

General condition and comorbidity of long-term survivors of adult acute lymphoblastic leukemia

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Received: August 8, 2022.
Accepted: February 2, 2023.
Early view: February 9, 2023.

<https://doi.org/10.3324/haematol.2022.281820>

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General Condition and Comorbidity in Acute Lymphoblastic Leukemia Survivors are Influenced by Stem Cell Transplantation

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Table S1: Major clinical characteristics for patients with/without available questionnaire (N=1413)

	<i>No Questionnaire</i>	<i>Questionnaire</i>
<i>N</i>	852	561
<i>Lineage</i>		
<i>B</i>	66.1%	64.6%
<i>T</i>	33.9%	35.4%
<i>BCR-ABL pos</i>	9.7%	8.7%
<i>Age: Median</i>	29	29
<i>15-35</i>	66.7%	66.8%
<i>36-55</i>	27.9%	27.6%
<i>>55</i>	5.4%	5.7%
<i>Leukocytes at diagnosis</i>		
<i>≤30.000</i>	69.7%	65.3%
<i>>30.000</i>	30.3%	34.7%

Table S2: Cumulative Doses of Cytostatic Drugs in GMALL Protocols

GMALL Study	02/84	03/87	04/89	05/93	06/99	07/2003
Open for accrual	1983-1988	1987-1989	1989-1993	1993-1999	1999-2003	2003-2011
Risk Groups	LR, HR	LR, HR	SR, T, HR	LR, T, HR	SR, HR, VHR	SR, HR, VHR
Cranial irradiation (cum.dose [Gray])	24	LR: 24; HR 0 or 24	24	LR/T: 24; HR: none	24	24
HD Methotrexate (dose [g/m²])	-	-	SR/T: 0; HR**: 0 or 1,5	LR: 1,5; T/HR: 0 or 1,5	SR: 1,5-3; HR/VHR: 3	18-55 y: 1,5; 56-65 y: 1
HD Methotrexate (N doses)	-	-	SR/T: 0; HR: 0 or 3	LR: 6-12; T: 0 or 6; HR: 0 or 4-10	SR: 7-11; HR/VHR: 1	SR: 7; HR/VHR: 1
HD Cytarabine (dose [g/m²])	-	LR: 0; HR: 0 or 1-3	SR/T: 0; HR: 0 or 1,5	LR: 0; T: 1; HR: 3	2	18-55 y: 1-2; 56-65 y: 1
HD Cytarabine (N doses)	-	LR: 0; HR: 0 or 8	SR/T: 0; HR: 0 or 8	LR: 0; T: 8; HR: 8-16	2	SR: 5-11; HR/VHR: 2
Adriamycine (cum dose [mg/m²])	LR: 100; HR: 0 or 100	LR: 100; HR 0 or 100	SR/T: 100; HR: 0 or 100	LR/T: 100; HR: 0 or 100	SR: 100; HR/VHR: 0	SR: 30; HR/VHR: 0
Daunorubicine (cum dose [mg/m²])	LR: 100; HR: 140	LR: 180; HR: 0 or 180	180	180	180	18-55 y: 180; 56-65 y: 120
Cyclophosphamide (cum dose [mg/m²])	LR: 2600; HR: 1950-2600	LR: 1950; HR: 1300-1950	SR/T: 2600; HR: 1950-2600	LR: 4000-7000; T: 6000-9000; HR: 0 or 3000-6000	SR: 4600-6600; HR/VHR: 2600	SR: 4600-6600; HR/VHR: 2600
Vincristine (cum dose [mg])	LR: 12-12,75*, HR: 6-12,75	LR: 16-18*; HR: 8-18	SR/T: 16-18*; HR: 8-18	LR/T: 16-18*	6	6
Vindesine (cum dose [mg])	-	-	-	HR: 8-18	SR: 9; HR/VHR: 3	SR: 9; HR/VHR: 3
Dexamethasone (cum dose [mg/m²], po)	LR: 306,25; HR: 0 or 306,25	-	-	-	310	160
Prednisolone (cum dose [mg/m²], po)	1837,5-2047,5*	LR: 3675-4095*; HR: 1837,5-4095	SR;T: 3675-4095*; HR: 1837,5-4095	LR/T: 3675-4095*; HR: 1837,5-4095	SR: 997,5; HR/VHR: 0	SR: 997,5; HR/VHR: 0
Etoposide (cum dose [mg/m²])	-	-	-	-	500	500
Teniposide (cum dose [mg/m²])	LR: 0; HR: 300-1200	-	SR: 1200; T: 600; HR: 0 or 600	LR/T: 1500-3000; HR: 0 or 500-2000	SR: 500-1500; HR/VHR: 0	-
L-Asparaginase (cum dose [U/m²])	70000	70000	SR/T: 70000; HR: 70000-100000	LR: 130000-190000; T: 70000-130000; HR: 50000-170000		
PEG-Asparaginase (cum dose [U/m²])	-	-	-	-	SR: 4000-6000; HR/VHR: 10000	18-55 y: SR 14000-22000, HR/VHR 2000; 56-65 y: SR 7000-11000, HR/VHR 1000

LR, Low risk; HR, high risk; T, T-ALL; VHR, very high risk (Ph/BCR-ABL positive); SR, standard risk; y, years; cum, cumulative

*depending on Prephase; other doses identified by 'or' depending partly on randomizations and stratification

Table S3: Items of questionnaire		
No.	Question	Answer options
1.	Skin general	Yes/no
2.	Mucositis	CTCAE
3.	Cutis/subcutis	CTCAE
4.	Alopecia	Yes/no
5.	Further	Free text
6.	Lunge general	Yes/no
7.	Dyspnea	CTCAE
8.	Lung fibrosis, restrictive lung disease	CTCAE
9.	Interstitial pneumonitis	Free text
10.	Obstructive Lung disease, asthma	CTCAE
11.	Lung function	CTCAE
12.	Further	Free text
13.	Neurology general	Yes/no
14.	Neuropathy	CTCAE
15.	Sensory deficiency	CTCAE
16.	Motor deficiency	CTCAE
17.	Memory function	Free text in C1, items in C2
18.	Cognitive function	Yes/no and CTCAE
19.	Mood alteration	CTCAE in C1; not included in C2
20.	Psychiatric diseases	Yes/no and 4 items
21.	Fear	C2: Yes/no and CTCAE
22.	Insomnia	C2: Yes/no and CTCAE
23.	Depression	C2: Yes/no and CTCAE
24.	Further psychiatric diseases	C1: Free text, not included in C2
25.	Epilepsy	CTCAE
26.	Reflexes	Only in pilot phase: 2 grades
27.	CT/MRT	CTCAE
28.	Leukoencephalopathy	Free text
29.	Further	Free text
30.	Endocrine system	Yes/no
31.	Infertility	Yes/no
32.	Diabetes mellitus	Yes/no
33.	Further endocrine system	Yes/no
34.	Ovarian insufficiency	2 items
35.	Osteoporosis	CTCAE
36.	Menopause	2 items
37.	Hormones	In C1 Free text, in C2 not included
38.	Further endocrine (female)	Free text
39.	Erection disability	CTCAE
40.	Sperm quality	Pathological, Free text
41.	Hormones	Pathological, Free text
42.	Further endocrine (male)	Free text
43.	Kidney/Liver general	Yes/no
44.	Kidney insufficiency	CTCAE
45.	Liver dysfunction	Free text

46.	Cardiac disease	Yes/no
47.	Cardiomyopathy	CTCAE
48.	Ischemia, angina pectoris, infarction	CTCAE
49.	Heart insufficiency	CTCAE
50.	Ejection fraction, left ventricular dysfunction	CTCAE
51.	Cardia dyspnea	CTCAE
52.	Cardiac arrhythmia	CTCAE
53.	Hypertension	CGCAE
54.	Further	Free text
55.	Stomach/digestive system	Yes/no
56.	Gastritis	CTCAE
57.	Colitis	CTCAE
58.	Further	Free text
59.	Eye disease	Yes/no
60.	Eye impairment	CTCAE
61.	Conjunctivitis, keratitis	CTCAE
62.	Cataract	CTCAE
63.	Others	Free text
64.	Blood disorder	Yes/no in C1; in C2 not included
65.	Teeth	Yes/no
66.	Fatigue	Yes/no and CTCAE
67.	Sicca syndrome	Yes/no; organ
68.	Chronic GvHD	Yes/no; organ
69.	Infection	Yes/no and CTCAE
70.	Infection type	Free text
71.	Osteonecrosis	Yes/no and CTCAE
72.	Secondary malignancies	Yes/no and type
73.	Thyroid	Yes/No
74.	Hyperthyroidism	CTCAE
75.	Hypothyroidism	CTCAE
76.	Further specific diseases	Free text
77.	Pain	Free text
78.	Allergies	Free text
79.	ECOG	Grades 0-4
80.	Further general health condition	Free text

The CRF was slightly modified during the project periods (C1=first period, C2=second period) after inclusion of 249 patients for several items

Table S4: ECOG Status in Different Age Groups and Trial Generations

ECOG	<= 25 yrs [n (%)]	> 25-55 yrs [n (%)]	> 55 yrs [n (%)]	Trials 2-4	Trials 5-7
N	183	314	45	113	409
0	148 (81)	207 (66)	12 (48)	79 (70)	288 (70)
1	27 (15)	89 (28)	9 (36)	30 (27)	95 (23)
2	5 (3)	13 (4)	1 (4)	1 (1)	18 (4)
3	3 (2)	4 (1)	2 (8)	3 (3)	6 (2)
4	0	1 (0.3)	1 (4)	0	2 (0.49)
0 - 1	175 (96)	296 (94)	21 (84)	109 (96)	383 (94)
2 - 4	8 (4)	18 (6)	4 (16)	4 (4)	26 (6)
Median ECOG	1	1	2	1	1

Table S5: Overview Details on Osteonecrosis and Fatigue

	Number [N]	Median age at diagnosis [years]	Median age at event [years]	Median time diagnosis - event [years]	Location ^f
Osteonecrosis					
Any grade ^a	41	24	27	3	8x hip, 4x shoulder, 1x both
Grade 1 – 2	7	25	30 ^b	5 ^b	
Grade 3	19	25.5	28 ^c	2.5 ^c	5 x hip
Grade 4	14	23	26 ^d	2 ^d	3x hip, 3x shoulder, 1x both
Unknown grade	1	20	^b	^b	1x shoulder
Fatigue					
	Number [N]	Median age at diagnosis [years]	Median age at event [years] ^e	Median Time Diagnosis - event [years] ^e	Status at evaluation: ongoing, not ongoing, unknown
Any grade	71	31	36	4.8	55, 9, 7
Grade 1 – 2	63	31	36	4.7	47, 9, 7
Grade 3	7	30	33	4.8	7, 0, 0
Grade 4	1	54	^b	^b	1, 0, 0

^a 7 dates of event missing; ^b 1 data missing, ^c 3 data missing, ^d 2 data missing, ^e 29 data missing, ^f location missing in the rest

Table S6: List of Secondary Malignancies

Secondary malignancies	Age at diagnosis [years]	Age at event [years]	Time diagnosis - event [years]
Glioblastoma	17	26	9
Breast Cancer	20	26	7
Breast Cancer	21	43	23
Cervical Cancer	16	32	15
Prostate Cancer	49	64	15
Prostate Cancer	64	72	8
Stomach Cancer	36	48	12
Small intestine Cancer	46	65	2
Sarcoma	28	46	18
Melanoma*	18	22	4
Melanoma	18	24	7
Melanoma	18	39	22
Melanoma *	27	39	3
Basal cell Cancer	24	37	13
Basal cell Cancer	47	58	12
Basal cell Cancer	49	68	19
Basal cell Cancer*	59	70	12
AML*	47	49	2
AML	53	57	4
MDS/AML	58	64	7
CML*	36	NA	NA

* Patients with SCT

Table S7: Impact of Age at Evaluation (<= 55 yrs) and Age at Diagnosis (<= 25 yrs) on General Condition and Incidence of Comorbidities

	<=55 years		> 55 years		P-uni (multi)	<=25 years		26 - 55 years		P-uni (multi)
	N	%	N	%		N	%	N	%	
ECOG grade 0 - 1	416	95	76	88	0.01 (0.0005)	175	96	296	94	ns (ns)
>= one disease	289	64	66	75	ns (0.0062)	105	55	230	72	<.0001 0.0020)
Skin	81	18	16	18	ns (ns)	31	16	61	19	ns (ns)
Lung	32	7	9	10	ns (0.0453)	12	6	27	8	ns (ns)
Cardiac system	49	11	21	24	0.0009 (0.0013)	17	9	46	14	ns (ns)
GI system	24	5	6	7	ns (ns)	7	4	20	6	ns (ns)
Neurologic system	112	25	35	40	0.0042 (0.0013)	36	19	100	31	0.002 (0.0083)
Kidney/liver	46	10	10	11	ns (ns)	15	8	36	11	ns (ns)
Endocrine system (f)	41	24	9	23	ns (ns)	13	19	34	26	ns (ns)
Endocrine system (m)	44	16	11	23	ns (ns)	10	8	39	21	0.0036 (0.0195)
Eye impairment	53	12	12	14	ns (ns)	19	10	40	13	ns (ns)
Infection	57	13	7	8	ns (ns)	23	12	38	12	ns (ns)
Fatigue	57	13	14	16	ns (ns)	20	11	47	15	ns (ns)
GvHD	71	16	8	9	ns (ns)	18	9	57	18	0.0099 (0.0111)
Osteonecrosis	38	8	3	3	ns (ns)	24	13	17	5	0.0034 (0.007)
Secondary malignancies	13	3	8	9	0.0060 (0.092)	8	4	10	3	ns (ns)
Hypothyroidism	19	4	7	8	Ns (ns)	6	3	20	6	Ns (ns)
Hyperthyroidism	5	1	2	2	Ns (ns)	5	2	1	1	Ns (ns)

ns: non-significant >.05; GI: Gastrointestinal; f: female; m: male; GvHD: Graft versus Host disease; P-uni: P value for univariate analysis; multi: P value for multivariate analysis