MYC rearrangements in HIV-associated large B-cell lymphomas: EUROMYC, a European retrospective study

Chiara Pagani,[1] Chiara Rusconi,[2] Alessia Dalla Pria,[3] Emanuele Ravano,[4] Philipp Schommers,[5] Mariana Bastos-Oreiro,[6] Luisa Verga,[7] Guido Gini,[8] Michele Spina,[9] Luca Arcaini,[10,11] Sara Steffanoni,[12] Davide Dalu,[13] Lara Crucitti,[4] Luisa Lorenzi,[14] Piera Balzarini,[14] Chiara Cattaneo,[1] Lucia Bongiovanni,[15,16] Andreas Rosenwald,[17] Fabio Facchetti,[14] Mark Bower,[3] Andrés J. M. Ferreri,[12,16] Giuseppe Rossi,[1] Alessandra Tucci,[1] and Alessandro Re[1]

[1]Department of Hematology, ASST Spedali Civili di Brescia, Brescia, Italy; [2]Department of Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [3]National Centre for HIV Malignancy, Chelsea and Westminster Hospital, London, United Kingdom; [4]Division of Hematology, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [5]Department of Internal Medicine, Medical Faculty and University Hospital Cologne, University of Cologne, Cologne, Germany; [6]Hematology Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain; [7]Division of Hematology, Azienda Ospedaliera San Gerardo, Monza, Italy; [8]Division of Hematology, Azienda Ospedaliera Universitaria Ospedali Riuniti, Ancona, Italy; [9]Medical Oncology Division, Centro Riferimento Oncologico, Aviano, Italy; [10]Department of Molecular Medicine, University of Pavia, Pavia, Italy; [11]Division of Hematology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [12]Lymphoma Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy; [13]Department of Oncology, Luigi Sacco Hospital, ASST Fatebenefratelli Sacco, Milan, Italy; [14]Pathology Unit, ASST Spedali Civili di Brescia and Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy; [15]Pathology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy; [16]Università Vita-Salute San Raffaele, Milan, Italy; and [17]Institute of Pathology, University of Würzburg, and Comprehensive Cancer Center Mainfranken, Würzburg, Germany

Key Points

- HIV-associated lymphomas with *MYC* rearrangement could be considered for an intensive therapeutic approach.

- Standard (R)CHOP seems to give inferior complete remission rate and PFS in this subset of patients.

Large B-cell lymphoma (LBCL) carrying *MYC* rearrangement, alone or together with *BCL2* and/or *BCL6* translocations, have shown a poor prognosis when treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in the HIV population. Scanty data are available on the prevalence and prognostic impact of *MYC* rearrangements in HIV-associated LBCL. We conducted a retrospective study to evaluate the clinical effect of *MYC* rearrangement in HIV-associated LBCL. We evaluated clinical characteristics, treatment received, and outcome of LBCL in patients with HIV with *MYC* rearrangement (*MYC*+) and without *MYC* rearrangement (*MYC*–). A total of 155 patients with HIV who had received fluorescence in situ hybridization analysis for *MYC* were enrolled in 11 European centers: 43 with *MYC*+ and 112 *MYC*–. Among patients with *MYC*, 10 had double-/triple-hit lymphomas, and 33 had isolated *MYC* rearrangement (single-hit lymphoma). Patients with *MYC*+ had more frequently advanced stage, >2 extranodal site at presentation, and higher proliferative index. There were no significant differences in overall survival and progression-free survival (PFS) between the 2 groups. However, patients with *MYC*+ received more frequently intensive chemotherapy (iCT) (44%) than (R)CHOP alone (35%) or infusional treatment (DA-EPOCH-R and R-CDE) (19%). Among patients with *MYC*+, those who received iCT achieved a better outcome than patients who received nonintensive treatment (complete remission, 84% vs 52%; *P* = .028; 5-year PFS, 66% vs 36%; *P* = .021). Our retrospective results suggest that HIV-associated LBCL with *MYC*+ could be considered for an intensive therapeutic approach whenever possible, whereas (R)CHOP seems to give inferior results in this subset of patients in terms of complete remission and PFS.

Introduction

Diffuse large B-cell lymphomas (DLBCL) and high-grade B-cell lymphomas (HGBCL) are recognized as a group of heterogeneous diseases in the general HIV⁻ population, and *MYC* rearrangement is present in a minority of cases (5%-15%).[1] The presence of concomitant *BCL2* and/or *BCL6* translocation ("double-hit" or "triple-hit" lymphomas [DHL or THL]) is known to confer a worse prognosis to these aggressive B lymphomas when treated with standard therapy.[1,2] Recent data have shown a distinct biology for *MYC* and *BCL6* rearrangement compared with *MYC* and *BCL2*, and the International Consensus Classification of Mature Lymphoid Neoplasms has proposed a specific provisional entity.[3] Some studies suggest that this subtype is even more aggressive and has worse overall survival (OS) than DHL with *BCL2* translocation, whereas other studies indicate a similar or better prognosis. The conflicting conclusion may be the result of a limited sample population.[4,5] Few data are available about the prognosis of *MYC* rearrangement alone ("single-hit" lymphomas [SHL]), and frequently, these lymphomas are analyzed together with DHL/THL. However, most authors have shown a poor prognosis for SHL, mainly in patients treated with standard rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).[6-9]

Patients without HIV with SHL and DHL/THL treated with R-CHOP show a 2-year OS and progression-free survival (PFS) ranging from 28% to 46% and from 15% to 46%, respectively.[10-12] Some authors reported that the immunoglobulin gene as partner of *MYC* translocation confers the shortest survival time,[13] and conflicting data have also been reported for the prognostic role of an increased number of *MYC* copy genes even without its rearrangement.[14,15]

Given the unfavorable prognosis with standard therapies, patients without HIV with DHL/THL are potential candidates for intensive chemotherapy (iCT), and some studies, mainly retrospective, have shown better results with regimens designed to treat Burkitt lymphoma (such as Hyper-CVAD, DA-EPOCH-R, and R-CODOX-M/IVAC) with 2-year OS of 44% to 82% and PFS of 41% to 65%.[12,13,16,17] Consolidative autologous stem cell transplantation (ASCT) may represent a way to pursue, even though in retrospective studies, it was associated with improved OS only in patients who received R-CHOP, and not iCT, as first-line treatment.[12,18,19] However, no prospective controlled studies in SHL and DHL/THL have been reported and a standard treatment has not yet been defined.

In consideration of the peculiar pathogenesis and tumor biology of lymphomas associated with HIV infection, the biological and prognostic features of the HIV⁻ population cannot be directly translated into patients infected with HIV. Indeed, several studies demonstrated different molecular characteristics in DLBCL occurring in patients infected with HIV and in the general HIV⁻ population.[20,21] In a recent study, in HIV-associated DLBCL, treated with EPOCH and vorinostat, Myc protein expression was associated with significantly inferior outcomes.[22] However, data regarding the prevalence and prognostic impact of *MYC*, *BCL2*, and *BCL6* rearrangements, and the overexpression of the respective proteins in patients with HIV infection with lymphoma are few and inconclusive.[23-25] Many questions are still unanswered. Do *MYC* rearrangements matter in HIV-associated large B-cell lymphomas (LBCLs) with or without *BCL2*/*BCL6* translocations? Do SHL and DHL/THL have the same aggressive characteristics and worse outcome compared with LBCL without *MYC* rearrangements as it happens for HIV⁻ population? Do we need "ad hoc" treatment for HIV-associated LBCL with *MYC* rearrangements?

Herein, we report the experience of 11 centers from 4 countries on a series of 155 consecutive cases of HIV-associated LBCL assessed for *MYC* rearrangement, and *BCL2* and *BCL6* translocations. The role, prognostic value, and effect on treatment efficacy of these genetic abnormalities were addressed in this setting, and patients' characteristics, treatment received, and outcome were analyzed and compared with those of patients not carrying *MYC* rearrangement.

Materials and methods

Study design

We conducted a multicentric retrospective study involving 11 centers from 4 countries to evaluate the impact of *MYC* rearrangements (isolated or with *BCL2* and/or *BCL6* translocations) on clinical features and outcome of HIV-associated LBCL. Eligibility included age >17 years and a confirmed histological diagnosis of HGBCL NOS, DLBCL NOS, and HGBCL DHL/THL according to the 2017 World Health Organization classification, with fluorescence in situ hybridization (FISH) data available for *MYC*, *BCL2*, and *BCL6*.

This study was approved by the institutional review boards of participating centers and conducted in accordance with the Declaration of Helsinki.

The collected clinical data included: sex, age, Ann Arbor stage, LDH, number and type of involved extranodal sites, performance status according to the Eastern Cooperative Oncology Group (ECOG) at baseline, International prognostic index (IPI), histological subtype, FISH analysis, EBV-encoded RNA expression, immunohistochemistry results for Myc, Bcl2, and ki67 percentage, cell of origin (COO) according to Hans algorithm,[26] baseline CD4 count and HIV viral load, date of HIV diagnosis, history of AIDS defining events before lymphoma, antiretroviral therapy (cART) use, hepatitis B virus and hepatitis C virus infections, type of CT used as first-line treatment, date of last follow-up (or date of death), status of disease at last follow-up, survival status, cause of death, relapse status and type and date of relapse if any, and salvage treatment received and response.

Double expressor lymphoma (DEL) was defined as overexpression by immunohistochemical staining of Myc and Bcl2 proteins, using cutoffs of 40% and 50%, respectively.[1]

All histological samples were analyzed by expert pathologists and reviewed to be classified according to the 2017 World Health Organization classification, whenever necessary.[1]

The main objectives of the study were to evaluate the baseline clinical characteristics, treatment received, and outcome of patients with LBCL and *MYC* rearrangement, evaluated by FISH analysis, comparing these results with those of patients with LBCL without *MYC* alteration. We also evaluated separately the outcome of the DHL/THL subgroup.

Outcome assessment and statistics

Disease response was defined by the revised response criteria for malignant lymphoma.[27]

PFS was defined as the interval between diagnosis and disease progression, last follow-up in remission, or death from any cause; and OS was defined as the interval between diagnosis and death or last follow-up while alive. Baseline characteristics are described as median and range for quantitative variables and as numbers and percentage for categorical variables. Categorical data were analyzed by Fisher exact test and χ^2 test and continuous variables by the Wilcoxon–Mann-Whitney test. Survival curves were plotted in accordance with the Kaplan-Meier method and were compared using the log-rank test. The Cox proportional hazard model was used for univariable and multivariable survival analyses. Statistical significance was set at P <.05 (2-sided). Statistical analyses were performed using the SPSS statistical package (version 22.0 for Windows; IBM).

Results

Clinical characteristics

A total of 155 consecutive patients were included. They were diagnosed between May 2000 and January 2020. Forty-three patients (28%) had *MYC* rearrangements (*MYC*+), and 112 patients (72%) were negative for *MYC* rearrangements (*MYC*−). Seven patients had *MYC* increased copy number/amplification in the absence of rearrangement and were included in *MYC*− group. One hundred and twenty-nine patients had DLBCL NOS; 16 HGBCL NOS; and 10 HGBCL DHL/THL. Table 1 shows the clinical characteristics of patients at diagnosis. There were no significant differences between the 2 groups (*MYC*+ and *MYC*−) with respect to most demographic and clinical characteristics, including CD4 count (median, 200; range, 8-1170 cells/mcL for the entire series), presence of detectable HIV viremia, PS, LDH, and IPI risk group. Forty-four patients had a diagnosis of HIV and lymphoma concomitantly. A previous diagnosis of AIDS was more frequent in the *MYC*− group (27% vs 12%; P = .054). Patients with *MYC*+ had more frequently advanced stage (93% vs 80%; P = .05) and the involvement of >2 extranodal sites (50% vs 32%; P = .05) and of central nervous system (CNS) at presentation (14% vs 3%; P = .052). Patients with DHL/THL showed similar clinical characteristics compared with those with SHL (data not shown), other than more frequent AIDS diagnosis before lymphoma onset (33% vs 6%; P = .028).

Histopathological characteristics

The main histological features of the *MYC*+ and *MYC*− lymphomas are shown in Table 2. Patients with *MYC*+ had more frequent translocation of *BCL2* (14% vs 3%; P = .019), germinal center B phenotype according to Hans algorithm (87% vs 49%; P = .0001), and a higher median proliferative index (median Ki-67, 91% vs 85%; P = .012). There were no significant differences between the 2 groups with respect to the number of DEL and incidence of EBV-encoded RNA positivity. Among patients with *MYC*+, 10 (23%) had HGBCL DHL/THL, and 33 (77%) had SHL (25 within the DLBCL NOS and 8 within the HGBCL NOS). Of note, SHL had a significantly higher proliferative index than DHL/THL (median ki67, 95% [range, 60%-100%] vs 80% [range, 60%-100%]; P = .003).

Table 1. Clinical characteristics of 2 groups of HIV-associated aggressive B lymphomas with or without *MYC* rearrangement

	Patients with *MYC*+, n = 43	Patients with *MYC*−, n = 112	Total, N = 155	*P* value
Median age (range), y	46 (26-74)	48 (23-83)	47 (23-83)	ns
Age >60 y	7 (16%)	14 (12%)	21 (14%)	ns
Male sex	37 (86%)	88 (79%)	125 (81%)	ns
Stage III-IV	40/43 (93%)	88/110* (80%)	128/155 (82%)	.05
B symptoms	22/43 (51%)	55/108* (51%)	77/151* (51%)	ns
Increased LDH	30/39* (77%)	70/104* (67%)	100/143* (70%)	ns
Extranodal sites				.05
≤ 2	19/38* (50%)	68/100* (68%)	87/138* (63%)	
> 2	19/38* (50%)	32/100* (32%)	51/138* (37%)	
CNS involvement	4/29* (14%)	2/64* (3%)	6/93* (6%)	.052
Kidney/adrenal gland involvement	8/29* (27%)	8/64* (12%)	16/93* (17%)	.074
ECOG performance status ≥2	19/34* (56%)	42/87* (48%)	61/121* (50%)	ns
IPI intermediate high-high	23/39* (64%)	49/92* (53%)	72/131* (55%)	ns
HCV seropositivity	11/38* (29%)	34/93* (36%)	45/131* (34%)	ns
Positive HBsAg	3/36* (8%)	8/89* (9%)	11/125* (9%)	ns
Median CD4+ cell baseline (range), n/mmc	215 (32-1170)	198 (8-990)	198 (8-1170)	ns
CD4+ cell <200/mmc	19/38* (50%)	51/100* (51%)	70/138* (51%)	ns
Detectable HIV load	24/40* (60%)	65/107* (61%)	89/147* (60%)	ns
AIDS before lymphoma diagnosis	5/41* (12%)	30/111* (27%)	35/152* (23%)	.054
cART before lymphoma diagnosis	20/42* (48%)	62/110* (56%)	32/152* (54%)	ns

HCV, Hepatitis C Virus; HBsAg, Hepatitis B surface antigen; ns, not significant.
*Denominators regard assessed patients.

Table 2. Histopathological characteristics of 2 groups of HIV-associated aggressive B lymphomas with or without *MYC* rearrangement

	Patients with *MYC*+ n = 43	Patients with *MYC*− n = 112	Total N = 155	*P* value
Histology				
DLBCL NOS	25 (58%)	104 (93%)	129 (83%)	.0001
HGBCL NOS	8 (19%)	8 (7%)	16 (10%)	.036
HGBCL DH-TH	10 (23%)	0	10 (7%)	-
Median Ki67% (range)	91 (40-100)	85 (40-100)	90 (40-100)	.012
Ki67 ≥90%	25/38* (66%)	38/83* (46%)	63/121* (52%)	.041
DEL†	15/39* (38%)	27/95* (28%)	42/134* (31%)	ns
BCL2 translocation	6/43 (14%)	3/93* (3%)	9/136* (7%)	.019
BCL6 translocation	7/40*‡ (17%)	25/91* (27%)	32/131* (24%)	ns
EBV−encoded RNA positive	3/14* (21%)	17/52* (33%)	20/66* (30%)	ns
COO GCB	25/32* (87%)	45/91* (49%)	73/123* (59%)	.0001
COO non-GCB	5/32* (16%)	46/91* (51%)	51/123* (41%)	

EBV, Epstein-Barr virus; GCB, germinal center B; HGBCL DH-TH, high-grade B-cell lymphoma "double or triple hit"; ns, not significant.
*Denominators regard assessed patients.
†The double expression was considered in the entire series (DLBCL NOS; HGBCL NOS; and HGBCL DH-TH).
‡In 3 patients with HGBCL DH-TH, *BCL6* translocation was not available.

Among the 104 patients with *MYC*− DLBCL NOS, only 3% had *BCL2* rearrangement, whereas 27% had *BCL6* rearrangement.

Treatment

The treatment received by the 2 groups (*MYC*+ and *MYC*−) is reported in Table 3. In the *MYC*+ group, 44% of patients received iCT (GMALL, CODOX IVAC, CARMEN regimen,[28] standard CT followed by ASCT as consolidation, and others), 35% received (R)CHOP or (R)CHOP-like regimens, 19% infusional therapy (R-DA-EPOCH, R-CDE), and 2% supportive care. In the *MYC*− group, 68% received (R)CHOP or (R)CHOP-like regimens, 20% iCT, 8% infusional therapy, and 3% supportive care. Therefore, patients with *MYC*+ received more frequently iCT (*P* = .003) and less often (R)CHOP regimen (*P* = .0001) than the *MYC*− group. In all series, patients with ki67 percentage >90% received more frequently iCT than patients with ki67 <90% (25/63 [39%] vs 9/58 [15%]; *P* = .003).

Table 3. Treatment received in 2 groups of HIV−associated aggressive B lymphomas with or without *MYC* rearrangement
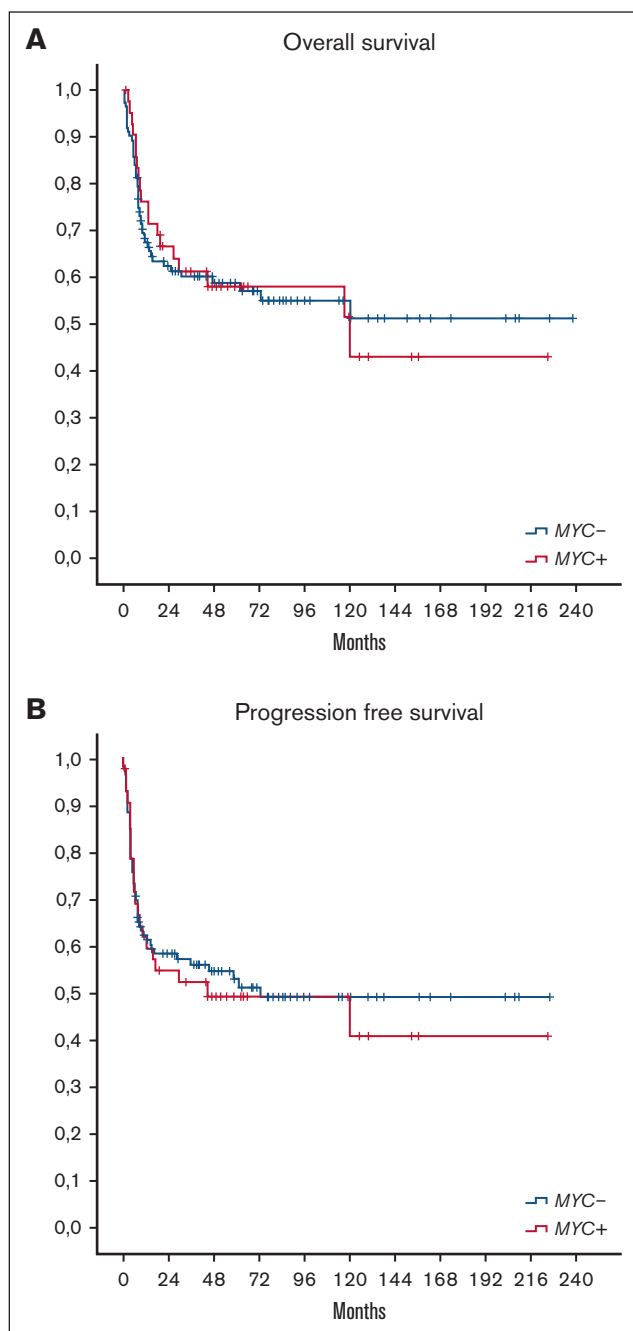
	Patients with *MYC*+ n = 43	Patients with *MYC*− n = 112	Total N = 155	*P* value
Rituximab	41 (95%)	99 (88%)	140 (90%)	ns
CHOP/CHOP-like	15 (35%)	76 (68%)	91 (59%)	.0001
Infusional therapy	8 (19%)	9 (8%)	17 (11%)	.063
DA-EPOCH	6	6	12	
CDE	2	3	5	
iCT	19 (44%)	23 (20%)	42 (27%)	.003
CARMEN Regimen[28]	9	1	10	
GMALL	3	2	5	
CODOX IVAC	2	1	3	
CT* + ASCT consolidation	3	15	18	
Other†	2	4	6	
Palliative care	1 (2%)	4 (3%)	5 (3%)	ns
CNS prophylaxis	32/37‡ (86%)	62/94‡ (66%)	94/131‡ (72%)	.011
IT (MTX ± ARA-C)	24	55	79	
Iv MTX ± IT	8	7	15	
Radiotherapy	2 (5%)	9 (8%)	11 (7%)	ns

IT, intrathecal; ns, not significant.
*Mainly CHOP regimen.
†Other terapies included HD MTX plus HD ARAC, as well as stanford regimen for Burkitt.
‡Denominators regard assessed patients.

Figure 1. **OS and PFS according to *MYC* status.** OS (A) and PFS (B) of patients with *MYC*+ and those with *MYC*– (*P* not significant).

Rituximab was administered in 95%, 100%, and 88% of patients treated with (R)CHOP or (R)CHOP-like regimens, infusional therapy, and iCT, respectively.

Of the 10 patients with DHL/THL, 30% received (R)CHOP or (R)CHOP-like regimens, 30% received infusional therapy, 30% iCT, and 10% palliative care. Of the 33 patients with SHL, 36% received (R)CHOP ore (R)CHOP-like, 15% infusional therapy, and 49% iCT. All patients received cART during lymphoma treatment.

Clinical outcome

In the *MYC*+ group, 42 of 43 patients were evaluable for response (1 patient received palliative care). Twenty-eight patients (66%) achieved a complete remission (CR), 2 (5%) a partial remission (PR), and 12 (28%) no response or progressive disease. CR rate was 53% in patients who received (R)CHOP or (R)CHOP-like regimens, 50% in patients who received infusional therapy, and 84% in patients who received iCT (iCT vs [R]CHOP; *P* = .05; iCT vs other treatments; *P* = .028). In the *MYC*– group, 102 of 112 patients were evaluable for response (10 patients had an early death or received palliative care). Seventy-one patients (70%) achieved a CR, 10 (10%) a PR, and 21 (20%) no response or progressive disease. CR was 69%, 78%, and 65% in patients treated with (R)CHOP or (R)CHOP-like regimens, infusional therapy, and iCT, respectively (*P* = not significant).

After a median follow-up of 57 months (range, 1-238) in all populations, including 58 months in the *MYC*+ group and 53 months in the *MYC*– group, there were no significant differences in OS and PFS between patients with *MYC*+ and patients with *MYC*–, respectively (5-year OS and PFS, 58% and 49% in patients with *MYC*+, respectively, and 59% and 53% in patients with *MYC*–; as shown in Figure 1). In *MYC*+ group, 19 of 43 patients (44%) died (15 patients [35%] due to lymphoma progression, 1 [2%] to HIV complications, 2 [4%] to other cancers, and 1 [2%] from unknown cause). In *MYC*– group, 47 of 112 patients (42%) died (29 patients [26%] due to lymphoma progression, 6 [5%] to treatment toxicities [all patients had received [R]CHOP or [R]CHOP-like regimens], 3 [3%] to HIV complications, 1 [1%] to a second malignancy, and 8 [7%] from other causes). The main cause of death was progressive disease for both groups. Of note, no patient treated with iCT died due to treatment toxicity. Patients with relapsed/refractory disease had a little chance to be salvaged with second-line therapy. Of 53 patients with documented disease progression, 12 and 26 patients received salvage treatment in the *MYC*+ and *MYC*– groups, followed by ASCT consolidation in 4 and 8 patients, respectively. Only 3 and 6 patients achieved a second CR in *MYC*+ and *MYC*– groups, respectively.

No difference in OS was seen between SHL and DHL/THL (5-year OS, 61% vs 50%; *P* = .145), whereas PFS was better in SHL vs DHL/THL (55% vs 30%; *P* = .045) (Figure 2).

In the *MYC*+ group, 5-year PFS and OS were 65% and 66% with iCT, 37% and 47% with infusional therapy, and 37% and 57% with (R)CHOP, respectively. The use of iCT correlated with significantly better PFS than with other treatments (*P* = .021) and with a trend toward better OS (*P* = .19) (Figure 3). Although iCT maintained a statistically significant advantage in PFS vs (R)CHOP treatment (*P* = .025), no statistically significant difference in survival was registered between patients receiving iCT and the low number of patients receiving infusional therapy.

In patients with *MYC*–, there were no significant differences in OS and PFS according to the different treatments received.

Analyzing the homogeneous group of patients with DLBCL treated with nonintensive regimens ([R]CHOP or [R]CHOP-like regimens) a nonstatistically significant better outcome was reported in patients with *MYC*– than those with *MYC*+, with a 5-year PFS of 52% and 36% (*P* = .3), respectively.
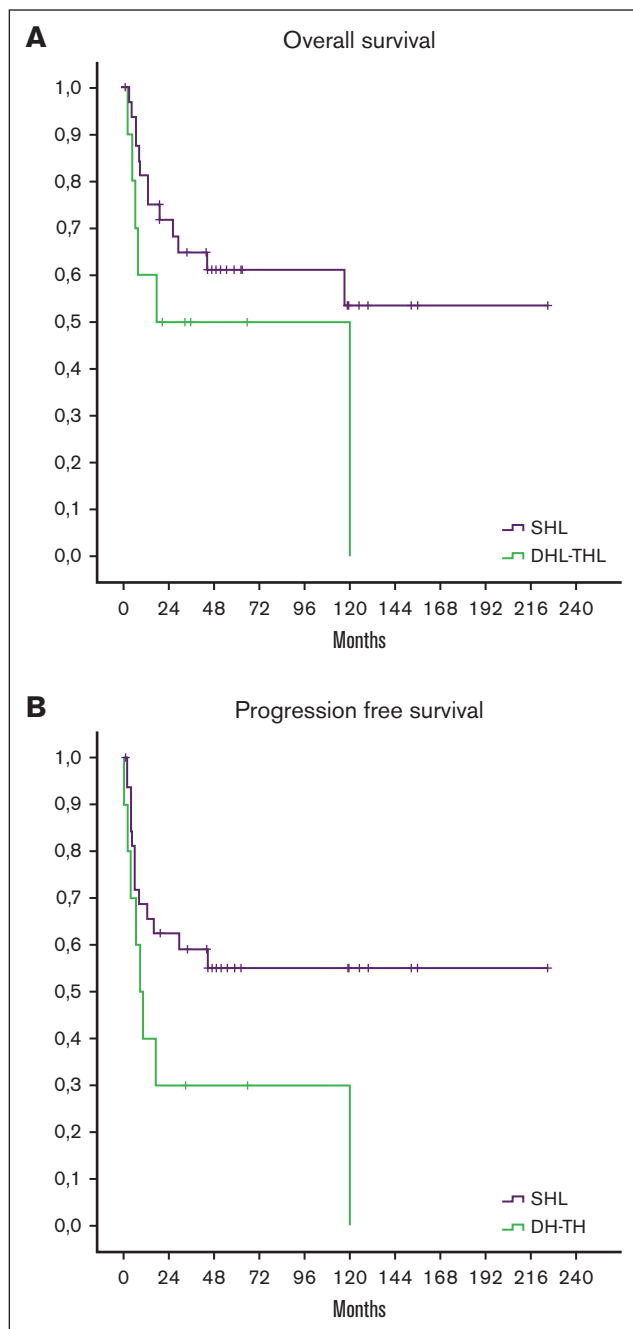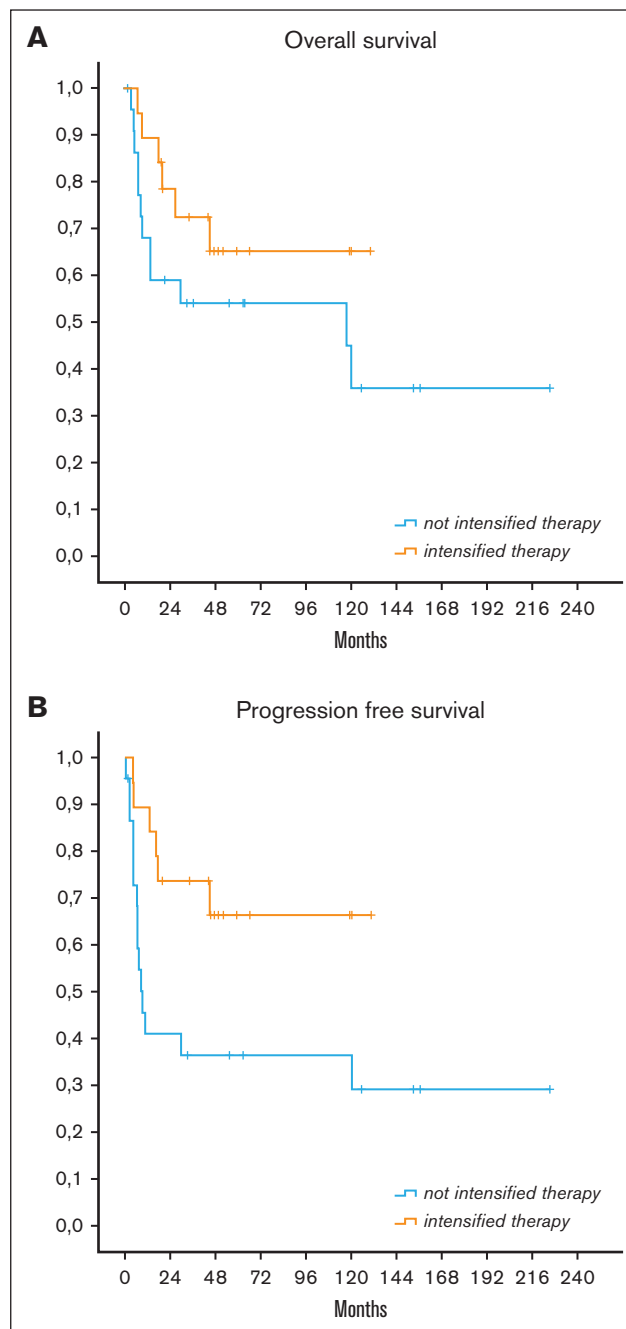
Figure 2. OS and PFS in SHL and DHL-THL lymphoma. OS (A) and PFS (B) of "single-hit" and "double-triple hit" lymphomas ($P = .145$ for OS; and $P = .045$ for PFS between 2 groups).

Figure 3. OS and PFS in patients with _MYC_+ according to treatment received. OS (A) and PFS (B) according to treatment received in _MYC_+ group ($P = .021$ for PFS between intensified and not intensified therapy; P was not significant for OS).

Considering only DEL, there were no significant differences in OS and PFS in patients who received (R)CHOP or (R)CHOP-like therapy or iCT.

Prognostic factors

In the univariate analysis of the whole population (n = 155), IPI ≥3, ECOG performance status ≥2, and increased LDH were related to worse OS and PFS, whereas _BCL2_ translocation and DHL/THL were correlated with shorter PFS and ki67 >90% with better PFS.

Ann Arbor stage III-IV predicted a worse OS and PFS, even if not statistically significant; ki67>90% predicted a better OS, B symptoms a worse OS, and _BCL6_ translocation a worse PFS. Major prognostic factors, including those with significant or borderline impact on survival and those with a major clinical impact are reported in Table 4. In the multivariate analysis, ECOG performance status ≥2 and elevated LDH maintained their negative prognostic impact on OS and PFS, ki67 >90% was related to a

Table 4. Univariate analysis for OS and PFS of the entire population of 155 patients

Variable	n	OS				PFS			
		Median, mo	IC 95%	% 5y	*P*	Median, mo	IC 95%	% 5y	*P* value
Age, y									
≤50	102	120	42-198	55	.26	46	0-124	47	.115
>50	53	NR	-	65		NR	-	61	
Stage									
III-IV	128	120	42-192	54	.054	46	1-90	48	.057
Not III-IV	27	NR	-	77		NR	-	70	
B symptoms	77	120	0-265	52	.095	36	0-114	47	.173
Not B symptoms	78	NR	-	64		NR	-	57	
ECOG performance status not									
≥2	94	NR	-	72	.0001	NR	-	63	.0001
≥2	61	13	4-23	38		8	3-13	34	
Not increased LDH	55	NR	-	81	.002	NR	-	70	.002
Increased LDH	100	31	-	46		15	0-40	42	
IPI									
Not int. high-high	83	NR	-	69	.012	NR	-	59	.027
Int. high-high	72	31	0-84	47		13	0-47	43	
CD4 <200/uL	70	73	0-155	51	.13	46	0-102	47	.357
Not CD4 <200/uL	85	NR	-	64		NR	-	56	
Ki67 ≥90%	63	NR	-	65	.058	NR	-	64	.007
Not Ki67 ≥90%	92	117	35-200	53		16	0-42	43	
MYC+	43	120	12-228	58	.942	50	0-143	49	.712
MYC−	112	NR	-	59		NR	-	53	
BCL2 rearranged	9	18	0-45	44	.37	9	5-13	0	.016
Not *BCL2* rearranged	146	120	-	59		NR	-	55	
BCL6 rearranged	32	120	0-270	52	.226	10	0-58	39	.089
Not *BCL6* rearranged	123	NR	-	60		NR	-	56	
DHL or THL									
Yes	10	18	0-76	50	.217	9	3-15	30	.048
No	145	NR	-	59		NR	-	53	
iCT									
Yes	42	NR	-	59	.297	NR	-	57	.181
No	113	120	62-178	58		59	0-135	50	

Only those parameters that achieved statistical or borderline significance on at least 1 end point or parameters with clinical relevance are listed.
DHL or THL, double-hit or triple-hit lymphoma; NR, not reached.

better OS and PFS, and *BCL6* translocation to a worse PFS (Table 5). COO did not have a prognostic impact on survival, as did the double expression of Myc and Bcl2.

Discussion

MYC gene rearrangements are usually recorded in 5% to 15% of HIV− DLBCL,[8,10] whereas old studies analyzing the pathogenesis of HIV-associated lymphoma in the pre-cART era reported this genetic abnormality in ~20% of AIDS-related diffuse large cell lymphomas.[29] However, no data on *BCL2* and *BCL6* translocations were reported in this subgroup of patients, and the potential prognostic value of *MYC* translocations was not investigated. In the more recent cART era, only few data are available on

the incidence, clinical characteristics, and outcome of SHL and DHL/THL in the setting of HIV.[22-25] Our study aims to analyze HIV-associated BCL, comparing those with or without *MYC* genetic alteration, associated or not to *BCL2* and *BCL6* translocations, from clinical presentation to treatment choice and survival outcome, to add knowledge in a field with really scanty information.

In our series, 28% of patients had *MYC* rearrangement. The only significant clinical differences between *MYC*+ and *MYC*− groups were a more frequent involvement of >2 extranodal sites and advanced stage in the *MYC*+ group and a more common previous diagnosis of AIDS in the *MYC*− group. Patients with *MYC*+ also tend to have more often CNS localization at onset. As already reported in the HIV-negative setting, patients with *MYC*+ had

Table 5. Multivariate analysis for OS and PFS of the entire population of 155 patients

	Hazard ratio	95% confidence interval	*P* value
OS			
ECOG PS ≥2	2.8	1.4-5.6	.003
Increased LDH	2.2	1.1-4.1	.018
Ki67>90%	0.56	0.3-0.96	.035
PFS			
ECOG PS ≥2	2.9	1.5-5.7	.002
Increased LDH	2.4	1.3-4.4	.006
Ki67>90%	0.5	0.3-0.9	.014
BCL6 rearranged	2	1.1-3.6	.018

significantly more frequent germinal center B phenotype. Moreover, higher ki67 percentage and more frequent translocation of *BCL2* were found in the patients with *MYC*+. As a result, we could not find clinicopathological factors able to adequately discriminate patients who deserve to investigate the presence of *MYC* translocation, which appears advisable in all patients with aggressive HIV+ LBCL.

Of note in DLBCL cases, the frequency of *BCL6* rearrangement (21%) was similar to those described in patients without HIV infection, whereas *BCL2* rearrangement was infrequent (2.6%), with an incidence substantially lower than that reported in immunocompetent patients, in line with the study of Baptista et al.[25]

In our retrospective series, the clinical outcome of patients with *MYC*+ was not significantly different compared with patients with *MYC*−, but the different performed treatment among the 2 groups of patients could be a bias of final results. Patients with *MYC*+ more frequently received iCT (including intensive CT schedules and high dose CT with ASCT consolidation after standard (R) CHOP) than patients with *MYC*−. This choice was probably a consequence of the analogous translocation (*MYC*) that characterizes the Burkitt lymphoma and of the experience in the HIV-negative setting. Indeed, in our series, the use of iCT demonstrated to confer a better outcome than other treatments and standard (R)CHOP, particularly in the *MYC*+ group. On the other hand (R)CHOP seems to better perform in patients with *MYC*−. This appears in line with results of retrospective studies in patients without HIV[12,13,18,19] and underlines the role of intensive first-line treatment in this subset of LBCL. Moreover, because patients with *MYC* rearrangements had a higher incidence of CNS involvement, diagnostic lumbar puncture and CNS prophylaxis is highly recommended in this group of patients. Notably, no patients treated with iCT died from toxicity in our study. The main cause of death remains lymphoma for both patients with *MYC*+ and those with *MYC*−.

Although DA-EPOCH-R is associated with durable remissions in HIV-negative *MYC*+ aggressive B-cell lymphomas and should be considered for the treatment of these diseases,[16] we were not able to confirm its favorable outcome in the HIV-positive setting, maybe due to low number of patients treated with infusional therapy in our series, and no firm conclusion can be drawn.

Only 10 of our patients were diagnosed with DHL/THL; however, they showed a particularly poor outcome, despite most patients receiving iCT or infusional therapies, thus, confirming what is known from the experience in the HIV-negative setting.

In our series, in the *MYC*+ group, 2-year OS and PFS were 57% and 36% in patients treated with (R)CHOP/CHOP-like regimens, respectively, and 79% and 74% in patients treated with iCT.

These results compare favorably with those reported on SHL and DHL/THL in patients without HIV, in which 2-year OS and PFS ranged from 28% to 46% and 15% to 46%, respectively, for patients treated with (R)CHOP/CHOP-like regimens and 44% to 82% and 41% to 65% for patients treated with iCT.[10-13,16,17]

Some other information may come from our study. The frequency of DEL in the entire series was similar between the 2 groups (38% in *MYC*+ and 28% in *MYC*−) and did not confer different prognosis, in contrast to what has been reported in several studies on HIV-negative lymphoma.[30] Although the role of COO has a recognized impact on the outcome of lymphomas of the general population, in our study there was no impact of COO on survival. However, conflicting results are reported in previous studies in the HIV setting.[31,32] In our series, by multivariate analysis, higher PS and increased LDH correlated with worse survival, whereas ki67 >90% resulted to be a prognostic factor of better survival. The predictive positive role of elevated proliferation index had been demonstrated also in a previous study,[31] suggesting an increased chemosensitivity in this subgroup.

This study has several limitations that underpowered the conclusions: its retrospective design, some missing data, low numbers for single subgroups, and the wide time period of patient enrollment. Considering the retrospective and multicentric design of this study, the patients were treated based on the choice of the treating physician, and likely, the more aggressive lymphomas received the more aggressive therapy, leading to better outcomes with iCT. The strength of this study relies in the high number of patients with FISH available for *MYC* abnormalities and the comparison with *MYC*− lymphomas, as well as the ability to describe a real-world series of non-Burkitt *MYC* rearranged HIV+ LBCL, in a setting in which data are very rare. Anyway, we are conscious that prospective studies are needed to draw definitive and more useful conclusions.

Based on our data, it could be reasonable to treat patients with HIV infection with *MYC*+ with iCT schedules, usually used for Burkitt lymphoma, or with ASCT consolidation after induction therapy, at least in fit and young patients with a good control of HIV infection from cART. Due to the encouraging results obtained in patients with *MYC*+ with DA-EPOCH-R in the HIV-negative setting, we think it remains however reasonable to apply the same strategy in patients with HIV infection.[16] However, our data regarding this treatment do not help due to the low number of patients.

Because lymphoma progression remains the major cause of death in these patients and patients with relapsed and refractory have few chances to be cured even with ASCT, a better knowledge of the pathogenetic mechanisms of these diseases could help improving the therapeutic approach also in terms of target

therapies.[33] Nowadays, combination of targeted or immunomodulators drugs with standard CT are being evaluated in patients without HIV infection. If effective, they hopefully will be used also in patients with HIV infection who are usually excluded from experimental clinical trial.

Interestingly, recent studies, using gene expression profiling, developed signatures derived from genes differentially expressed between DHL and non-DHL DLBCL.[34,35] Notably, this signature could identify most DHL even among patients with DLBCL who did not harbor gene rearrangements of *MYC* and *BCL2,* suggesting the existence of alternative genetic or epigenetic alterations causing a high-grade lymphoma phenotype.

In the meantime, a FISH analysis for *MYC* and, if positive, also for *BCL2* and *BCL6* is advisable for all aggressive BCL in patients with HIV infection. All patients with *MYC*+ BCLs might be considered for an intensive therapeutic approach whenever possible because (R)CHOP seems to give inferior results in these patients. A diagnostic intrathecal puncture and CNS prophylaxis are also highly recommended.

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Authorship

Contribution: A. Re. designed the research study; C.P., A. Re., and C.R. designed and completed the database; C.P. conducted the statistical analysis; C.P., A. Re., and A.D.P. were involved in data analysis and interpretation; C.P., C.R., A.D.P., E.R., P.S., M.B-O., L.V., G.G., M.S., L.A., S.S., D.D., L.C., L.L., P.B., C.C., M.B., F.F., L.B., A. Rosenwald., A.J.M.F., G.R., A.T., and A. Re registered and treated patients, collected clinical data, and performed histological, molecular, and phenotypical analysis; and all authors reviewed and approved the manuscript.

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ORCID profiles: P.S., 0000-0003-3375-6800; D.D., 0000-0002-8017-2149; L.L., 0000-0003-2483-2955; C.C., 0000-0003-0031-3237; M.B., 0000-0002-4077-6351; A.J.M.F., 0000-0001-9606-6124; A.T., 0000-0003-3052-7463; A.R., 0000-0003-1156-6395.

Correspondence: Chiara Pagani, Department of Hematology, ASST Spedali Civili di Brescia, Piazzale Spedali Civili 1, 25123 Brescia, Italy; email: chiara.pagani@asst-spedalicivili.it.

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