Management of Adult Acute Lymphoblastic Leukemia. 2024 ELN Recommendations from a European Expert Panel

Supplementary Materials

Table S1: Distribution of Chapter to Coauthors

Paragraph	Author
1. Introduction / Methods	Gökbuget
2. Diagnostic Procedures and Classification	Chiaretti, Foa
3. Prognostic factors	Bassan
4. Response criteria and survival outcomes	Gökbuget
5. Treatment	
5.1. Induction and consolidation therapy	Bassan
5.2. Maintenance therapy	Doubek
5.3. CNS-Prophylaxis	Fielding
5.4. Minimal residual disease based treatment	Gökbuget
5.5. Stem cell transplantation	Giebel
6. Treatment of specific subgroups	
6.1. Adolescent patients	Boissel
6.2. Ph/BCR-ABL positive ALL	Ottmann, Rousselot, Martinelli
6.3. Ph/BCR-ABl-like ALL	Rijneveld
6.4. Treatment of older patients	Gökbuget
6.5. T-ALL	Marks
6.6. Lymphoblastic lymphoma	Hoelzer
7. Relapsed ALL	Ribera
8. Novel therapies	Dombret
9. Late effects	Gökbuget
10. Management of specific situations	Fielding
11. General setting and supportive care	Hunault
12. Summary and outlook	Gökbuget

Table S2: Published Outcomes of Trials in Newly Diagnosed Adult ALL

Trial (Ref.)	Age (y)	No.	CR (%)	CRD/RFS (%)	OS (%)	EFS (%)	FUP	Annotations and prognostic analysis
JALSG 202-U[1]	19 (16-24)	139	97	71	74	-	4-y	-
UKALL 2003[2]	16-24	229	97	-	76.4	72.3	5-y	Risk-oriented design; CR rate calculated upon induction failures (2.6%); EFS MRD- 93% vs. MRD+ 63-71% (P=0.0001)
PETHEMA ALL 96[3] **PETHEMA ALLRE08**[4]	 20 (15-30)	81 66	- 96	- -	69 74	61 62	6-y 5-y	- Risk-oriented design; OS 15-18 y 87% vs. 19-29 y 63% (P=0.021)
GMALL 05/93 **07/03**[5]	15-35	642 887	88 91	49 61	46 65	- -	5-y 5-y	Risk-oriented design (both trials); CRD/OS 07/03 (intensified Peg-ASP, Dexa and HD consolidation) vs. 05/93 P < 0.05
GIMEMA LAL 1308[6]	18-35	76	91	60	60			Risk-oriented design; RFS T-ALL 88% vs. B-ALL 50% (P=0.005) OS/RFS d33 MRD- 67/75% vs. MRD+ 27/43% (P<0.025) OS/RFS d78 MRD- 71/77% vs. MRD+ 26/39% (P<0.001)
MDACC HyperC-VAD, **augmented BFM**[7]	27 (15-40) 22 (13-39)	106 102	98 93	55 53	60 60	-	5-y	Hyper-CVAD vs. augmented BFM P=NS Cumulative analysis: OS d29 MRD- 75% vs. MRD+ 40% (P=0.004) OS d84 MRD- 75% vs. MRD+ 22% (P=0.0004) CRD d29 MRD- 64% vs. MRD+ 33% (P=0.017) CRD d84 MRD- 63% vs. MRD+ 26% (P=0.0018)
U.S. Intergroup C10403[8]	24 (17-39)	295	89	66	73	59	3-y	EFS Ph-like 42% vs. non-Ph-like 69% (P=0.008) OS Ph-like 63% vs. Non-Ph-like 81% (P=0.0371) RFS end of induction MRD- 85% vs. MRD+ 54% (P=0.001)
NOPHO ALL2008[9]	26 (18-45)	295	-	-	78	74	5-y	Risk-oriented design;

								EFS SR 87%, IR 78%, HR 66%, HR to allogeneic SCT (including MRD+) 61%
DFCI 01-1756[10] **DFCI 06-254**[11]	28 (18-50) 32 (18-50)	92 110	86 89	71 73	70 75	- -	4-y 3-y	RFS T-ALL 87% vs. B-ALL Ph- 66% (P=0.14) EFS T-ALL 77% vs. B-ALL Ph- 57% (P=0.11) Intensified Peg-ASP consolidation (toxicity: reduced from 2500 to 2000 IU/m^2 and from 16 to 10 doses); OS age 18-19 y 100% vs. 20-29 y 85% vs 30-39 y 75% vs. 40-50 y 60% OS BMI underweight/normal 85% vs. overweight 71% vs. obese/morbidly obese 63%
GMALL 07/03[12]	35 (15-55)	1226	91	-	60-67	-	3-y	Risk-oriented design; Intensified Peg-ASP (1000 vs 2000 UI/m^2 in cohort 1 vs cohort 2, x7 in SR), Dex and HD consolidation; CRD SR cohort 1 61% vs. cohort 2 74% (P=0.02) CRD AYA cohort 1 60% vs. cohort 2 78% OS cohort 1 60% vs. cohort 2 67% OS SR cohort 1 68% vs. cohort 2 80% (P=0.02) OS AYA cohort 1 77% vs. cohort 2 86%
MRC UKALL/ XII/ECOG E2993[13]	15-59	1418	-	-	43	-	5-y	Phase 3 risk-oriented design; OS donor 53% vs. no donor 45% (P=0.01) OS HR donor vs. no donor P=NS OS SR donor vs. no donor P=0.02 OS chemotherapy 46% vs. autologous SCT 37% (P=0.03)
RALL 2009[14]	30 (15-60)	250	87	69.3	65.6	-	4-y	RFS < 30 y 71.5% vs. > 30 y 61.2% (P=0.1) OS < 30 y 73.6% vs. >30 y 52.7% (P=0.0009)
MDACC Hyper-CVAD-nelarabine (T-ALL/LL)[15]	30 (13-78)	81	88	-	57	52	5-y	OS non-ETP 63% vs. ETP 32% (P<0.001). Non-ETP: OS nelarabine 83% vs. no nelarabine 38% (P=0.003)
GRAALL 2003[16] **GRAALL 2005**[17]	31 (15-60) 36 (18-60)	225 787	93.5 92	- -	60 58.5	55 52	3.5-y 5-y	Risk-oriented design; CRD 15-45 y 61% vs. >45 y 53% (P=0.21) OS 15-45 y 64% vs. >45 y 47% (P=0.004) Risk-oriented design;

								Phase 3: hyper vs. standard dose cyclophosphamide: comparable results except for patient >55 years [hyper favorable]); EFS < vs. > 55 y 55.7% vs. 25.8% (P<0.001) EFS 18-34 vs. 35-54 y 58.7% vs. 52.2% (P=0.019) GRAALL 2003-2005 cumulative analysis: 5-y relapse incidence MRD- 23-31% vs. MRD+ 60% (P <0.01)
Toronto DFCI 91-01[18]	37 (18-60)	85	89	71	63	-	3-y	OS < vs. > 35 y 83% vs. 52% (P=0.003) OS WBC < vs. > 30/100 [B/T] 73% vs. 38% (P=0.007)
PETHEMA HR-11[19]	38 (max.60)	307	86	-	49	40	5-y	Risk-oriented design; OS chemotherapy/MRD- 59% vs. allogeneic SCT/MRD+ 38% (P<0.001)
JALSG ALL 202-O[20]	24-65	250	86	42	-	52	5-y	Phase 3: MTX 0.5 vs 3 g/m^2; RFS MTX 0.5 vs 3 g/m^2 32% vs 58% (P=0.0218) RFS SR < 40 y 71% vs. SR > 40 y 52% vs. HR 27% (P=0.001)
MDACC Hyper-CVAD[21]	40 (15-92)	288	92	38	38	-	5-y	OS < 40 y 51% vs. 40-59 y 30% vs. 60+ y 17% (P<0.001) OS WBC <50 40-44% vs. >50 16% (P<0.001)
GIMEMA LAL 1913[22]	40 (18-65)	203	91	63	66	57	3-y	Risk-oriented design; EFS age 18-40 72% (P<0.0001), T-ALL 67% (P=0.038), end of induction MRD- 78% (P=0.023), week 10 MRD- 75% (P=0.048)
NILG 10/07[23]	41 (17-67)	161	87	52	53	46	5-y	Risk-oriented design; CR < vs. > 55 y 92% vs. 61% (P=0.0002) OS < vs. >55 y 60% vs. 21% (P<0.0001) RFS MRD- 78% vs. MRD+ 34% (P<0.0001) OS MRD- 66% vs. MRD+ 29% (P<0.0001) OS B-ALL 47% vs. T-ALL 73% (P=0.003)
HOVON-100[24]	43 (18-70)	340	87	58	52-51	61-64	5-y	Phase 3: clofarabine vs. no clofarabine (P=NS); Allogeneic SCT suggested; EFS < vs. > 40 y 61-64% vs. 44-40% (P=NR)
GMALL 08/2013[25]	35 (18-55)	770	93	n.r.	76	n.r.	3-y	MRD based and conventional risk stratification OS B-Lin Ph- 77%, Ph+ 74%, T-ALL 74% OS MolFail 84%

Abbreviations: JALSG, Japan Adult Leukemia Study Group; UKALL, United Kingdom ALL Study Group; GMALL, German Multicenter Group for Adult ALL; MDACC, M.D. Anderson Cancer Center; NOPHO, Nordic Society of Pediatric Haematology and Oncology; DFCI, Dana Farber Cancer Institute; ECOG, Eastern Cooperative Oncology Group; GRAALL, Group for Research on Adult ALL; RALL, Russian ALL Group; PETHEMA, Programa Español de Tratamientos en Hematologia; NILG, Northern Italy Leukemia Group; HOVON, Hemato-Oncology Foundation for Adults in the Netherlands; y, years; FUP, follow-up; Peg-ASP, pegylated asparaginase; Dex, dexamethasone; HD, high dose; MTX, methotrexate; BMI, body mass index

Therapeutic results from representative trials for Ph- adult ALL (pediatric-inspired chemotherapy and risk-oriented consolidation/maintenance or allogeneic SCT where applicable; minimum of 50 patients; outcome estimates at 3+ years). The trials are ordered according to increasing patient age (median and/or range, in years), excluding the patients <18 years and >65 years whenever possible. Trials with new immunotherapeutics upfront were excluded, with only exception of the GRAALL-2005 study randomizing the subgroup of CD20+ ALL patients to additional rituximab or not and the GMALL 07 trial using Rituximab in CD20+ patients.

Table S3 Subclasses within Ph-like subgroup

ABL-class fusions	11-14%	Rearrangements involving ABL1, ABL2, CSFR1 and PDGFRB
CRLF2 alterations with or without activating point mutations in Janus kinase 1 (*JAK1)* or Janus kinase 2 (*JAK2) or more rarely CRLF2 mutations*	50%	CRLF2 alterations result from a rearrangement that fuses immunoglobulin heavy chain locus with CRLF2 or an interstitial deletion with the pseudo-autosomal region of chromosome X or Y that results in fusion of CRLF2 to the P2RY8 promotor
JAK2 or erythropoietin receptor *EPOR* rearrangements activating JAK-STAT signalling	7-8% and 3%	
Activated mutations or alterations in JAK-STAT signaling		*CRLF2* deregulated cases or other rare kinase alterations (*BLNK*, *DGKH*, FGFR1, *IL2RB*, *LYN*, *NTRK3*, *PDGFRA*, *PTK2B*, *TYK2* and RAS signalling pathway).

Table S4: Results of Representative Studies on Outcome of Relapsed/Refractory ALL Treated with Chemotherapy.

Author (year), reference	**Thomas et al** [26]	**Fielding et al**[27]	**Tavernier et al**[28]	**Oriol et al**[29]	**Gökbuget et al**[30]	**Gökbuget et al**[31]
Year	**1999**	**2007**	**2007**	**2010**	**2012**	**2016**
N	314	609	421	263	547	1706
CR (%)	31	NA	44	45	42	40
Early death (%)	21	NA	NA	17	NA	NA
Refractory (%)	49	NA	NA	38	NA	NA
HSCT in ≥CR2 (%)	NA	25	55	30	75	NA
CR duration (median), months	6	NA	5.2	6	NA	NA
OS (median), months	5	6	6.3	4.5	8.4	5.8
OS probability (years)	3% (5 years)	7% (5 years)	8% (5 years)	10% (5 years)	24% (3 years)	11% (3 years)
Prognostic factors	Age <40 years CR1 > 1 year No blasts in PB	Age <20 years CR1 >2 years	Transplant in 2nd line therapy	Age <30 years CR1 >2 years	Age <25 years CR1 >1.5 year Response to 1st/2nd salvage	Younger age Longer CR1 duration Lower WBC count at 1st diagnosis

N: number of patients; CR: complete response; CR1: first complete response; CR2: second complete response; HSCT: hematopoietic stem cell transplant; OS: overall survival; NA: not available.

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