

# Outcome of and prognostic factors for relapse in children and adolescents with mature B-cell lymphoma and leukemia treated in three consecutive prospective “*Lymphomes Malins B*” protocols. A Société Française des Cancers de l’Enfant study

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## **ON LINE SUPPLEMENT**

### **METHODS**

#### ***Patients***

CR was assessed by CT scan as well as by histology if there was a residual mass. Forty-eight patients who did not achieve CR with induction therapy (35 had tumour progression and 13 had partial remission salvaged by treatment intensification) and six patients who developed a second lymphoma defined by a different biology or a long delay [5 Burkitt lymphoma (BL), 1 diffuse large B-cell lymphoma (DLBCL)], were not included in the study. Patient characteristics at initial diagnosis (pathological diagnosis, Murphy stage, initial risk group, LDH level subdivided into less than or equal to and more than 2 times ( $\leq$  or  $>2N$ ) the upper limit of the institution's normal range), first-line treatment, date and sites of relapse were extracted from the LMB databases. Additional information on treatment of relapse was collected from patient medical records and from direct contact with the investigating centers when necessary.

#### ***Initial treatment***

Differences among the different LMB studies were minor and as follow: i) B-AL with  $<70\%$  blasts in BM were assigned to Group B in the LMB89 study, whereas they have been placed in risk Group C in the other two studies, ii) maintenance course in Group B was omitted when results of the FAB/LMB96 randomization were known, and iii) cranial irradiation (24 Gy) was only delivered in the LMB89 study and to patients with blasts in the CSF or cranial palsies.

#### ***Histopathology/Immunophenotyping***

Patients with mature B-cell lymphoma [i.e. BL, DLBCL and primary mediastinal B-cell lymphoma (PMBL), the last two being "large cell histology"], and mature B-cell leukemia (B-AL) with more than 25% Burkitt blasts in bone marrow (BM)] were enrolled in one of the

three LMB studies. Histology was reviewed nationally (LMB89) and internationally (FAB/LMB96) according to the classification of the time.<sup>2,3,5,6</sup> Five of the cases in this study were classified as aggressive B-NHL “not otherwise specified” and were analyzed with BL.

### ***Response***

CR was defined as complete disappearance of all tumor masses on imaging studies (ultrasound, CT scan and/or MRI) or absence of viable tumor cells in a residual mass, normal BM examination, and no evidence of CNS disease. Positron Emission Tomography (PET) scan results were not considered in the response assessment. Partial response (PR) was defined by tumor reduction greater than 50%, stable disease (SD) as tumor reduction of less than 50%, and all other cases were classified as progression.

### ***Statistical Analysis***

Survival was defined as the time between the diagnosis of relapse and the date of death from any cause or the date of last contact for patients who were still alive. Survival was estimated by the Kaplan-Meier method. The 95% confidence intervals (95% CI) of the survival rates were calculated using the Rothman method. Follow-up duration was estimated by the reverse Kaplan-Meier method. The prognostic effect of the following variables were evaluated: age, sex, histological diagnosis, initial risk group, initial LDH level, time between initial diagnosis and relapse, relapse site, and type of salvage chemotherapy. The influence of these parameters on survival was defined by univariate analysis using the log-rank test, and all variables that had a p-value less than 0.20 were evaluated using a multivariable Cox model. All analyses were performed using SAS Software, version 9.1.

**Supplement Table A:** High Dose Chemotherapy regimen used for B-NHL relapses following LMB 89, 96 and 2001 protocols

<b><i>BEAM</i></b>		
BCNU	300 mg / m <sup>2</sup>	D-8
VP 16	100 mg / m <sup>2</sup> / 12h	D-7 D-6 D-5 D-4
Aracytine	100 mg / m <sup>2</sup> / 12h	D-7 D-6 D-5 D-4
Melphalan	140 mg / m <sup>2</sup>	D-3
Autograft		D0
<b><i>BAM</i></b>		
Busulfan	60 mg / m <sup>2</sup> /d	D-11 and D-7
Busulfan	120 mg / m <sup>2</sup> /d	D-10 D-9 D-8
Aracytine	3 g / m <sup>2</sup> x 2 /d	D-6 D-5 D-4
Melphalan	140 mg / m <sup>2</sup> /d	D-3
Autograft		D0
<b><i>BUMEL</i></b>		
Busulfan	75 mg / m <sup>2</sup> /d	D-8 D-4
Busulfan	150 mg / m <sup>2</sup> /d	D-7 D-6 D-5
Melphalan	140 mg / m <sup>2</sup>	D-3
Autograft		D0
<b><i>TAM</i></b>		
TBI	6 Gy x 2 /d	D-12 D-11 D-10
Aracytine	3 g / m <sup>2</sup> x 2 /d	D-8 D-7 D-6 D-5
Melphalan	140 mg / m <sup>2</sup>	D-3
Allograft		D0
<b><i>TBI ENDOXAN</i></b>		
TBI	2x2 Gy/d	D-8, D-7, D-6
Endoxan	60 mg/kg/d	D-5, D-4, D-3
Allograft		D0

Abbreviations: D, day; d, day; h, hour; TBI, Total body irradiation; Gy, Grays

**Supplement Table B: Characteristics, treatment and outcome of the patients who relapsed in CNS, either isolated (patients 1 to 15, either combined (16 to 25))**

Pat ient	Site at diagno sis	histo	Initial Murphy Staging	Gro up	LDH level	Sites of relapse	Salvage CT	Rit uxi ma b	Respon se	HDC/HSCT	RT X	outcome
1	node	BL	I	A	<2N	CNS	Group C	no	CR2	BAM/auto	no	alive
2	abd	BL	II	A	<2N	CNS	CYVE	no	NE	no	no	TRT death
3	node	BL	II	B	<2N	CNS	CYVE	no	NA	no	no	DOD
4	abd	BL	III	B	>2N	CNS	HDMTX/ CYVE	no	CR2	BEAM/ auto	no	alive
5	abd	BL	III	B	>2N	CNS	HDMTX	no	CR2	BEAM/ auto	yes	DOD
6	abd	BL	IV BM	B	<2N	CNS	CYVE	no	CR2	BAM/auto	no	alive
7	node	BL	IV CNS	C	<2N	CNS	HDMTX/IT /topotecan	no	CR2	BEAM/ auto	no	DOD
8	abd	BL	IV BM	C	>2N	CNS	HDMTX/IT	no	CR2	BEAM/ auto	yes	alive
9	abd	BL	IV CNS	C	>2N	CNS	VENOMID	no	progr	no	no	DOD
10	abd	BL	B-AL	C	>2N	CNS	HDMTX/ HDcyta	no	CR2	BEAM/ auto	no	DOD
11	B-AL	BL	B-AL	C	>2N	CNS	HDMTX	no	CR2	BAM/auto	no	DOD
12	B-AL	BL	B-AL	C	>2N	CNS	HDMTX	no	progr	no	no	DOD
13	B-AL	BL	B-AL	C	>2N	CNS	HDMTX/ HDcyclo	no	progr	no	no	DOD
14	abd	BL	B-AL CNS	C	>2N	CNS	NA	yes	CR2	NA/allo	no	DOD
15	abd	BL	B-AL CNS	C	>2N	CNS	HDMTX	no	CR2	BAM/auto	no	DOD
16	abd	DLBC	III	B	>2N	BM/CNS	HDMTX/ HDcyta	yes	CR2	TBI/cyclo/ allo	no	alive
17	abd	BL	III	B	>2N	BM/CNS/ other	CYVE	no	CR2	BEAM/ auto	no	DOD
18	abd	BL	III	B	>2N	CNS/other	CYVE	no	CR2	BEAM/ auto	no	DOD
19	abd	BL	IV BM	B	>2N	1 <sup>ary</sup> /BM/ CNS/other	CYVE	no	NE	TAM/allo	no	DOD
20	abd	BL	III	B	>2N	1 <sup>ary</sup> /BM/ CNS/other	CYVE	no	PR	BEAM/ auto	no	DOD
21	abd	BL	III	B	<2N	CNS/other	COD	no	PR	no	yes	DOD
22	B-AL	BL	B-AL CNS	C	>2N	BM/ CNS/other	VENOMID	no	CR2	BAM/auto	no	DOD
23	abd	BL	III	B	>2N	BM/CNS	LMB grC	yes	prog	no	no	DOD
24	abd	BL	IV CNS	C	>2N	BM/CNS	HDMTX	no	prog	no	no	DOD
25	abd	BL	IV CNS	C	>2N	BM/CNS	VENOMID	no	prog	no	no	DOD

Abbreviations: abd: abdomen; B-AL: mature B-cell leukemia BM: bone marrow; CNS: central nervous system; 1<sup>ary</sup>: primary site; other: other site than primary, BM or CNS;

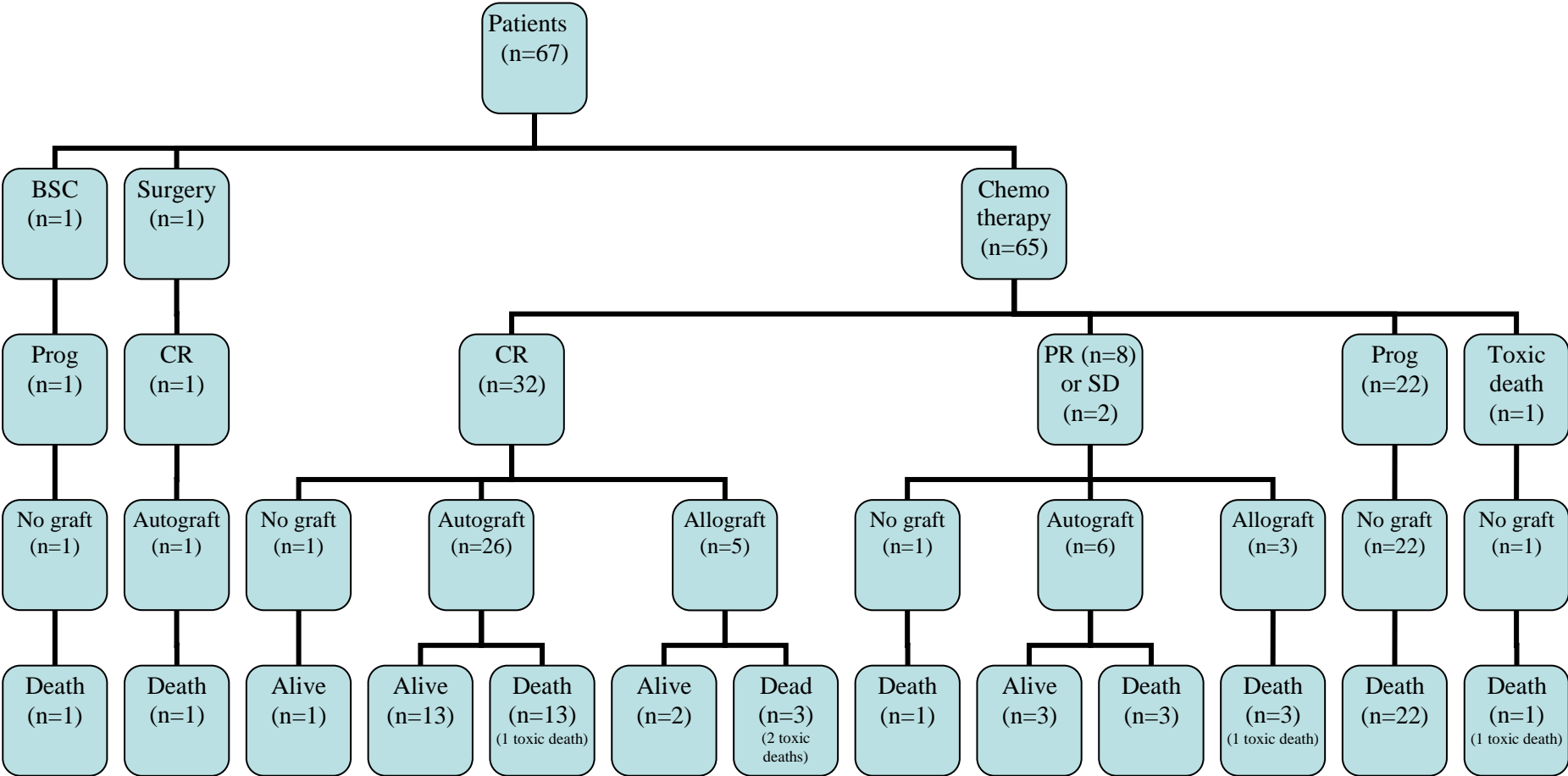
LDH<Nx2: LDH level below twice the normal value; >nx2: above twice the normal value;  
BL: Burkitt lymphoma; DLBCL: diffuse large B cell lymphoma; PMBL: primary mediastinal  
B cell lymphoma; NE: not evaluated; NA: not available; progr: progression; CR2: 2<sup>nd</sup>  
complete remission; PR: partial remission; HDMTX: high dose methotrexate; CYVE: HD  
cytarabine + etoposide; VENOMID: vindesine, Novantrone, methylprednisolone, Ifosfamide;  
BEAM :BCNU, VP-16, Aracytine and Melphalan; BAM: busulfan, Aracytine, melphalan;  
TRT: treatment related toxicity; DOD: dead of disease

**Supplement Table C: Characteristics of the patients with large cell histology**

Patient	Age /sex	Site at diagnosis	Initial Murphey Staging	Group	LDH level	Sites of relapse	Salvage CT	Rituximab	Response	HDC/SCT	RTH	Outcome
1	19/F	bone	I	B	<2N	one (local)	CYVE	0	CR	BEAM	yes	Alive
2	6/M	nasopharynx	II	B	<2N	one (other)	CYVE	4	CR	BEAM	no	Alive
3	3/M	abdomen	III	B	<2N	one (local)	CYVE	0	CR	BEAM	no	Alive
4	18/M	abdomen	III	B	<2N	multiple (BM&CNS)	HDMT X+ CYVE	1	CR	TBI-cyclo/Allo	no	Alive
5	12/F	Bone + BM	BM> 25%	C	<2N	multiple (bone)	ICE	4	CR	BEAM /Auto	no	Alive
6	15/F	abdomen + BM	BM> 25%	C	<2N	one (BM)	ICE/ DHAP	0	CR	BEAM /Auto	no	TRT death
7	14/F	MED (PMBL)	III	B	<2N	one (local)	CYVE	4	PR (CRu)	BEAM	yes	Alive
8	17/F	MED (PMBL)	III	B	<2N	one (local)	DHAP	0	PR (CRu)	BEAM /Auto	yes	Alive
9	16/F	MED (PMBL)	III	B	>2N	multiple (local +BM)	CYVE/ other	0	PR	BEAM /Auto	yes	DOD
10	15/M	MED (PMBL)	III	B	>2N	multiple (local+bone)	CYVE/ other	0	PROG	0	no	DOD

Abbreviations: MED: mediastinum; BM: Bone marrow; PMBL: primary mediastinal B cell lymphoma; TRT: treatment related toxicity; DOD: dead of disease

**Supplement Figure:** Outcome of the 67 children and adolescents with relapse of mature B-cell lymphoma and B-AL according to the consolidation therapy



Abbreviations: BSC, best supportive care; CR, complete response; PR, partial response; SD, stable disease; Prog, progression