et al. [6] reported that a high content of tumor-associated macrophages (TAMs) in the tumor was a predictor of poor overall survival (OS) and progression-free survival (PFS) for FL patients, independent of the International Prognostic Index. Several other studies [7–9] also showed that a high TAM content in the tumor was associated with the survival of FL patients, although it was largely influenced by their treatment.

TAMs are derived from circulating monocytes in the peripheral blood that are recruited to the tumor site [10,11]. Wilcox et al. [12] investigated the prognostic impact of the peripheral blood monocyte number and found that an elevated absolute monocyte count (AMC) was associated with inferior OS, independent of FLIPI, in FL patients receiving various treatments. In recent studies,

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an elevated AMC was reported to be an adverse prognostic factor for other histological subtypes of lymphoproliferative disease [13–16]. However, the prognostic impact of the AMC is uncertain in FL patients exclusively treated with rituximab-containing therapy.

In this study, we retrospectively evaluated the prognostic impact of the AMC at diagnosis in FL patients treated exclusively with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) therapy.

2. Design and methods

2.1. Patients

A total of 157 consecutive FL patients were treated with R-CHOP therapy at 7 participating hospitals between 2001 and 2009. Seven patients were excluded because of incomplete data, while the remaining 150 patients were reviewed for this study. Since 2001, the Yokohama City University Hematology Group has uniformly treated all FL patients, except those with stage 1 disease, with immediate systemic therapy consisting of 6 cycles of standard R-CHOP therapy at 3-week intervals starting from the time of diagnosis. Those who show partial response after an initial 4 cycles of R-CHOP are administered a total of 8 cycles, whereas patients who do not achieve partial response after the initial 4 cycles or those who show disease progression at any time receive salvage therapy. Patients with a bulky mass at diagnosis also receive irradiation of the tumor field after 6–8 cycles of R-CHOP therapy. None of the patients included in this study had dose reductions of >20% of the initial therapy dose. This study was approved by the institutional review board of Yokohama City University Hospital.

2.2. Statistical analysis

PFS was defined as the time between the start of treatment to the date of disease progression, death from any cause, or date of last follow-up, whichever occurred first. OS was defined as the time between the start of treatment and the date of last follow-up or death. Survival was estimated using Kaplan–Meier analysis and compared using the log-rank test. A P value of <0.05 was considered statistically significant. Differences between groups were evaluated using the χ^2 test (nonparametric analysis). The Cox proportional hazards model was used to evaluate whether the AMC was a prognostic factor for PFS and to adjust for other known prognostic variables included in the FLIPI. All statistical analyses were performed using Statistical Package for the Social Sciences software (IBM PASW Statistics 19.0, IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Patient profile

This study included 77 men and 73 women, with a median age of 57 years at diagnosis (range: 25–76 years) (Table 1). In the 150 patients, FL was classified as histological grade 1 ($n = 61$), grade 2 ($n = 59$), grade 3a ($n = 19$), or grade 3b ($n = 11$) according to the World Health Organization [17]. Forty-two patients (28%) had a low FLIPI, whereas 49 (33%) and 59 (39%) patients had intermediate and high FLIPI, respectively. The median observation period was 43 months. The 5-year PFS and OS rates estimated for the entire cohort were 46.3% and 90.0%, respectively. The median AMC at diagnosis was 0.34×10^9/L (range: 0.01–1.11×10^9/L), with 3 patients showing an elevated AMC above the upper limit of normal ($\geq 0.80 \times 10^9$/L).

3.2. Prognostic impact of the AMC in FL

The optimal cut-off value for the AMC was set at 0.34×10^9/L (median value). The 150 FL patients were divided into 2 groups, those with an AMC $\leq 0.34 \times 10^9$/L ($n = 74$) and those with an AMC $>0.34 \times 10^9$/L ($n = 76$), and their clinical characteristics were compared (Table 2). The 2 groups did not differ significantly with respect to age, gender, Ann Arbor stage, serum LDH levels, involvement of more than 4 nodal regions, B symptoms, bone marrow involvement, hemoglobin levels, histological grade, or FLIPI. However, an advanced Ann Arbor stage tended to be more frequent among patients with an AMC $>0.34 \times 10^9$/L rather than among

Table 1
Characteristics of the 150 patients with FL.

Characteristic	Number (%)
Median age, years (range)	57 (25–76)
Gender	
Male	77 (51)
Female	73 (49)
Ann Arbor stage	
I–II	31 (21)
III–IV	119 (79)
LDH	
≤Normal	104 (69)
>Normal	46 (31)
Site of nodal disease	
≤4	69 (46)
>4	81 (54)
Hemoglobin level	
≥120 g/L	124 (83)
<120 g/L	26 (17)
Histological grade	
Grade 1	61 (41)
Grade 2	59 (39)
Grade 3a	19 (13)
Grade 3b	11 (7)
Median AMC (range)	0.34×10^9/L (0.01–1.11×10^9/L)
FLIPI	
Low	42 (28)
Intermediate	49 (33)
High	59 (39)

LDH, lactate dehydrogenase; AMC, absolute monocyte count; FLIPI, Follicular Lymphoma International Prognostic Index.

those with an AMC $\leq 0.34 \times 10^9$/L ($P = 0.058$). PFS ($P = 0.464$) (Fig. 1) and OS ($P = 0.537$) did not differ significantly when patients were stratified according to their AMC values (median-follow up: 43 months). There was a significant difference of PFS among patients who were stratified into low-, intermediate-, and high-risk groups by the FLIPI (Fig. 2).

The influence of the following variables on PFS was assessed: (1) AMC $>0.34 \times 10^9$/L; (2) age >60 years; (3) hemoglobin level <120 g/L; (4) elevated serum LDH levels; (5) >4 sites of nodal disease; and (6) Ann Arbor stage III–IV. Results of univariate and multivariate analysis for factors influencing PFS are shown in Table 3. According to univariate analysis, the presence of more than 4 sites of nodal disease (hazard ratio [HR] = 2.720, 95% confidence interval [CI] 1.619–4.568, $P < 0.001$) and an Ann Arbor stage of III–IV (HR = 2.802, 95% CI 1.279–6.136, $P = 0.010$) were associated with poor PFS. However, according to multivariate analysis, only the presence of more than 4 sites of nodal disease (HR = 2.332, 95% CI 1.285–4.231, $P = 0.005$) was associated with poor PFS. Therefore, both univariate and multivariate analyses determined that AMC was not a prognostic indicator for PFS.

Table 2
Comparison of FL groups according to the AMC level.

	AMC $\leq 0.34 \times 10^9$/L ($n = 74$)	AMC $>0.34 \times 10^9$/L ($n = 76$)	P value
Age ≤60/>60	48/26	48/28	0.828
Male/female	36/38	41/35	0.516
Ann Arbor stage I–II/III–IV	20/54	11/65	0.058
LDH ≤normal/>normal	51/23	53/23	0.914
Site of nodal disease ≤4/>4	37/37	32/44	0.332
B symptoms −/+	71/3	68/8	0.128
Bone marrow involvement −/+	42/32	37/39	0.322
Hemoglobin level ≥120 g/L/<120 g/L	64/10	60/16	0.223
Histological grade 1–3a/3b	68/6	71/5	0.719
FLIPI low/intermediate/high	24/26/24	18/23/35	0.216

AMC, absolute monocyte count; LDH, lactate dehydrogenase; FLIPI, Follicular Lymphoma International Prognostic Index.