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

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doi:10.3324/haematol.2018.213512

Supplementary Material

Online Supplementary Methods

All patients from each data source who met criteria for age ≥18 years, HIV-negative serology, first-line treatment including at least one cycle of curative intent systemic chemotherapy and availability of a minimum dataset comprising clinical characteristics at diagnosis (age, performance status, Ann Arbor stage, number of extranodal sites >1, lactate dehydrogenase (LDH) value, bone marrow involvement) were considered for analysis.

Patient characteristics and response rates were compared using the χ^2 test or Fisher's exact test when appropriate for qualitative data and the Student *t* test for quantitative data. Progression-free survival (PFS) was measured from the date of study entry for patients included in clinical trials or the date of diagnosis for patients outside clinical trials, until the date of the first event among progression, relapse or death from any cause, or the date of last contact for those who were progression-free. Similarly, overall survival (OS) was measured from the date of study entry for patients included in clinical trials or the date of diagnosis for patients outside clinical trials, until death from any cause, or the date of last contact for those who were alive at the end of follow-up. Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. PFS and OS at fixed time were estimated with 95% confidence intervals (95% CI). Median follow-up was estimated by the reverse Kaplan-Meier method. Competing risk analysis by Fine and Gray approach was used to determine the cumulative incidences of first relapse/progression. The associations between patient characteristics or treatment type and progression-free survival (PFS) or overall survival (OS) were analyzed by Cox survival models stratified by cohort and assessed by Log-Likelihood Ratio tests. Effect sizes of covariates were quantified by the hazard ratios (HR). Predictive performances of prognostic models were also quantified by the Harrell C-index measurement.

Statistical tests were considered significant if two-sided p values were <0.05. All statistical analyses were performed using R v3.3.

Assessment of prognostic factors: As the pattern of missing data was not random and largely dependent on each cohort, only the data available for all patients (ie, the required minimum dataset including IPI [International Prognostic Index] and PIT [Prognostic Index for Peripheral T-Cell Lymphoma, Not Otherwise Specified] scores and their individual components) were considered for the multivariate analysis, performed by Cox models stratified by cohort. Other prognostic factors with significant impact in univariate analysis, but for which there were missing data, were studied in a stratified Cox model adjusting for the IPI and restricted to the dataset for which this factor was available.

The impact of etoposide on outcome was assessed by dividing the whole cohort into two subgroups: patients who received etoposide as part of induction ("etoposide-based induction chemotherapy group"), i.e. etoposide was administered for at least the first cycle of chemotherapy), and patients who did not ("no etoposide-based induction chemotherapy group"). This approach was to avoid the potential selection bias that may occur by the inclusion of patients receiving etoposide only during consolidation (e.g. the sequential consolidation following doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone [ACVBP] induction), who are by definition responsive to induction. These latter patients were placed within the "no etoposide-based induction chemotherapy group". A second analysis restricting the comparison to patients treated with CHOP versus CHOP + etoposide (CHOEP) was also performed.

All studies assessed response to treatment by using computed tomography scan criteria.

Online Supplementary Table S1. Studies included in the pooled analysis.

	Source	Population	Study type	Patients included in clinical trials	Dates	Adults with ALK+ ALCL included in the pooled analysis (n)
Suzuki et al (2000)[2]	Japan	ALK+ and ALK- ALCL Children and adults n=143 (83 ALK+ ALCL)	Retrospective	No	1985-1999	44
Savage et al (2008)[3]	IPTCLP	ALK+ and ALK- ALCL Adults n=159 (87 ALK+ ALCL)	Retrospective	No	1990-2002	74
Simon et al (2010)[4]	LYSA	PTCL Adults n=88 (10 ALK+ ALCL)	Retrospective	Yes	1996-2002	10
Schmitz et al (2010)[5]	DSHNHL	PTCL Adults n=320 (78 ALK+ ALCL)	Retrospective	Yes	1993-2007	78
Sibon et al (2012)[6]	LYSA	ALK+ and ALK- ALCL Adults n=138 (64 ALK+ ALCL)	Retrospective	Yes	1987-2003	48
Parrilla Castellar et al (2014)[7]	Mayo Clinic	ALK+ and ALK- ALCL Children and adults n=105 (32 ALK+)	Retrospective	No	1982-2012	9

ALCL: anaplastic large-cell lymphoma; ALK: anaplastic lymphoma kinase; DSHNHL: German High-Grade Non-Hodgkin Lymphoma Study Group; IPTCLP: International Peripheral T-Cell Lymphoma Project; LYSA: the Lymphoma Study Association; PTCL: peripheral T-cell lymphoma.

Online Supplementary Table S2. Treatment of the 263 adults with systemic ALK-positive ALCL included in the pooled analysis.

Study	n	Chemotherapy regimen (n)	Upfront HDT-ASCT (n)	RT (n)
Suzuki et al (2000)[5]	44	ALL regimen (1) BACOD (1) **CAMBO-VIP (2)** CHOP-14 (1) CHOP-21 (23) CHOP-21 without vincristine (1) CHOP-Methotrexate (1) Cis-VACD (3) LSG9 (1) THP-COP-21 (2) **VABCOP (5)** VEPA (3)	8	3
Savage et al (2008)[6]	74	**ACE (4)** ACVBP (1) **AIE (1)** CAPBOP (2) CBDCA-CHOP (1) CHLVPP-CNOP (1) **CHOEP-ND* (2)** CHOP-14 (1) CHOP-ND* (40) CNOP (6) DEXA-PAMB (1) **EPOCH (11)** i-HDS (1) **ProMACE-CytaBOM (1)** **VAPEC-B (1)**	6	14
Simon et al (2010)[7]	10	CHOP-21 (3) **VIP-rABVD (7)**	0	7
Schmitz et al (2010)[8]	78	**CHOEP-14 (12)** **CHOEP-21 (24)** CHOP-14 (14) CHOP-21 (7) **High-CHOEP-21 (9)** **MegaCHOEP-21 (12)**	12	25
Sibon et al (2012)[9]	48	ACVBP (34) CHOP-21 (2) ECVBP (8) NCVBP (4)	7	4
Parrilla Castellar et al (2014)[10]	9	CHOP-ND* (7) **ProMACE-CytaBOM without doxorubicin (1)** Solumedrol & Nitrogen-mustard (1)	1	1
Total	263	---	34	54

ACE: doxorubicin, cyclophosphamide, etoposide; ACVBP (induction): doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; AIE: cytarabine, idarubicin, etoposide; ALL (acute lymphoblastic leukemia) regimen (induction): vincristine, daunorubicin, asparaginase, prednisone; BACOD: bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone; CAMBO-VIP: cyclophosphamide, doxorubicin, methotrexate, bleomycin, vincristine, etoposide, ifosfamide, prednisolone; CAPBOP: cyclophosphamide, doxorubicin, procarbazine, bleomycin, vincristine, prednisone; CBDCA-CHOP: carboplatin, cyclophosphamide, doxorubicin, vincristine, prednisone; CHLVPP-CNOP: chlorambucil, vinblastine, procarbazine, prednisone, cyclophosphamide, mitoxantrone, vincristine, prednisone; CHOEP: cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; Cis-VACD: cisplatin, vindesine, doxorubicin, cyclophosphamide, dexamethasone; CNOP: cyclophosphamide, mitoxantrone, vincristine, prednisone; DEXA-PAMB: dexamethasone, procarbazine, cytarabine, mitoxantrone, bleomycin; ECVBP: epirubicin, cyclophosphamide, vindesine, bleomycin, prednisone; EPOCH: etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; HDT-ASCT: high-dose therapy–autologous stem-cell transplantation; i-HDS (induction): doxorubicin, vincristine, prednisone; LSG9 (induction): vincristine, cyclophosphamide, prednisone, doxorubicin, bleomycin (VEPA-B); NCVBP: mitoxantrone, cyclophosphamide,

vindesine, bleomycin, prednisone; ProMACE-CytaBOM: prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide, cytarabine, bleomycin, vincristine; RT: radiotherapy post chemotherapy; THP-COP-21: pirarubicin, cyclophosphamide, vincristine, prednisone; VABCOP: etoposide, doxorubicin, bleomycin, cyclophosphamide, vincristine, prednisolone; VAPEC-B: vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide, bleomycin; VEPA: vincristine, cyclophosphamide, prednisone, doxorubicin; VIP-rABVD: etoposide, ifosfamide, cisplatin, doxorubicin, bleomycin, vinblastine, dacarbazine.
Bold: etoposide-based induction regimens
* ND: no data on the frequency of administration of CHOP or CHOEP (every 14 or 21 day).

Online Supplementary Table S3. Univariate analysis of the impact of clinical and laboratory features on progression-free survival (PFS) and overall survival (OS).

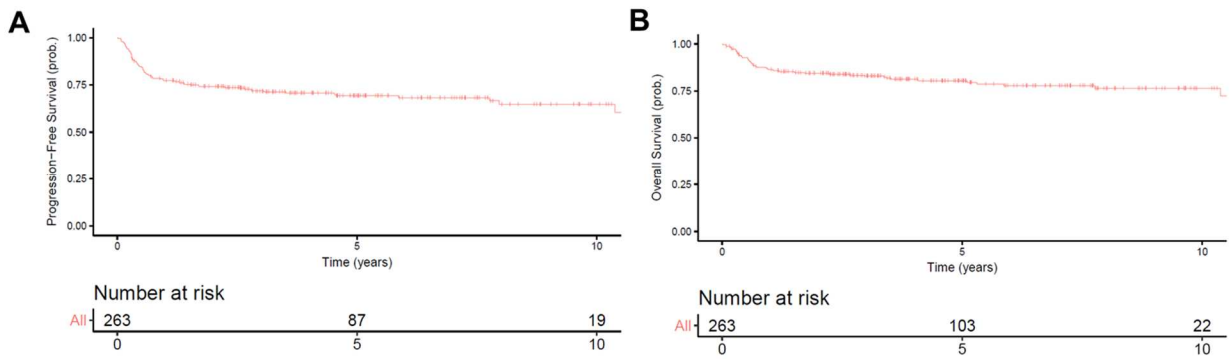
Parameter	n with available data	PFS		OS	
		P	HR	*P*	HR
Age >60	263	0.009	2.077	<0.001	3.041
Male sex	263	0.551	1.147	0.410	1.266
Performance status >1	263	<0.001	2.267	0.001	2.461
Ann Arbor stage III-IV	263	0.014	1.800	0.006	2.390
No. of extranodal sites >1	263	<0.001	2.711	<0.001	3.362
Mediastinum involvement	179	0.119	1.622	0.280	1.501
Spleen involvement	176	0.426	0.704	0.742	0.851
Bone involvement	256	0.226	1.518	0.009	2.655
Lung/trachea involvement	261	0.005	2.398	0.084	1.968
Skin involvement	262	0.306	1.428	0.520	1.334
Bone marrow involvement	263	0.573	1.255	0.804	1.125
Liver involvement	253	0.008	2.749	0.005	3.442
Gastrointestinal involvement	234	0.551	0.652	0.591	0.583
Soft tissue involvement	137	0.051	2.696	0.06	2.987
Elevated lactate dehydrogenase	263	0.045	1.582	0.007	2.107
Elevated β2-microglobulin	66	0.172	2.519	0.093	3.348
Hemoglobin ≤12 g/dL	121	<0.001	4.054	<0.001	5.183
Platelets ≤ 150 G/L	115	0.050	2.648	0.035	3.122
CD2 positive	78	0.200	1.614	0.060	2.338
CD3 positive	169	0.006	2.199	0.001	2.820
CD5 positive	99	0.590	0.798	0.451	1.420
EMA positive	139	0.040	0.430	0.209	0.520
TIA1 positive	99	0.915	0.958	0.283	0.635
IPI score	263	<0.001		<0.001	
2			2.103		3.272
3			2.915		5.970
4-5			4.451		4.872
PIT score	263	0.001		<0.001	
1			1.564		2.580
2			2.758		4.165
3-4			3.273		4.917

EMA: Epithelial membrane antigen; HR: Hazard ratio; IPI: International Prognostic Index; OS: Overall survival; PFS: Progression-free survival; PIT: Prognostic Index for Peripheral T-Cell Lymphoma, Not Otherwise Specified; TIA1: T-cell intracellular antigen-1.

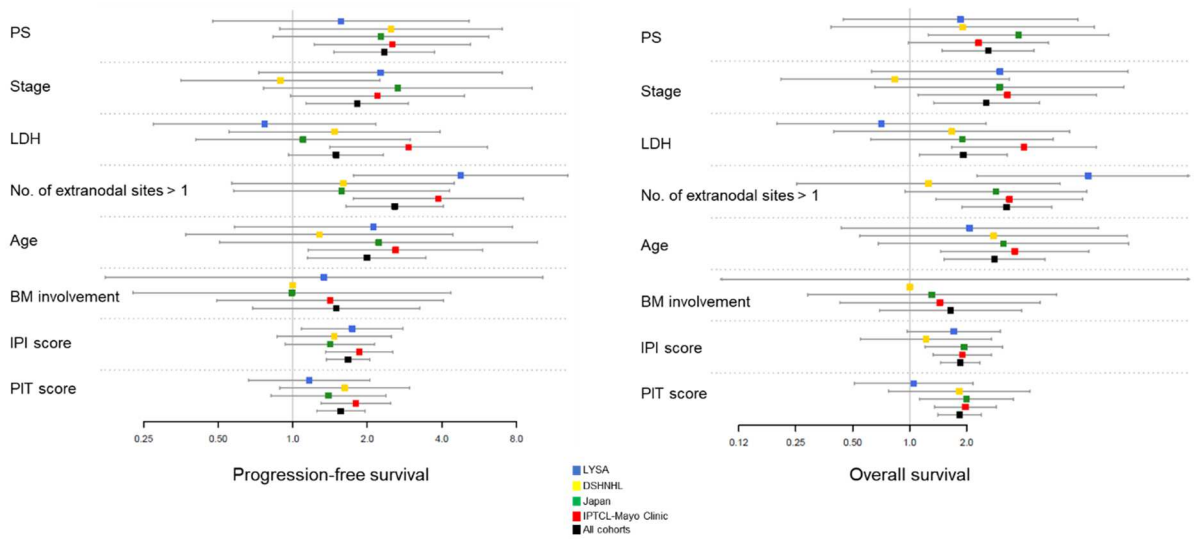
Online Supplementary Table S4. Parameters influencing PFS and OS in multivariate analysis in all patients.

Parameter	PFS			OS		
	P	HR	95% CI	*P*	HR	95% CI
All patients (n=263)						
Age >60 years	0.008	2.2	1.2 to 3.9	<0.0001	3.5	1.8 to 6.9
Performance status >1	0.134	1.5	0.9 to 2.6	0.58	1.2	0.6 to 2.3
Ann Arbor stage III-IV	0.353	1.3	0.8 to 2.2	0.18	1.7	0.8 to 3.5
No. of extranodal sites >1	0.002	2.3	1.3 to 3.8	<0.0001	2.8	1.5 to 5.4
Elevated lactate dehydrogenase	0.591	1.1	0.7 to 1.9	0.36	1.3	0.7 to 2.5
Bone marrow involvement	0.552	0.8	0.3 to 1.8	0.38	0.7	0.2 to 1.7

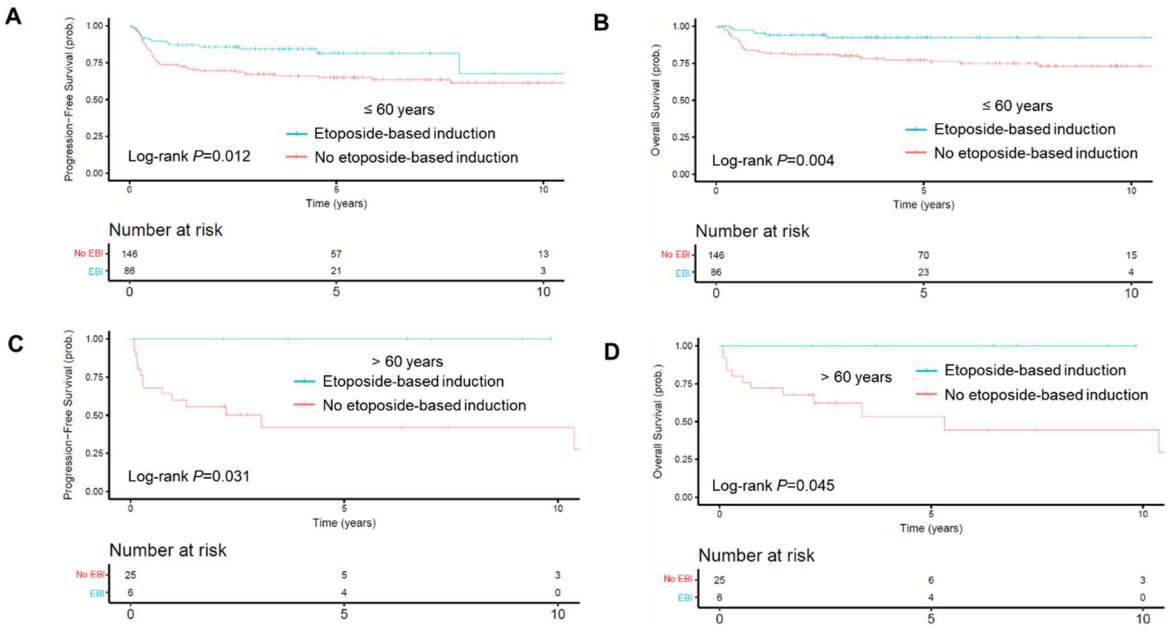
The multivariate analysis included only factors for which data were available for all 263 patients, ie individual IPI and PIT factors. HR: hazard ratio; OS: overall survival; PFS: progression-free survival.



Online Supplementary Figure S1. Survival of the 263 ALK-positive ALCL patients. (A) Progression-free survival and (B) overall survival. Median follow-up was 4·9 years.



Online Supplementary Figure S2. Homogeneity between cohorts for progression-free survival and overall survival. BM, bone marrow; LDH, lactate dehydrogenase; IPI, International Prognostic Index; PIT, Prognostic Index for Peripheral T-Cell Lymphoma, Not Otherwise Specified; PS, performance status. There was no significant heterogeneity between cohorts.



Online Supplementary Figure S3. Survival according to induction regimen and age. Progression-free survival and overall survival according to induction regimen in patients ≤60 years (A, B) and in patients >60 years (C, D).