SUPPLEMENTARY APPENDIX

Second malignancies after treatment of childhood non-Hodgkin lymphoma – a report of the Berlin-Frankfurt-Muenster study group

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 doi:10.3324/haematol.2019.244780

Received: December 11, 2019.

Accepted: April 9, 2020.

Pre-published: April 16, 2020.

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Online supplemental appendix

Supplemental methods

NHL classification

NHL were classified using classifications valid at the time of diagnosis: Kiel-,[1] Revised European-American Lymphoma-,[2] and WHO-classification,[3] respectively.

Treatment in the consecutive multicentre non-Hodgkin lymphoma-Berlin-Frankfurt-Muenster (NHL-BFM)-protocols

In all protocols, patients with lymphoblastic lymphoma (LBL) received an acute lymphoblastic leukemia (ALL)-type-BFM-regimen consisting of an eight-drug induction, consolidation with methotrexate 4 x 0.5-5g/m²/24 hours intravenously, re-intensification, and oral maintenance up to two years of total therapy duration. The cumulative doses of daunorubicine/doxorubicine (equivalence ratio 1:1) and cyclophosphamide were 120-240mg/m² and 2-3g/m², respectively. Advanced stage (III and IV) patients received prophylactic cranial radiotherapy of 12-18Gy up to the trial NHL-BFM-90. Patients with LBL and CNS-involvement received cranial radiotherapy of 12-24Gy throughout the study period. Until NHL-BFM-86, patients with LBL and persisting mediastinal tumor after induction received local radiotherapy (30Gy).

Patients with mature B-cell-NHL or anaplastic large cell lymphoma (ALCL) received two to six courses of five-day block-type chemotherapy based on dexamethasone, cyclophosphamide/ifosfamide (equivalence ratio 1:4), methotrexate, doxorubicine, etoposide, cytarabine, and intrathecal methotrexate/cytarabine/prednisolone therapy. Treatment intensity was stratified according to stage and initial LDH from study NHL-BFM-90. In the R2-group the cumulative doses were 2-4g/m² for cyclophosphamide, 50-100mg/m² for doxorubicine, and 400mg/m² for etoposide, whereas in the group R3 they were 2.4-9g/m², 100-200mg/m², and 600-900mg/m², respectively. From trial NHL-BFM 86 no prophylactic/therapeutic cranial radiotherapy was applied. Local radiotherapy was not recommended for patients with mature B-NHL. All cumulative drug- and radiation doses are listed in the supplemental tables S1 and S2.

Follow-up

In all patients registered to the NHL-BFM datacentre, follow-up status after therapy was ascertained semi-annually within the first 5 years after diagnosis and annually for the following 5 years. Thereafter it was assessed every 2 years. Standardized forms including the date of the most recent contact and the status of the patient were completed by the treating institution. In addition, the NHL-BFM study centre was notified of all SMNs after NHL reported to the GCCR. The long-term follow-up of patients was ascertained by the GCCR on the basis of five-yearly inquiries. Lost to follow-up (LFU) has been defined as lack of information about a patient after two consecutive updates.

Supplemental information, including verification of the diagnosis, pathology reports, and the outcome of the patient, was obtained for all cases of SMNs. In cases of multiple second malignancies after a NHL, only the first second cancer was taken into the analysis.

Definition of SMN

Second malignant neoplasm was considered to be proven when (i) it was a non-lymphoid malignancy, (ii) in lymphoid malignancy there was a lineage change, i.e., B lineage to T lineage and vice versa, (iii) in lymphoid malignancy there was a change with respect to the

differentiation compartment, i.e., from a precursor B (or T) neoplasm to mature B (or T) neoplasm or vice versa, (iiii) in Burkitt lymphoma/Burkitt leukemia there was a MYC rearrangement at different break points between the first and the second cancer or (iiiii) in mature B-NHL there was a different immunoglobulin light-chain restriction between the first and second malignancy i.e. λ to κ or vice versa. Not included as SMNs were eight late-recurring lymphoid malignancies with different clonal rearrangements of IgH- and T-cell-receptor-genes, but no differences with respect to discriminators listed above (ii-iiiii), since clonal evolution in these cases cannot be excluded. Evaluation of clonal origin via multiplex-PCR (BIOMED-2 method[4]) was performed for all available tumor samples in cases of second lymphoid malignancy.

References supplemental appendix

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Supplemental tables

Supplemental Table 1: Therapy strategy and cumulative doses of drugs and radiotherapy in the NHL-BFM-studies: ALL-type therapy

Therapy trials ALL/NHL-BFM-81, -83, -86, NHL-BFM-90, -95V, -95, EURO-LB-02: therapy strategy and cumulative doses of drugs and radiotherapy																		
ALL-type therapy																		
Trial	Group	Stage	Courses	N*	Cumulative doses in mg/m² BSA (Asparaginase in IU/m² BSA)												RT dosis in Gy	
					DNR	DOX	CPM	Ifo	VCR	MTX iv	ARAC	ASP	6MP	6TG	Pred	Dex	i.th. MTX**	CRT	LRT
81	NB 1	I, II	I-CNSp-MT18	8	120	0	3000	0	6	500x4	1200	5000x21	23320	0	1680	0	x4	0	TR30
	NB 2	III, IV	I-int-III-MT18	30	120	60	2000	0	9	0	1800	+1000x4	24720	840	1680	140	x6	0	TR30
		CNS+		2						500x4							x10	30§	
83	NB L	I, II	I-int-MT18	4	120	0	3000	0	6	500x4	1200	10000x8	22620	0	1680	0	x6	0	0
	NB H	III, IV	I-int-III-MT18	58	120	60	2000	0	9	500x4	1800	10000x12	19820	840	1680	140	x8	18#	0
		CNS+															x11	30§§	0
86	NB-SRG	I, II	I-M-MT18	5	160	0	2000	0	6	5000x4	1200	10000x8	22330	0	1680	0	x7	0	TR30

	NB-RG	III, IV	I-M-II-MT18	62	160	60	3000	0	12	5000x4	1800	10000x12	19820	840	1680	210	x9	12[#]	TR30
	NB-EG	NR/PR	I-E-II-MT18	4	160	60[&]	3000	8000	12	5000x4	17800	10000x12	18395	840	4480	210	x9	18[#]	TR30
		CNS+															x13	24[§§]	
90	SRG	I, II	I-M-MT24	23	120	0	2000	0	6	5000x4	1200	10000x8	28630	0	1680	0	x9	0	0
	RG	III, IV	I-M-II-MT24	143	120	120	3000	0	12	5000x4	1800	10000x12	28630	840	1680	210	x11	12[#]	0
		CNS+		1													x13	24[§§]	
95V	SRG	I, II	I-M-MT24	3	120	0	2000	0	6	5000x4	1200	5000x8	28630	0	1680	0	x9	0	0
	RG	III, IV	I-M-II-MT24	26	120	120	3000	0	12	5000x4	1800	5000x12	28630	840	1680	210	x11	12[#]	0
		CNS+		2													x13	24[§§]	
95	SR	I, II	I-M-MT24	24	120	0	2000	0	6	5000x4	1200	5000x8	32130	0	1680	0	x9	0	0
	MR	III, IV	I-M-II-MT24	198	120	120	3000	0	12	5000x4	1800	+10000x4	28630	840	1680	210	x11	0	0
	HR	TR>30%	Ia-6xHR-II-MT24	9															
		CNS+															x13	18[§§]	

Euro-LB	Pred	I, II	I-M-MT24/18	28	120	0	2000	0	6	5000x4	1200	10000x8	32130	0	1680	0	x9	0	0
	Dexa	I, II	I-M-MT24/18	1					12						420	236			
	Pred	III, IV	I-M-II-MT24/18	154	120	120	3000	0	12	5000x4	1800	10000x12	28980	840	1680	236	x11	0	0
	Dexa	III, IV	I-M-II-MT24/18	54											420	452			
		CNS+															x13	18§§	

* information about exact assignment to respective therapy group within the ALL-type therapy missing in 43 patients

**: i.th. MTX (patients >3 years of age: 12mg, 2-3 years of age: 10mg, <2 years of age:8 mg)
§: CRT therapeutic including spinal cord
§§: CRT therapeutic without spinal cord
#: CRT prophylactic
&: additional therapy with mitoxantron 40mg/m² BSA
MT18: maintenance therapy up to 18 months total therapy duration

MT24: maintenance therapy up to 24 months total therapy duration
MT18/24: maintenance therapy up to 18 months versus 24 total therapy duration (randomized)

Abbreviations:
drugs: ARA-C: cytarabine; ASP: asparaginase; CPM: cyclophosphamide; Dex: dexamethasone; DNR: daunorubicin; DOX: doxorubicin; IFO: ifosfamide; MTX: methotrexate; Pred: prednisone; VCR: vincristine; 6MP: mercaptopurine; 6TG: thioguanine

BSA: body surface area; CRT: cranial radiotherapy; Intens: intesified if tumor residual after 2 courses; i.th.: intrathecal therapy; LRT: local radiotherapy; MT: maintenance therapy; N: number of patients; NR: not resected; R: resected; RF: risk factors; RT: radiotherapy; TR: tumor residual

Supplemental Table 2: Therapy strategy and cumulative doses of drugs and radiotherapy in the NHL-BFM-studies: B-NHL-type therapy

Therapy trials NHL-BFM-81, -83, -86, NHL-BFM-90, -95V, -95, -B04; ALCL99: therapy strategy and cumulative doses of drugs and radiotherapy																	
B-Type therapy																	
Trial	Group	Stage	Courses	N[$]	Cumulative doses in mg/m² BSA											RT dosis in Gy		
					VM26	VP16	DOX	CPM	Ifo	VCR	MTX iv	ARA-C	Pred	Dex	i.th.	CRT	LRT	OP
B-NHL																		
81	B1	I, II-R	V-1-2-1-2	21	330	0	100	5000	0	0	500x4	600	1680	0	x4*	0	30	
	B2	II-NR, III, IV, B-AL	V-1-2-1-2-1-2-1-2	61	660	0	200	9000	0	0	500x8	1200	1680	0	x8*	24[#], 30[§]	Indiv	SL
83	B-L	I, II-R	V-1-2-1	32	330	0	50	4000	0	0	500x3	600	150	150	x3*	0	TR30	
	B-H	II-NR, III, IV, B-AL	V-1-2-1-2-1-2	98	495	0	150	7000	0	0	500x6	900	150	300	x6*	24[#]		SL
	B-H/CNS	IV/B-AL, CNS+	V-1-2z-1z-2z-1z-2z	1	495	0	150	7000	0	0	500x6	900	150	300	x1*+ OM	30[§§]		SL
86	B-SR	I, II-R	V-A-B-A	40	400	0	50	2000	8000	0	500x3	1200	150	150	x3**	0	TR30	SL
	B-RG	II-NR, III	V-A-B-A-B-A-B	110	600	0	150	4000	12000	0	500x6	1800	150	300	x6**	0	TR30	SL
	B-IV/ B-AL	IV, B-AL	V-AA-BB-AA-BB-AA-BB	75	600	0	150	4000	12000	9	5000x6	1800	150	300	x12**/	24[§§]	TR30	SL
90	R1	R	V-A-B	78	0	200	50	1400	4000	0	500x2	600	0	140	x3**	0	0	

	R2	NR!	V-AA-BB-AA-BB	211	0	400	100	2400	8000	6	5000x4	1200	0	240	x9**/	0		SL
	R3	Other, no CNS+	V-AA-BB-AA-BB-AA-BB	194	0	600	150	3400	12000	9	5000x6	1800	0	340	x13**	0		SL
	CNS+		V-AA-BBz-AAz-BBz-AAz-BBz	50	0	600	150	3400	1200	9	5000x6	1800	0	340	OM	0		SL
	Intens.		V-AA-BB-CC“-AA-BB-CC		0	1300	100	2400	8000	9	5000x4	17200	0	440	x11**	0		
95V	R1	R	V-A-B		0	200	50	1400	4000	0	500x2	600	0	140	x3**	0	0	
	R2	NR!	V-AA-BB-AA-BB		0	400	100	2400	8000	6	5000x4	1200	0	240	x9**//	0		SL
	R3	Other, no CNS+	V-AA-BB-AA-BB-AA-BB		0	600	150	3400	12000	9	5000x6	1800	0	340	x13**	0		SL
	CNS+		V-AA-BBz-AAz-BBz-AAz-BBz		0	600	150	3400	1200	9	5000x6	1800	0	340	OM	0		SL
95	R1	R	V-A-B	65	0	200	50	1400	4000	0	1000x2	600	0	140	x3**	0	0	
	R2	NR,I,II, III-LDH<500	V-A-B-A-B	321	0	400	100	2400	8000	6	1000x4	1200	0	240	x5**	0	0	
	R3	NR, III-LDH≥500 <1000, IV/B-AL-	V-AA-BB-CC-AA-BB““	114	0	900	100	2400	8000	7.5	5000x4	13200	0	340	x10**//	0	0	

		LDH <1000														
	R4	NR,III/IV/ B-AL-LDH≥1000	V-AA-BB-CC-AA-BB“”-CC	230	0	1400	100	2400	8000	9	5000x4	25200	0	440	x11**//	0	0
	CNS+		V-AA-BBz-CCz-AAz-BBz“”-CCz	6	0	1400	100	2400	8000	9	5000x4	25200	0	440	OM	0	0
B04	R1	R	V-A-B	48	0	200	50	1400	4000	0	1000x2	600	0	140	x3**	0	0
	R2	NR,I,II, III-LDH<500	V-A-B-A-B	215	0	400	100	2400	8000	6	1000x4	1200	0	240	x5**	0	0
	R3	NR, III-LDH≥500 <1000, IV/B-AL-LDH <1000	V-AA-BB-CC-AA-BB“”	82	0	900	100	2400	8000	7.5	5000x4	13200	0	340	x10**//	0	0
	R4	NR,III/IV/ B-AL-LDH≥1000	V-AA-BB-CC-AA-BB“”-CC	205	0	1400	100	2400	8000	9	5000x4	25200	0	440	x11**//	0	0
	CNS+		V-AAz1-BBz1-CC-AAz2-BBz2“”-CC		0	1400	100	2400	8000	9	5000x4	25200	0	440	x14**	0	0
	PMLBL 1	LDH<500	V-A-B-A-B-A-B	8	0	600	150	3400	12000	9	1000x6	1800	0	340	x7**	0	0

	PMLBL2	LDH≥500	V-AA-BB-CC-AA-BB-CC-BB	9	0	1400	150	3400	8000	9	5000x5	25200	0	440	x13**//	0	0
ALCL																	
81-86	In B-NHL																
90	K1	I, II-R	V-A-B-A	9	0	400	50	1400	8000	0	500x3	1200	0	140	x4**	0	0
	K2	II-NR, III	V-A-B-A-B-A-B	62	0	600	150	3400	12000	9	500x6	1800	0	340	x7**	0	0
	K3	IV	V-AA-BB-CC-AA-BB-CC	21	0	1300	100	2400	8000	9	5000x4	17200	0	440	x11**//	0	0
	CNS+		V-AA-BBz-AAz-BBz-AAz-BBz		0	600	150	3400	1200	9	5000x6	1800	0	340	OM	0	0
95V	K1	I, II-R	V-A-B-A	1	0	400	50	1400	8000	0	500x3	1200	0	140	x4**	0	0
	K2	II-NR, III	V-A-B-A-B-A-B	9	0	600	150	3400	12000	9	500x6	1800	0	340	x7**	0	0
	K3	IV	V-AA-BB-CC-AA-BB-CC	9	0	1300	100	2400	8000	9	5000x4	17200	0	440	x11**//	0	0
	CNS+		V-AA-BBz-AAz-BBz-AAz-BBz	1	0	600	150	3400	1200	9	5000x6	1800	0	340	OM	0	0

95	K1	I, II-R, no RF	V-A-B-A	4	0	400	50	1400	8000	0	500x3	1200	0	140	x4**	0	0
	K2	II-NR, III, no RF	V-A-B-A-B-A-B	24	0	600	150	3400	12000	9	500x6	1800	0	340	x7**	0	0
	K3	IV or/and RF	V-AA-BB-CC-AA-BB-CC	52	0	1300	100	2400	8000	9	5000x4	17200	0	440	x11**//	0	0
	CNS+		V-AA-BBz-AAz-BBz-AAz-BBz		0	600	150	3400	1200	9	5000x6	1800	0	340	OM	0	0
										VBL							
ALCL 99	VL	I-R	V-A-B-A	22	0	400	50	1400	8000	0	500x3	1200	0	140	x4**	0	0
	SR	NR, no RF	V-A-B-A-B-A-B	56	0	600	150	3400	12000	0	500x6	1800	0	340	x7**	0	0
			V-AM-BM-AM-BM-AM-BM		0	600	150	3400	12000	0	3000x6	1800	0	340	x1**	0	0
	HR	>1RF		89													
		lung, skin, mediastinum	V-A-BV-AV-BV-AV-BV-VBL weekly=		0	600	150	3400	12000	230	500x6	1800	0	340	x7**	0	0
		liver, spleen	V-AM-BMV-AMV-BMV-AMV-BMV		0	600	150	3400	12000	230	3000x6	1800	0	340	x1**	0	0
	CNS+		V-AA-BBz-AAz-BBz-AAz-BBz	6	0	600	150	3400	12000	9	5000x6	1800	0	340	OM	0	0

$ information about exact assignment to respective therapy group within the B-type therapy missing in 48 patients

*: i.th. MTX (12mg for age >3 years, age 2-3 years: 10mg, age 1-2 years:8 mg, age <1 year: 6mg)
**: i.th. Triple (age >3 years: MTX 12mg, ARA-C 30mg, Pred 10mg; age 2-3 years: MTX 10mg, ARA-C 26mg, Pred 8mg; age 1-2years: MTX 8mg, ARA-C 20mg, Pred 6mg; age<1 year: MTX 6mg, ARA-C 16mg, Pred 4mg)
**/: i.th. Triple with half of the dosis
**//: i.th. Triple with half of the dosis in AA, BB
§: CRT therapeutic including spinal cord
§§: CRT therapeutic without spinal cord
#: CRT prophylactic
“: if vital tumor residual after 3rd therapy course subsequent ASCT
““: if vital tumor residual after 5th therapy course subsequent ASCT
=: up to 12 months duration
!: NR and only extra-abdominal or abdominal and LDH<500 U/L, no BM-, CNS- or multilocular bone involvement

Abbreviations:
drugs: ARA-C: cytarabine; ASP: asparaginase; CPM: cyclophosphamide; DEXA: dexamethasone; DNR: daunorubicin; DOX: doxorubicin; IFO: ifosfamide; MTX: methotrexate; PRED: prednisone; VBL: vinblastin; VCR: vincristine; VM26: vimentin; VP16: etoposide;

BSA: body surface area; CRT: cranial radiotherapy; Intens: intesified if tumor residual after 2 courses; HR: high risk group; LRT: local radiotherapy; NR: not resected; OM: Omaya reservoir with intraventricular therapy; OP: operation; PMLBL-1: primary mediastinal B-cell lymphoma and LDH<500 U/L; PMLBL-2: primary mediastinal B-cell lymphoma and LDH≥500 U/L; R: resected; RF: risk factors; SL: second-look operation; SR: standard risk group; TR: tumor residual; VL: very low risk group

Supplemental Table 3: Patients with second lymphoid malignancy after Non-Hodgkin lymphoma (NHL) in childhood

Patients developing second lymphoid malignancy							
Sex	Age (years) at first NHL-Dx	1.NHL	Stage of 1. NHL	SLM	Definition	Time to SLM (years)	Outcome
M	0.7	T-LBL	III	B-NHL	Lineage switch (T-B)	3.6	Death (SMN)
M	11.1	T-LBL	III	PTCL	Change in differentiation compartment (precursor-mature)	1.9	HSCT, alive
M	8.0	BL	III	T-LBL	Lineage switch (B-T)	7.6	alive
M	8.5	B-AL	IV	T-LBL	Lineage switch (B-T)	2.9	alive
F	6.7	BL	I	BL	Light chain restriction switch (K –λ)	3.5	alive
M	10.5	BL	IV	B-AL	Different breakpoint (c-myc/IgH)	2.9	Death (TRM) after allo HSCT
M*	9.6	CB	III	c-ALL	Change in differentiation compartment (mature-precursor)	4.4	Death (SMN)
F	14.7	CB	III	HD	Different histology	3.6	LFU
M	4.8	CB	II	c-ALL	Change in differentiation compartment (mature-precursor)	2.9	HSCT, alive
F*	5.6	CB	III	ALCL-T	Lineage switch (B-T)	3.8	Death (other)

F*	9.6	CB	III	c-ALL	Change in differentiation compartment (mature-precursor)	2.4	3rd MN, alive
M	1.6	CB	III	HD	Different histology	20.1	LFU
F*	9.5	PB	III	BL	Different histology	3.4	3rd MN-death
M	14.9	TCRB	II	HD	Different histology	10.5	Alive
M	5.3	BL	I	PTCL	Lineage switch (B-T)	6.0	3rd MN-alive
F	8.2	ALCL	III	ALL	Change in differentiation compartment (mature-precursor), lineage switch	1.5	Alive
M	12.0	ALCL	II	HD	Different histology, lineage switch	12.8	LFU
M*	9.3	ALCL	III	CB	Different histology, lineage switch	4.8	3rd MN-death
F*	1.2	T-LBL	III	B-NHL	Lineage switch (T-B)	11.1	3rd MN-alive
M	10.4	B-NHL nfc	III	T-LBL	Lineage switch (B-T)	3.1	Death (SMN)

* Known cancer predisposing condition

Abbreviations: ALCL: anaplastic large cell lymphoma; ALL: acute lymphoblastic leukemia; B-AL: Burkitt leukemia; BL: Burkitt lymphoma; B-NHL: mature B-cell lymphoma (other than BL/B-AL); c-ALL: common-antigen (CD10+)-acute lymphoblastic leukemia; CB: centroblastic lymphoma; Dx: diagnosis; F: female; HD: Hodgkin disease; HSCT: hematopoetic stem cell transplantation; LFU: lost to follow-up; M:male; nfc: not further classified; PB: plasmoblastic lymphoma; PTCL: peripheral T-cell lymphoma; SLM: second lymphoid malignancy; TCRB: T-cell rich B-cell lymphoma; T-LBL: T-cell lymphoblastic lymphoma; TRM: therapy-related mortality; 3rd MN: third malignant neoplasm