ALK-positive anaplastic large-cell lymphoma in adults: an individual patient data pooled analysis of 263 patients

Anaplastic lymphoma kinase (ALK)-positive anaplastic large-cell lymphoma (ALCL) comprises 0.5% of adult lymphomas.[1] In many prior retrospective adult series, despite clear differences in outcome, ALK-positive ALCL has been pooled with ALK-negative ALCL, impairing the exploration of prognostic factors and impact of different treatments for ALK-positive ALCL.[2–8]

Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)/CHOP-like regimen remains the standard treatment of ALK-positive ALCL, with a 5-year overall survival (OS) rate of 70-90%.[9] Most patients are young (median age 35 years) with some studies suggesting this is the predominant reason outcomes are generally more favorable than in ALK-negative ALCL.[3,6]

A retrospective study from the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL) and a population-based study from the Danish and Swedish lymphoma registries suggested a possible benefit from the integration of etoposide in the front-line therapy, but definitive conclusions are lacking, and the role of etoposide is still a matter of debate.[5,10]

Herein, we conducted a pooled analysis of individual patient data (IPD) from six studies of first-line therapy in adult ALK-positive ALCL to identify the key prognostic factors and treatment impact. IPD were collected and pooled from six previously published studies: two from the Lymphoma Study Association (LYSA),[4,6] one from the DSHNHL,[5] one from Japan,[2] one from the International Peripheral T-Cell Lymphoma Project (IPTCLP),[3] and one from the Mayo Clinic.[7] Patients recruited to the six studies met criteria for diagnosis of ALK-positive ALCL by the REAL (The Revised European American Lymphoma Classification)/World Health Organization classification[11,12] with a centralized pathologic review. Eligibility criteria and statistical analyses are available in the *Online Supplementary Methods*.

In total, there were 263 patients diagnosed between 1985 and 2008, 136 (52%) of which had been enrolled in clinical trials (*Online Supplementary Table S1*). Given the small number of patients included from one of the LYSA studies (n=10) and from the Mayo Clinic (n=9), the six studies were subsequently grouped in four cohorts (LYSA [two studies]), DSHNHL, Japan and [IPTCLP+Mayo Clinic]). Table 1 lists the main clinical, biologic and immunohistochemical characteristics. The median follow-up was 4.9 years (range, 0.1 to 20.4 years). The treatment details are available in the *Online Supplementary Table S2*.

For the 255 patients evaluable for a response at the end of treatment, the reported CR/CRu, PR and SD/PD (complete response (CR), unconfirmed CR (CRu), partial response (PR), stable disease (SD), or progressive disease (PD)) rates to the first-line therapy were 85%, 5% and 10%, respectively.

For all 263 patients, the 5-year progression-free survival (PFS) and OS rates were 69% (95% CI, 64% to 75%) and 81% (95% CI, 76% to 86%), respectively (*Online Supplementary Figure S1*). Importantly, the PFS was not significantly different between cohorts (5-year PFS from 60% to 76%, *P*=0.110).

For patients >60 years (n=31, 11.8%), compared to those ≤60 years (n=232, 88.2%), 5-year PFS (55% *vs.* 71%, *P*<0.01, hazard ratio (HR) 2.077) and OS (64% *vs.* 83%, *P*<0.001, HR 3.041) rates were inferior (Figure 1 A-B) (*Online Supplementary Table S3*).

All individual international prognostic index (IPI) factors significantly affected the PFS and OS rates, with the number of extranodal sites >1 conferring the highest risk and with no significant heterogeneity between cohorts (*Online Supplementary Figure S2*).

In a multivariate analysis, only the number of extranodal sites >1 and age >60 years impacted the PFS and OS rates (*Online Supplementary Table S4*), and finally, the IPI score had a better predictive value for the OS than the prognostic index for peripheral T-cell lymphoma, not oth-

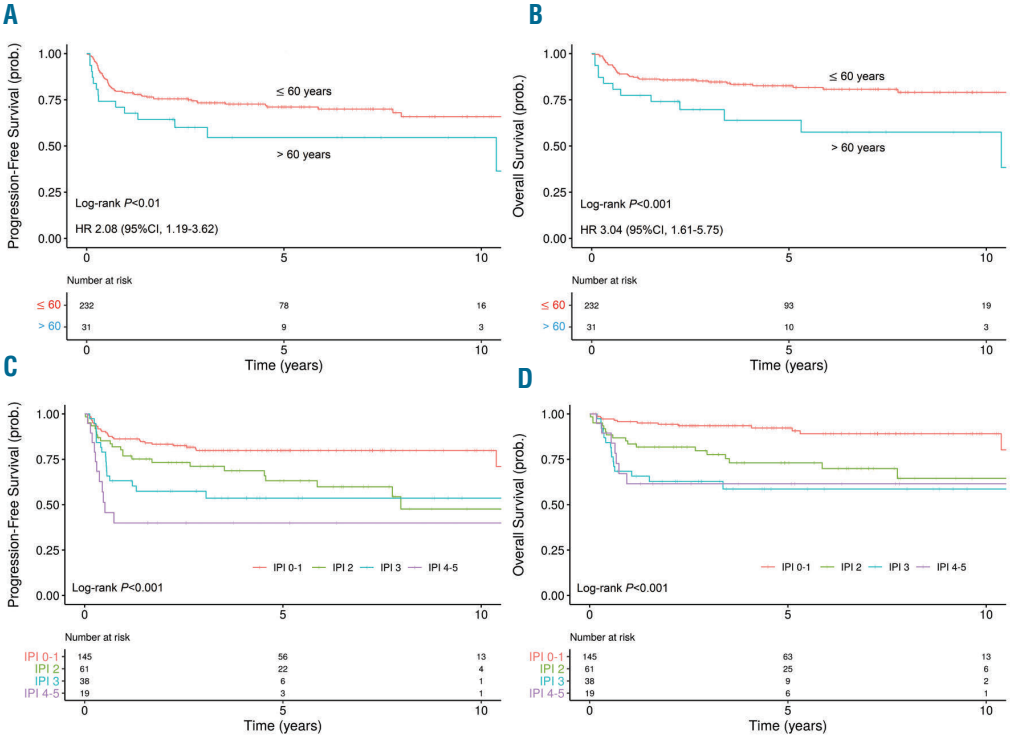

Figure 1. Survival according to age and international prognostic index (IPI). (A) Progression-free survival (PFS) and (B) overall survival (OS) of the 263 patients according to age. (C) PFS and (D) OS according to IPI.

Table 1. Demographics and clinical characteristics of adults with systemic ALK-positive ALCL.

Characteristic	All patients	No etoposide during induction, n (%)	Etoposide during induction, n (%)	P
No. of patients	263	171	92	
Study				<0.0001
LYSA-1	48 (18.3)	48 (28.1)	0	
LYSA-2	10 (3.8)	3 (1.8)	7 (7.6)	
DSHNHL	78 (29.7)	21 (12.3)	57 (62)	
Japan	44 (16.7)	37 (21.6)	7 (7.6)	
IPTCLP	74 (28.1)	54 (31.6)	20 (21.7)	
Mayo Clinic	9 (3.4)	8 (4.7)	1 (1.1)	
Cohort				<0.0001
LYSA	58 (22.1)	51 (29.8)	7 (7.6)	
DSHNHL	78 (29.7)	21 (12.3)	57 (62)	
Japan	44 (16.7)	37 (21.6)	7 (7.6)	
IPTCLP-Mayo Clinic	83 (31.6)	62 (36.3)	21 (22.8)	
Age				
Median (years)	34	34	35	0.978
Range (years)	18-76	18-76	19-71	
≤ 60 years	232 (88.2)	146 (85.4)	86 (93.5)	0.082
Male sex	159 (60.5)	100 (58.5)	59 (64.1)	0.446
Performance status >1	53 (20.2)	36 (21.1)	17 (18.5)	0.737
Ann Arbor stage III-IV	156 (59.3)	103 (60.2)	53 (57.6)	0.778
No. of extranodal sites >1	59 (22.4)	41 (24)	18 (19.6)	0.507
Site of involvement				
Mediastinum	36/179 (20.1)	25 (17.4)	11 (31.4)	0.104
Spleen	23/176 (13.1)	18 (12.7)	5 (14.7)	0.974
Bone	27/256 (10.5)	20 (12.2)	7 (7.6)	0.350
Lung/trachea	27/261 (10.3)	21 (12.4)	6 (6.5)	0.199
Skin	26/262 (9.9)	16 (9.4)	10 (10.9)	0.873
Bone marrow	16/263 (6.1)	12 (7)	4 (4.3)	0.553
Liver	14/253 (5.5)	11 (6.8)	3 (3.3)	0.379
Gastrointestinal	10/234 (4.3)	4 (2.8)	6 (6.5)	0.299
Soft tissue	5/137 (3.6)	4 (3.9)	1 (2.9)	1
Epidural	2/143 (1.4)	2 (1.9)	0	1
Central nervous system	1/177 (0.6)	0	1 (2.9)	0.447
Kidneys	0/154 (0.0)	0	0	---
Adrenal glands	0/154 (0.0)	0	0	---
Elevated lactate dehydrogenase	91/263 (34.6)	54 (31.6)	37 (40.2)	0.205
Elevated 2-microglobulin	12/66 (18.2)	7 (16.7)	5 (20.8)	0.928
Hemoglobin ≤12 g/dL	45/121 (37.2)	36 (38.7)	9 (32.1)	0.684
Platelets ≤150 G/L	8/115 (7.0)	4 (4.6)	4 (14.3)	0.185
CD2 positive	22/78 (28.2)	19 (28.8)	3 (25)	1
CD3 positive	35/169 (20.7)	27 (19.6)	8 (25.8)	0.596
CD5 positive	30/99 (30.3)	24 (30.4)	6 (30)	1
EMA positive	125/139 (89.9)	105 (90.5)	20 (87)	0.889
TIA1 positive	77/99 (77.8)	67 (77.9)	10 (76.9)	1
IPI score				0.968
0-1	145 (55.1)	94 (55)	51 (55.4)	
2	61 (23.2)	39 (22.8)	22 (23.9)	
3	38 (14.4)	26 (15.2)	12 (13)	
4-5	19 (7.2)	12 (7)	7 (7.6)	
PIT score				0.629
0	129 (49.0)	80 (46.8)	49 (53.3)	
1	88 (33.5)	62 (36.3)	26 (28.3)	
2	35 (13.3)	22 (12.9)	13 (14.1)	
3-4	11 (4.2)	7 (4.1)	4 (4.3)	
Anthracycline-based regimen	261/263 (99.2)	170 (99.4)	91 (98.9)	1
Upfront HDT–ASCT	34/263 (13.0)	19 (11.2)	15 (16.5)	0.307
Radiotherapy post chemotherapy	54/263 (20.5)	29 (17)	25 (27.2)	0.073

ALCL: anaplastic large-cell lymphoma; ALK: anaplastic lymphoma kinase; EMA: epithelial membrane antigen; HDT–ASCT: high-dose therapy – autologous stem-cell transplantation; IPI: international prognostic index; PIT: prognostic index for peripheral T-cell lymphoma, not otherwise specified; TIA1: T-cell intracellular antigen-1.

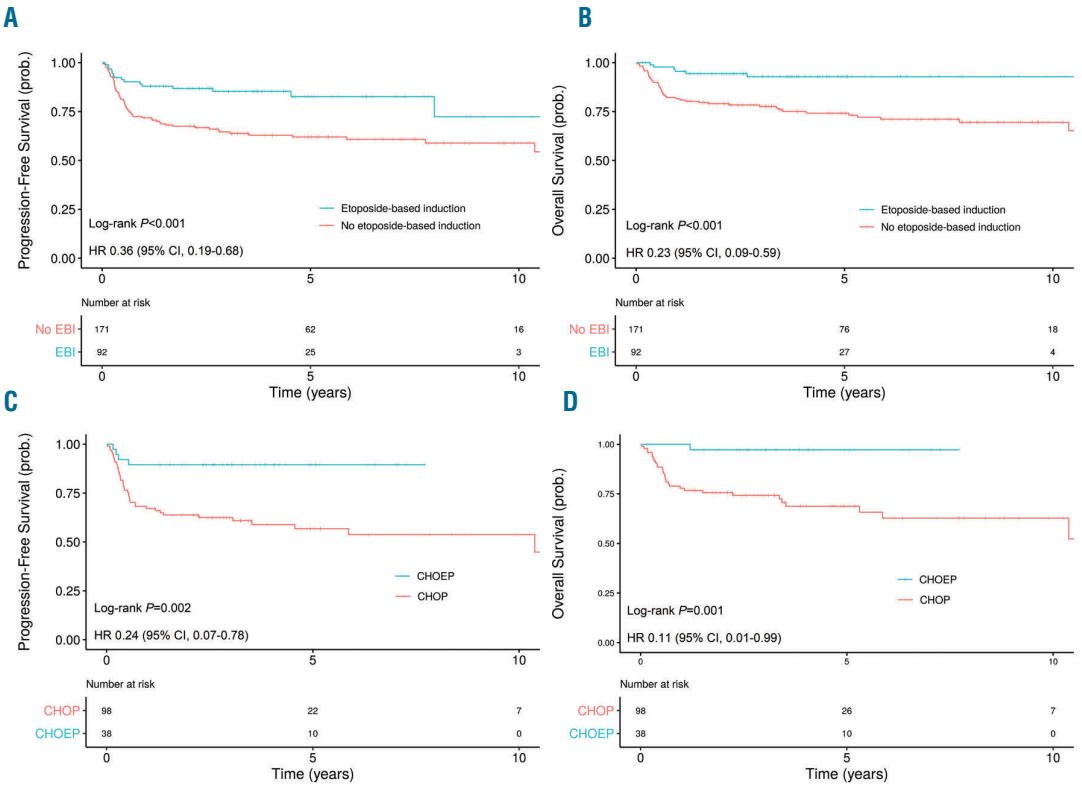

Figure 2. Survival according to treatment. (A) Progression-free survival (PFS) and (B) overall survival (OS) of the 263 patients according to induction regimen. (C) PFS and (D) OS for CHOEP and CHOP subsets.

erwise specified score (PIT) (C-index 0.72 *vs.* 0.67, respectively, *P*=0.03). The IPI effectively stratified patients within the whole cohort; the 5-year PFS was 80% (95% CI, 73% to 87%) for IPI 0 to 1 (n=145, 55.1%), 63% (95% CI, 51% to 78%) for IPI 2 (n=61, 23.2%), 54% (95% CI, 39% to 73%) for IPI 3 (n=38, 14.4%), and 40% (95% CI, 23% to 70%) for IPI 4 to 5 (n=19, 7.2%) (*P*<0.001, Figure 1 C); the 5-year OS was 92% (95% CI, 88% to 97%) for IPI 0 to 1, 73% (95% CI, 62% to 86%) for IPI 2, 59% (95% CI, 44% to 78%) for IPI 3, and 62% (95% CI, 43% to 89%) for IPI 4 to 5 (*P*<0.001, Figure 1 D).

In a stratified model adjusting for the IPI, CD3 positivity was associated with an inferior outcome: For $CD3^+$ (n=35, 21%) and CD3- (n=134, 79%) ALCL, respectively, the 5-year PFS rates were 53% *versus* 72% (*P*<0.01, HR 2.199), and the 5-year OS rates were 61% *versus* 83% (*P*<0.01, HR 2.82).

In total, 92 patients received an etoposide-based induction (Table 1 and *Online Supplementary Table S2*) and this was associated with an improved 5-year PFS [83%, (95% CI, 74% to 92%) *versus* 62% (95% CI, 55% to 70%) (*P*<0.001, HR 0.360)] and a 5-year OS [93% (95% CI, 87% to 99%) *versus* 74% (95% CI, 68% to 81%) (*P*<0.001, HR 0.232)] using etoposide *versus* non-etoposide regimens, respectively (Figure 2 A-B). In the whole cohort, there was no significant interaction between IPI and etoposide-based induction (*P*=0.97). To evaluate the impact of etoposide according to age, we performed separate analyses in patients ≤60 years or >60 years. In patients ≤60 years (n=232), the respective 5-year PFS and OS were 81% (95% CI, 72% to 91%) *versus* 65% (95% CI, 57% to 73%, *P*=0.012), and 92% (95% CI, 86% to 98%) *versus* 77% (95% CI, 70% to 85%, *P*=0.004, *Online Supplementary Figure S3*). In a stratified model assessing the IPI and the use of an etoposide-based induction, both factors remained independently prognostic for PFS (*P*<0.01 for both factors) and OS (*P*<0.01 for both factors). Among the 31 patients >60 years, only six (median age 68 years [62 to 71]) received etoposide with their induction and 25 (median age 65 years [61 to 76], *P*=0.6) did not, thus the interpretation is limited. The respective 5-year PFS and OS were 100% (95% CI, not defined) *versus* 42% (95% CI, 24% to 72%, *P*=0.031), and 100% (95% CI, not defined) *versus* 53% (95% CI, 34% to 83%, *P*=0.045, *Online Supplementary Figure S3*). In a stratified model assessing the IPI and etoposide-based induction, only the latter remained independently prognostic for the PFS (*P*=0.01) and OS (*P*=0.04). Finally, for all patients, etoposide-based induction significantly decreased the 5-year cumulative incidence of first relapse/progression (17% *versus* 37%, *P*=0.001). Because CHOP plus etoposide (CHOEP) (n=38) and CHOP (n=98) chemotherapy were the most commonly used regimens, we compared their respective results: 5-year PFS [89% (95% CI, 80% to 100%) *versus* 57% (95% CI, 47% to 69%, *P*=0.002, HR 0.24)], and 5-year OS [97% (95% CI, 92% to 100%) *versus* 69% (95% CI, 59% to 80%, *P*=0.001, HR 0.11)] favored CHOEP (Figure 2 C-D). In patients ≤60 years (CHOEP, n=36; CHOP, n=79), 5-year PFS [89% (95% CI, 79% to 100%) *versus* 59% (95% CI, 48% to 72%, *P*=0.005)], and 5-year OS [97% (95% CI, 92% to 100%) *versus* 72% (95% CI, 62% to 83%, *P*=0.004)] also favored CHOEP. In these younger patients, in a stratified model adjusting for IPI, CHOEP improved the PFS (*P*=0.03), and a similar trend was observed for the OS (*P*=0.1).

Thirty-four patients underwent upfront high dose therapy autologous stem-cell transplantation (HDT–ASCT) (all were <60 years). For patients <60 years in CR or PR, in stratified Cox models including etoposide-based induction, IPI and upfront HDT–ASCT, only the etoposide-based induction and the IPI remained independently prognostic for PFS and OS (*data not shown*).

In our study, all patients had a centralized pathologic review by expert hematopathologists. This is of particular

importance since the concordance rate between referral and expert diagnoses is only 82% for ALK-positive ALCL.[1] The IPI was a strong independent predictor of outcome, and we demonstrated that incorporation of etoposide into the induction chemotherapy was associated with a markedly improved PFS and OS independent of the IPI and age. Further, the cumulative risk of lymphoma relapse/progression was reduced from 37% to 17%. Although the treatment information at relapse/progression was not available for our analysis, given the period of diagnosis, it is unlikely that brentuximab vedotin (BV)[13] or crizotinib[14] was received.

Finally, the recently published phase 3 ECHELON-2 study comparing Brentuximab vedotin + Cyclophosphamide, doxorubicin, and prednisone (BV+CHP) to CHOP in CD30+ PTCLs, including ALK-positive ALCL with IPI ≥2, showed an improved 3-year PFS (57.1% *versus* 44.4%, HR 0.71 [95% CI 0.54-0.93]) and OS (76.8% *versus* 69.1%, HR 0.66 [95% CI 0.46-0.95]) in the BV arm in the intention to treat analysis, leading to Food and Drug Administration approval.[15] Although an individual survival analyses by histological subtypes has not yet been reported, the Hazard Ratios for ALK-positive ALCL were the lowest amongst the subtypes (PFS HR 0.29 [95% CI 0.11- 0.79]; OS HR 0.38 [95% CI 0.12, 1.22]). In our cohort, when restricting the analysis to patients with an IPI ≥2, CHOEP (n=12), compared to CHOP (n=44), markedly improved the 3-year PFS (92% vs. 49%, *P*=0.005; HR 0.2 [95% CI 0-1.776]) and OS (100% *vs.* 56%, *P*=0.002; HR not evaluable) are observed. Notably, very few patients > 60 years received etoposide given the additive toxicity, limiting definitive conclusions in this subgroup.

Our study has intrinsic limitations related to its retrospective nature and potential bias in the retrospective studies in the selection of patients for etoposide containing regimens. However, reassuringly, there was no significant difference in PFS between cohorts regardless of whether patients were included in clinical trials or not.

In conclusion, this is the largest analysis of adult patients with ALK-positive ALCL. Our data supports that the integration of etoposide into the primary therapy may be associated with important improvements in the PFS and OS and warrants prospective confirmation.

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