Monocyte count at diagnosis is a prognostic parameter in diffuse large B-cell lymphoma: results from a large multicenter study involving 1191 patients in the pre- and post-rituximab era

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ABSTRACT

In this study we assessed the prognostic significance of absolute monocyte count and selected the best cut-off value at diagnosis in a large cohort of patients with diffuse large B-cell lymphoma. Data were retrieved for therapy-naïve patients with diffuse large B-cell lymphoma followed in Israel and Italy during 1993-2010. A final cohort of 1017 patients was analyzed with a median follow up of 48 months and a 5-year overall survival rate of 68%. The best absolute monocyte count cut-off level was 630/mm^3 and the 5-year overall survival for patients with counts below this cut-off was 71%, whereas it was 59% for those with a count >630 mm^3 (P=0.0002). Of the 1017 patients, 521 (51%) were treated with chemo-immunotherapy, and in this cohort, using multivariate analysis, elevated monocyte count retained a negative prognostic value even when adjusted for International Prognostic Index (HR1.54, P=0.009). This large study shows that a simple parameter such as absolute monocyte count (>630/mm^3) can easily be used routinely in the evaluation of newly diagnosed diffuse large B-cell lymphoma to identify high-risk patients with a worse survival in the rituximab era.

Introduction

The International Prognostic Index (IPI) still remains the best model for risk stratification of patients with aggressive non-Hodgkin's lymphomas.[1,2] However, the treatment of diffuse large B-cell lymphoma (DLBCL) has changed since 2002 when rituximab was added to CHOP chemotherapy (R-CHOP), leading to a meaningful improvement in overall survival.[3,4] As a result, the IPI needed to be reassessed to determine whether it still maintained its predictive value in the rituximab era. Consequently in 2007, it was revised by Sehn and colleagues after a retrospective study involving patients treated with R-CHOP,[5] which showed that the IPI score could now identify only two major risk groups instead of the four originally reported.[1] They proposed a revised IPI (R-IPI), which re-stratified patients into three prognostic groups with significantly different outcomes. Other groups also re-evaluated the IPI in the era of R-CHOP therapy for DLBCL, showing that its discriminating power had diminished. They suggested combining the R-IPI with a simple value of the peripheral blood absolute lymphocyte count (ALC), which could serve as a surrogate marker for the degree of immune suppression in these patients.[6]

There is now increasing interest in the role of monocytes and their precursors in the pathogenesis of lymphoproliferative disorders.[7] It has been shown that absolute monocyte count (AMC) at diagnosis has prognostic significance in lymphoma and may serve as an independent parameter associated with poor prognosis and decreased overall survival.[8,9] However, there is no current consensus regarding the best AMC cut-off value to be applied in common practice.[8-13]

The main aim of this collaborative multicenter study was to verify the prognostic significance of AMC in a very large cohort of newly diagnosed patients with DLBCL and evaluate different cut-off levels (610, 620, 630, 800 and to 1000 cells/mm^3), reported to be significant in other recent reports. We also examined whether AMC could be utilized as a simple independent prognostic factor for survival, comparing it to the IPI. The prognostic roles of the ALC and the lymphocyte to monocyte ratio (LMR) were also analyzed to compare and correlate them with the IPI. In addition, we examined whether all the above parameters retained their prognostic significance and affected survival in patients treated in the era of immuno-chemotherapy.

Methods

Patients

We reviewed the clinical and laboratory data of consecutive "therapy-naïve" patients, treated in different centers in Haifa, Israel and in Italy between 1993-2010, after approval by local institutional review boards. A total of 1191 patients had received treatment with combination chemotherapy: cyclophosphamide, doxorubicin, vincristine,

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and prednisone (CHOP), CHOP-like, or third-generation anthracycline-containing regimens, with or without rituximab; 521 patients (51%) received the above therapies with rituximab as part of the regimen.

Statistical analysis

Survival was assessed by Kaplan-Meier estimates[14] and compared by risk groups using the log-rank test and Cox proportional hazard analysis.[15] The proportional hazard assumption was verified graphically by means of scaled Schoenfeld residuals.[16] The effect size was reported as a hazard ratio (HR) with the associated 95% confidence interval (95% CI).

We evaluated the following proposed cut-off values for monocytes: 610/mm^3,[10] 620/mm^3,[11] 630/mm^3,[12] 800/mm^3,[9,13] and 1000/mm^3.[8] As far as concerns the LMR, the proposed cut-off values evaluated were 1.1,[17] 2.1,[18] 2.6,[11,19] and 2.9.[20] Thereafter we chose cut-off values with the best power in discriminating patients with either good or poor outcome, after adjusting for the IPI. The performance of the different cut-offs was checked by means of the hazard ratios and respective z-score (from Wald's test) and by comparing the discriminating power, expressed as Harrell's C index.[21] The Harrell's C standard error and 95% confidence interval were estimated by means of a jackknife procedure.[22] We arbitrarily chose the cut-off on the basis of the compromise between the discriminative power of the factor and the size of the group at greatest risk. Whereas we analyzed different cut-off points for AMC and LMR, given the broad agreement regarding the definition of lymphopenia as an ALC<1000/mm^3, we used this cut-off for ALC.[23,24]

The effect of rituximab on the prognostic power of AMC, ALC and LMR was evaluated by interacting prognostic factors with rituximab, after adjustment by IPI score.

Results

Patients' characteristics

We analyzed data from 1191 patients with DLBCL diagnosed between 1993 and 2010. Patients with missing data on monocyte or lymphocyte counts or one of the IPI parameters before treatment were excluded, and the final cohort consisted of 1017 patients.

The median age at diagnosis was 60 years (range, 25-81 years) and 47% of the patients were more than 60 years old; 53% were male and 54% of the patients had advanced, stage III-IV disease (Table 1); the clinical characteristics at diagnosis were comparable in the Israeli and Italian cohorts.

A total of 496 patients (49%) were treated with chemotherapy alone, while 521 (51%) received immunochemotherapy including rituximab. The median follow-up of the entire cohort was 48 months (range, 0.2-180 months), and 64 months for patients still alive. Overall, 317 events were recorded with a death rate of 7.4x100 person-years (95% CI: 6.6-8.3x100 person-years) and a 5-year overall survival of 68% (95% CI: 65-71%). The overall survival at 5 years in patients treated with or without rituximab was 68% in both groups (HR 0.98, *P*=0.864). It is noteworthy that in our series there was an association between the use of rituximab and the IPI score; in the group of patients with IPI 0-2, only 43% of patients had been treated with rituximab compared to 70% of the patients with IPI 3-5. In a multivariate analysis, adjusted for IPI score, the risk of death in patients treated with rituximab was reduced by 30% (*P*=0.002).

Absolute monocyte count

The median AMC of all patients at diagnosis was 499/mm^3 (range, 30-8170/mm^3). When correlated by IPI score into risk groups, the median AMC in the groups with scores 0-1, 2 and 3-5 was 480, 461 and 554/mm^3, respectively (*P*=0.004). The most common AMC cut-off levels evaluated in the literature are 610/mm^3, 620/mm^3, 630/mm^3, 800/mm^3, and 1000/mm^3. All these proposed

Table 1. Baseline characteristics of the 1017 patients with DLBCL entered in the study.

Variable	N.	%
Age, years		
≤ 60	537	53
>60	480	47
Gender		
Male	538	53
Female	479	47
Stage		
I	156	15
II	305	30
III	187	18
IV	369	36
Bone marrow*		
-	819	84
+	157	16
B-symptoms*		
No	685	71
Yes	283	29
Lactate dehydrogenase		
≤ UNL	535	53
> UNL	482	47
IPI score		
0-1	437	43
2	260	26
3-5	320	31
Monocytes, /mm^3		
> 610	352	35
> 620	342	34
> 630	331	33
> 800	196	19
> 1000	100	10
Lymphocytes /mm^3		
≤ 1000	328	32
Regimens		
CHOP	101	10
ProMACE CytaBOM	395	39
R-CHOP	457	44
R-miniCEOP	64	6
Rituximab use		
Yes	521	51
	Median (2.5th - 97.5th)	
Age, years	60 (25-81)	
White blood cells 10^3/mm^3	7.2 (3.2-17)	
Monocytes /mm^3	499 (102-1413)	
Lymphocytes 10^3/mm^3	1.45 (0.30-3.73)	
ALC/AMC ratio	2.8 (0.6-15)	

*UNL: upper normal limit; IPI: International Prognostic Index; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; ProMACE CytaBOM: methylprednisolone, cyclophosphamide, epidoxorubicin, etoposide, cytarabine, bleomycin, vincristine, methotrexate; R-CHOP: rituximab plus CHOP; R-miniCEOP: rituximab plus cyclophosphamide, epidoxorubicin, vinblastine, prednisone. *Missing: bone marrow n=41 (4%), B-symptoms n=49 (5%).*

thresholds improved the predictive value, after adjustment for the IPI score in the Cox proportional hazard model, and as a result the hazard ratio increased from 1.34 (P=0.011) to 1.83 (P<0.001) using the cut-offs from 610/mm^3 to 1000/mm^3, respectively. AMC had a similar predictive value in patients treated with chemotherapy alone or with the addition of rituximab (Table 2). However, when the AMC value was added to the IPI score, the discriminating power, evaluated in all patients by Harrell's C index, increased from 65.7 for IPI alone to 67.3 for IPI plus AMC>1000/mm^3. Considering only patients treated with rituximab, the best cut-off level was 630/mm^3 with a Harrell's C index of 72.3 (95% CI: 68.1-75.6). Although the improvement in the discriminating power after adding AMC to the IPI score was similar using all the proposed cut-off values, we arbitrarily chose an AMC of 630/mm^3 as a reference value, because this threshold selected more cases (33%) with poorer survival compared to higher cut-offs, and also performed better in patients treated with rituximab-containing regimens (Table 2, Figure 1).

Monocytosis, defined as an AMC >630/mm^3, was observed in 331 patients. The AMC was associated with IPI score and 29% of the patients with an AMC >630/mm^3 had an IPI score 0-1, 31% had an IPI score of 2 and 39%

Table 2. Prognostic role of lymphocytes and different cut-off levels of monocytes and LMR in Cox proportional hazard regression.

	%	HR	95%CI	z	*P* value
Lymphocytes (/mm^3)					
All cases adjusted by IPI score (N=1017):					
≤ 1000	32	1.05	0.83-1.33	0.44	0.662
Interacted with rituximab and adjusted by IPI score: (N=1017)					
≤ 1000, -R		1.09	0.78-1.53	0.52	0.604
≤ 1000, +R		1.10	0.79-1.52	0.56	0.577
Monocytes (/mm^3)					
All cases adjusted by IPI score (N=1017):					
> 610	35	1.34	1.06-1.68	2.54	0.011
> 620	34	1.40	1.17-2.19	2.94	0.003
> 630	33	1.44	1.15-1.80	3.16	0.002
> 800	19	1.46	1.13-1.88	2.90	0.004
> 1000	10	1.83	1.35-2.48	3.87	<0.001
Interacted with rituximab and adjusted by IPI score: (N=1017)					
> 610, -R		1.24	0.91-1.70	1.38	0.168
>610, +R		1.45	1.05-2.00	2.24	0.025
> 620, -R		1.28	0.94-1.75	1.56	0.118
>620, +R		1.53	1.11-2.12	2.58	0.010
>630, -R		1.36	1.00-1.86	1.94	0.052
>630, +R		1.54	1.12-2.13	2.62	0.009
>800, -R		1.56	1.08-2.25	2.38	0.017
>800, +R		1.44	1.01-2.05	2.01	0.044
>1000, -R		2.09	1.34-3.24	3.27	0.001
>1000, +R		1.71	1.12-2.60	2.51	0.012
LMR					
All cases adjusted by IPI score (N=1017):					
≤ 1.1	10	1.50	1.09-2.07	2.52	0.012
≤ 2.1	32	1.18	0.94-1.49	1.40	0.161
≤ 2.6	45	1.14	0.91-1.43	1.13	0.258
≤ 2.9	52	1.11	0.88-1.41	0.92	0.358
Interacted by rituximab and adjusted by IPI score: (N=1017)					
≤ 1.1, -R		1.40	0.85-2.32	1.31	0.189
≤ 1.1, +R		1.67	1.10-2.52	2.43	0.015
≤ 2.1, -R		0.96	0.69-1.34	0.24	0.809
≤ 2.1, +R		1.49	1.07-2.06	2.37	0.018
≤ 2.6, -R		1.01	0.75-1.38	0.09	0.928
≤ 2.6, +R		1.35	0.96-1.89	1.72	0.085
≤ 2.9, -R		0.99	0.73-1.34	0.07	0.944
≤ 2.9, +R		1.30	0.92-1.84	1.49	0.136

-R: regimens without rituximab; +R: regimens containing rituximab; In multiple Cox proportional hazard regression the monocyte count was adjusted by IPI score. Cox proportional hazard regression with only IPI: reference group 0-1) IPI 2 HR=1.56, 95% CI 1.22-2.16, P=0.008; IPI 3-5, HR=3.42, 95% CI 2.58-4.55, P<0.001.

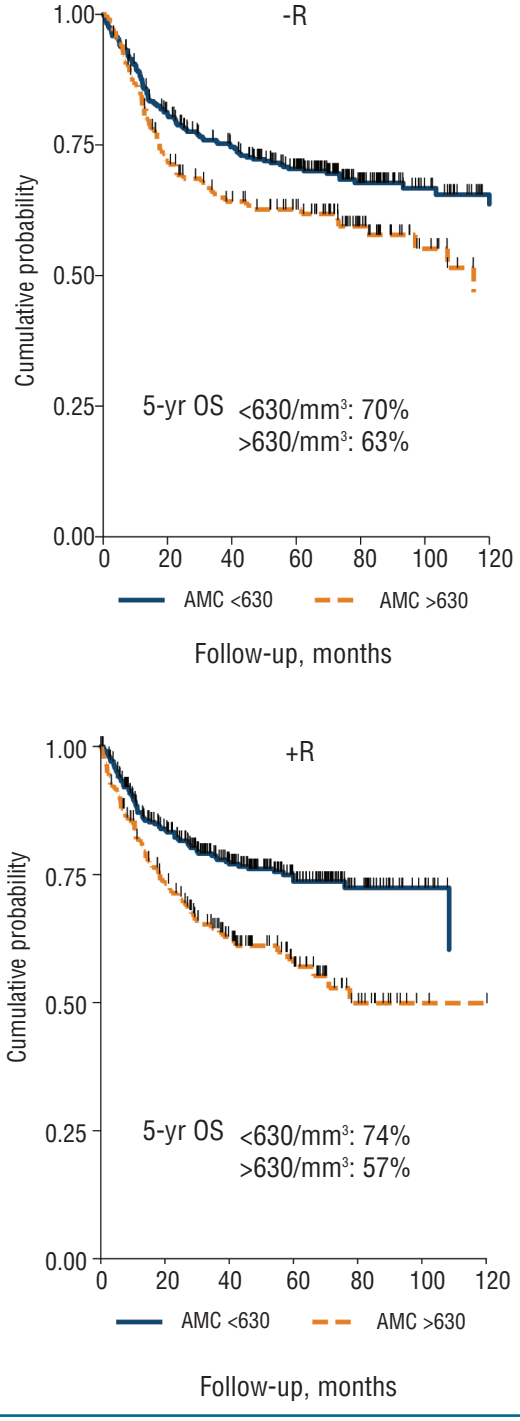

Figure 1. Kaplan-Meier curves for monocyte count (>630/mm^3) and rituximab use, unadjusted by IPI score. OS: overall survival; -R: regimens without rituximab; +R: regimens containing rituximab.

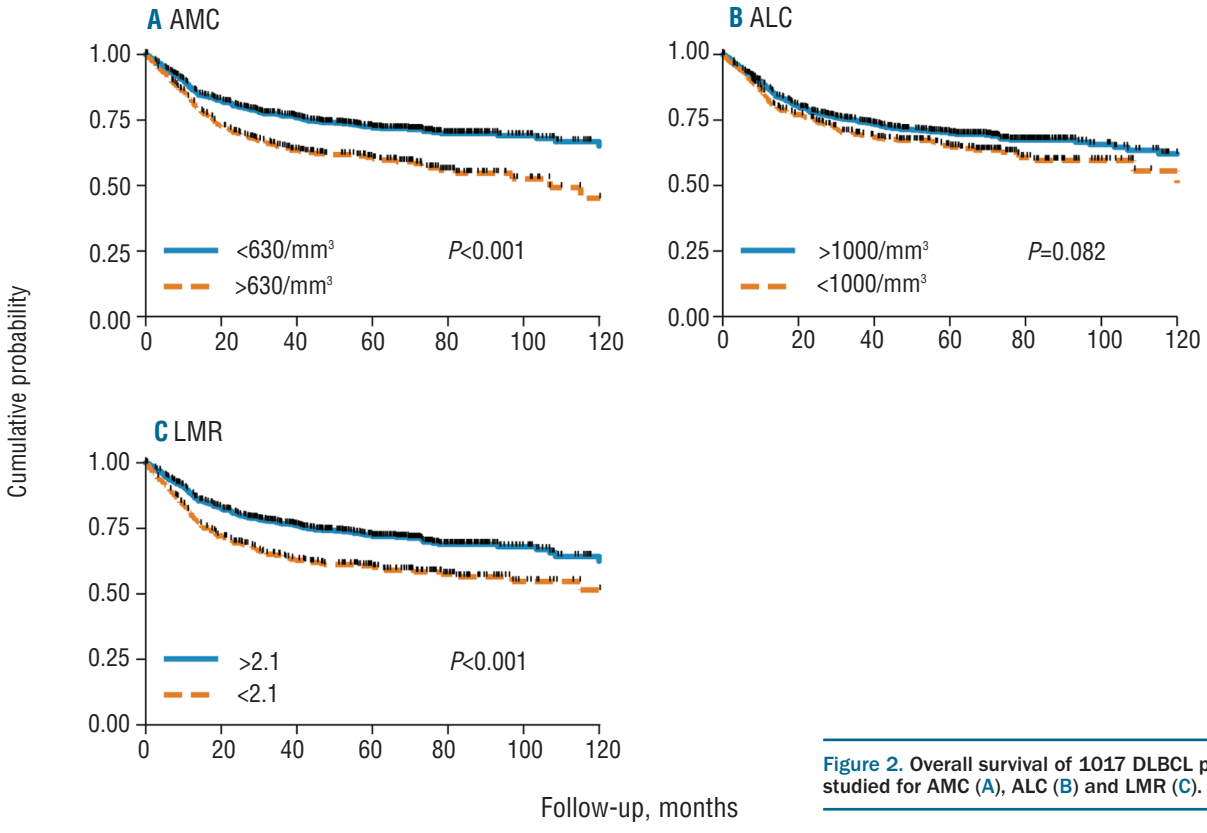

Figure 2. Overall survival of 1017 DLBCL patients studied for AMC (A), ALC (B) and LMR (C).

had an IPI score of 3-5 (P=0.006). Patients with an AMC ≤630/mm³ had a 5-year overall survival of 72%, compared to 60% for those with an AMC >630/mm³ (P<0.001) (HR 1.61, 95% CI: 1.29-2.02) as shown in Figure 2A. In multivariate analysis AMC, interacted with rituximab use after adjustment for IPI score, had a marginal prognostic impact in patients treated with chemotherapy alone (HR 1.36, 95% CI 1.00-1.86, P=0.052), while monocytosis showed a strong prognostic effect in patients treated with rituximab-containing regimens (HR 1.54, 95% CI 1.12-2.13, P=0.009) (Table 2 and Figure 3A).

Absolute lymphocyte count

The median ALC of all patients at diagnosis was 1450/mm³ (range, 105-42420/mm³). The internationally recognized cut-off of 1000/mm³ was chosen to define lymphopenia.

The ALC correlated with IPI score and 25%, 34 % and 40% of the patients with lymphopenia had an IPI score of 0-1, 2 and 3-5, respectively (P<0.001). The overall survival at 5 years for patients with an ALC >1000/mm³ was 70% compared to 65% for those with an ALC ≤1000/mm³ (P=0.082) (Figure 2B) (HR 1.23, 95% CI: 0.97-1.55). In multivariate analysis ALC, interacted with rituximab use and after adjustment by IPI score, lost its prognostic impact both in patients treated with chemotherapy alone and in those treated with immune-chemotherapy (HR 1.10, 95% CI: 0.79-1.52 and HR 1.09, 95% CI: 0.78-1.53, respectively) (Table 2).

Lymphocyte/monocyte ratio

We combined ALC and AMC to generate a prognostic value which stratified patients into two risk groups based on LMR. Four cut-off levels of LMR (1.1, 2.1, 2.6 and 2.9) were evaluated and the value with the best performance was 2.1, especially in the group treated with rituximab (Table 2).

LMR was associated with IPI score. For patients with a ratio ≤2.1, 21% had an IPI score of 0-1, 31% had an IPI score of 2 and 48% of the patients had an IPI score of 3-5 (P<0.001).

The 5-year overall survival rate was 60% and 72% for patients with LMR ≤2.1 and >2.1, respectively (Figure 2C). In multiple regression analysis LMR ≤2.1, interacted with rituximab use and after adjustment by IPI score, showed different patterns in patients treated with chemotherapy with or without the addition of rituximab (HR 1.49, P=0.018 and HR 0.96, P=0.809, respectively) (Table 2). The LMR value affects survival together with IPI score and influences the therapeutic role of rituximab; patients with LMR ≤2.1 were less responsive and had a shorter overall survival (Figure 3B).

Discussion

Recently, several groups have shown that AMC and LMR can be used to identify high-risk patients with lymphomas. Although cut-off values in the various studies were slightly different, similar conclusions were drawn by each group separately, indicating that an elevated monocyte count or lymphopenia at diagnosis has an adverse impact on survival in Hodgkin's lymphoma[17,18,25] and non-Hodgkin's lymphoma.[8-13,23-24]

Lymphopenia is a well-established prognostic marker in advanced Hodgkin's lymphoma and is included in the International Prognostic Score.[25] In non-Hodgkin's lymphoma, lymphocyte counts have mostly been evaluated in T-cell lymphomas and low levels are associated with infe-

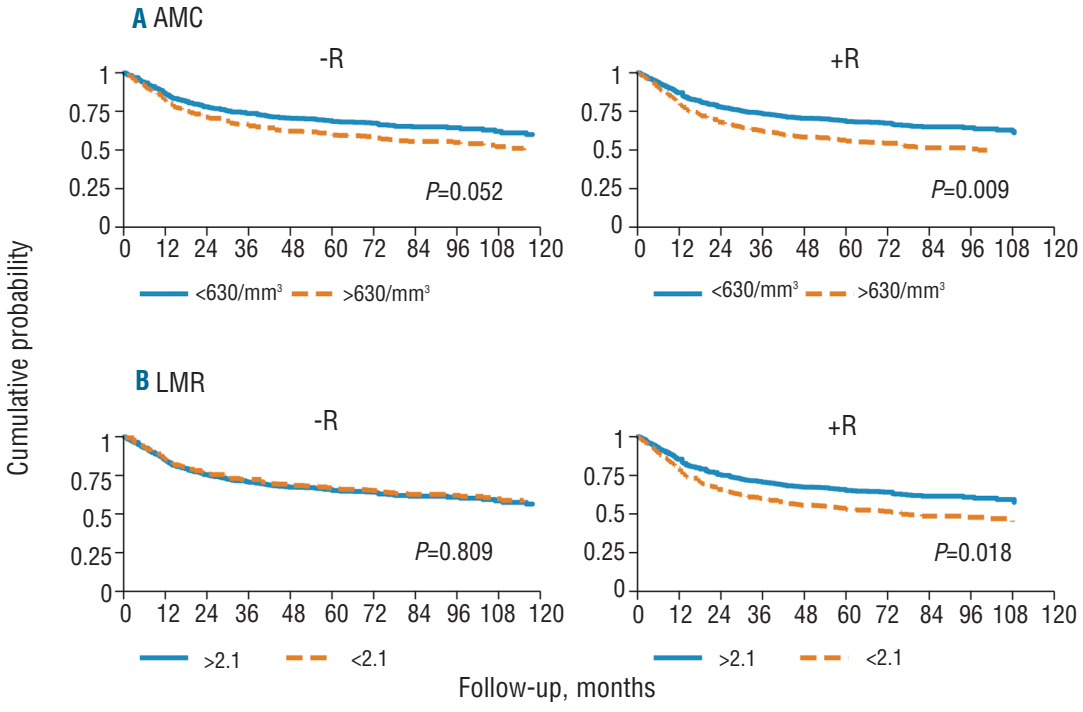

Figure 3. Overall survival estimated for AMC (A) and LMR (B) using Cox proportional hazard regression analysis, after interaction with rituximab as part of the chemotherapy regimen and after adjusting for IPI score. -R: regimens without rituximab; +R: regimens containing rituximab.

rior survival. In Hodgkin's lymphoma, lymphopenia is defined as an ALC ≤600/mm³,[25] while in T-cell lymphoma studies the value generally used was ≤1000/mm³.[23,24] Recently, the significance of lymphopenia was also investigated in patients with DLBCL; Cox *et al.* demonstrated that an ALC <840mm³ at diagnosis has a marked adverse prognostic impact independently of the R-IPI score. They incorporated ALC into the R-IPI creating a new score, the ALC/R-IPI, and showed it to be the most powerful predictor for overall survival.[6] A validation study by Bari *et al.* confirmed these results, but noted that the strong prognostic value of ALC was not evident in patients treated with chemotherapy without rituximab.[26] In our study, an ALC <1000/mm³ was found to correlate with a high IPI score (P<0.001) but was not statistically significant for overall survival in multivariate analysis.

In the present study, we confirmed our earlier results[8,13] obtained in a smaller cohort of patients and verified the results of other study groups.[10-12] Our study has several advantages compared to those reported earlier. It was performed in a large cohort of patients; results were obtained on both a bi-national and multicenter level and not from a single center; finally, we performed a comprehensive analysis to select the best cut-off for AMC, using a wide range of previously proposed values. In our large cohort of patients AMC >630/mm³ had a statistically significant adverse impact on survival after both univariate and multivariate analyses. Our results validate observations that AMC can be used routinely to identify higher-risk patients with worse outcome. Similar results can also be obtained when selecting 800/mm³ as the cut-off for AMC, although this value only stratified 19% of the entire cohort as high-risk patients, compared to 33% when a level >630/mm³ was used. Furthermore, we found that LMR ≤2.1 recognized a subpopulation with worse prognosis.

Another major objective of this study was to validate the prognostic significance of monocytosis and lymphopenia in DLBCL in the rituximab era of chemo-immunotherapy. In our cohort, 521 patients (51%) were treated with chemo-immunotherapy. Our results show that the addition of rituximab to chemotherapy did not abrogate the negative impact of monocytosis on overall survival. Furthermore, AMC was clearly found to have adverse clinical significance in patients treated with rituximab-containing regimens and the AMC identified the high-risk patients in this group even better.

Our study has some obvious limitations, including the fact that it is retrospective and that patients received different anthracycline-containing regimens. Nevertheless it is well established that all regimens induce the same overall response as CHOP,[27] and consequently we feel that this variable has a negligible effect on our results. In conclusion, this study shows that the AMC, used as a single parameter, can identify high-risk patients with DLBCL at the time of diagnosis. Its negative impact on outcome is unaffected by the use of chemo-immunotherapy containing rituximab.

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