Leucémies aiguës du nourrisson

12 juin2015

Virginie Gandemer, Rennes

Réunion POHO

Leucémies aiguës du nourrisson

PLAN

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2. Pathogénie moléculaire
3. Facteurs étiologiques
4. Les LA Lymphoblastiques
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5. Les LA Myéloblastiques
   - Présentation/ facteurs pronostiques/résultats
6. Toxicité et complications à long terme
7. Conclusion

1. Introduction

- Sujet difficile car **LA rares**

Données registre national des leucémies de l'enfant (J Clavel):

<u>Cas diagnostiqués sur 2000-2011</u> (date de point au 01/04/2015)

		n=	% NRS
LAL 4624	0-1 an	136	2,9%
	1-14 ans	4488	
LAM 857	0-1 an	132	15%
	1-14 ans	725	

1. Introduction

- Sujet difficile car **présentation clinique agressive**

	LAM(BFM 98-2004)	LAL (CCG 1953)
Leucocytose initiale	28% >100.000 P=0.003	35% >200.000
HSM		20%
Atteinte du SNC	24% P=0.00003	20%
Localisations extra hématopoïétiques : peau	36% P=0.0015	

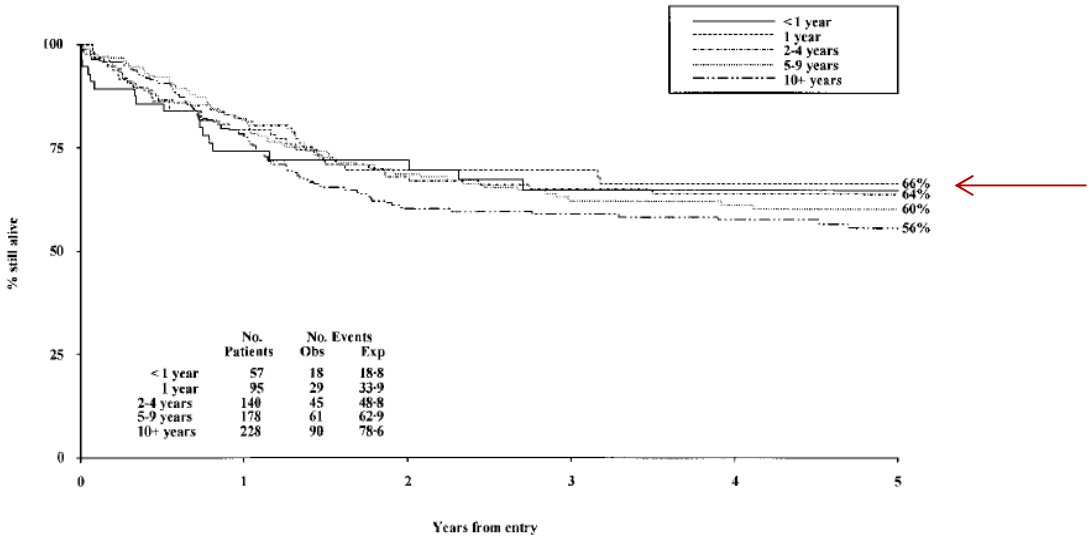
Creutzig U, Leukemia 2012
Hilden JM, Blood 2006

1. Introduction

- Sujet difficile car âge a un **pronostic différent selon lignée**

LAM : =

MRC AML10 et AML12



Webb D, Blood 2001

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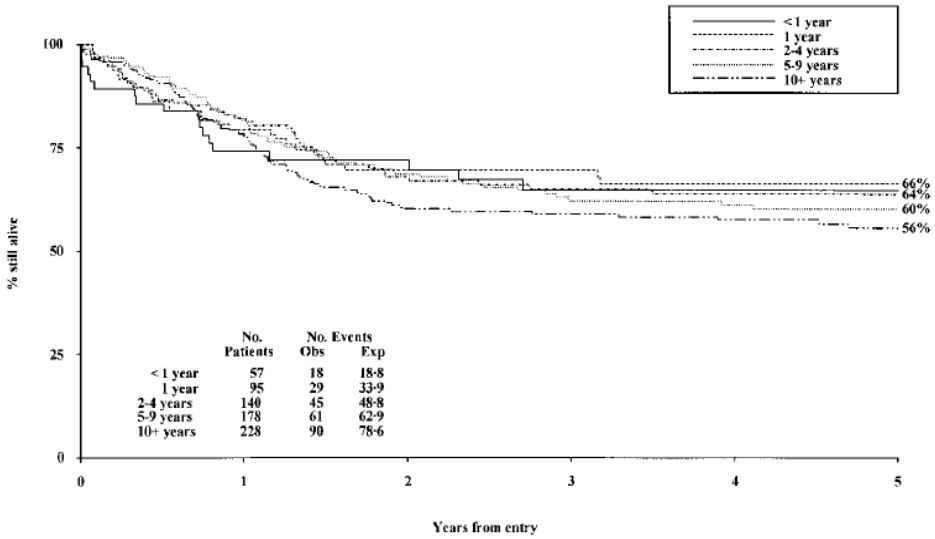


Webb D, Blood 2001

Registre national des leucémies de l'enfant

LAM	n=	OS 5 ans% [95% CI]
0-1 an	132	61.8 [52.8-69.6]
1-14 ans	725	66.7 [63.0-70.2]

1. Introduction

- Sujet difficile car âge a un **pronostic différent selon lignée**

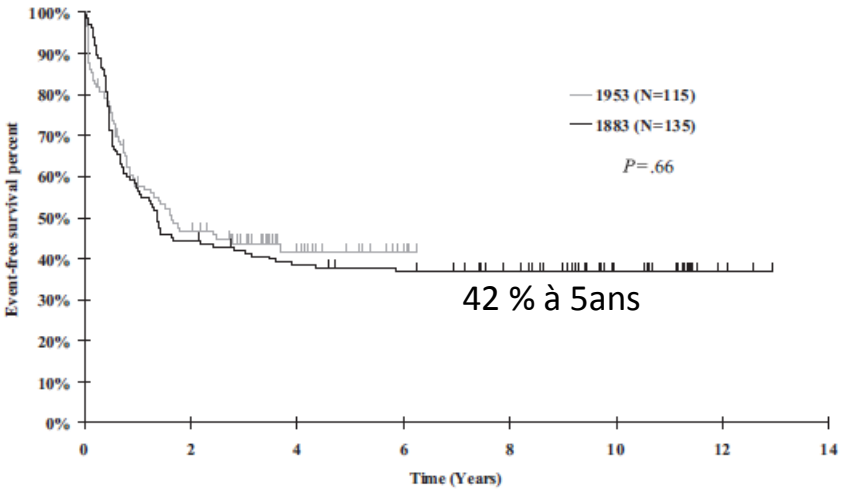
LAM		
Étude	Période	OS 5 ans
Japan infant leukemia Study Group	1995-1998	**76%** (IC95% 56,4-87,9%) (à 3 ans)
MRC AML 10 et 12	1988-2002	**65%**
AML-BFM 98 et 2004	1998-2010	**69% +/- 4%** (04 : 75% +/- 6 %)
ELAM02	2005-2011	**72%+/- 6%**

Kawasaki H, Blood 2001
Webb D, Blood 2001
Creutzig U, Leukemia 2012
Le Mouël L, SFH 2015

1. Introduction

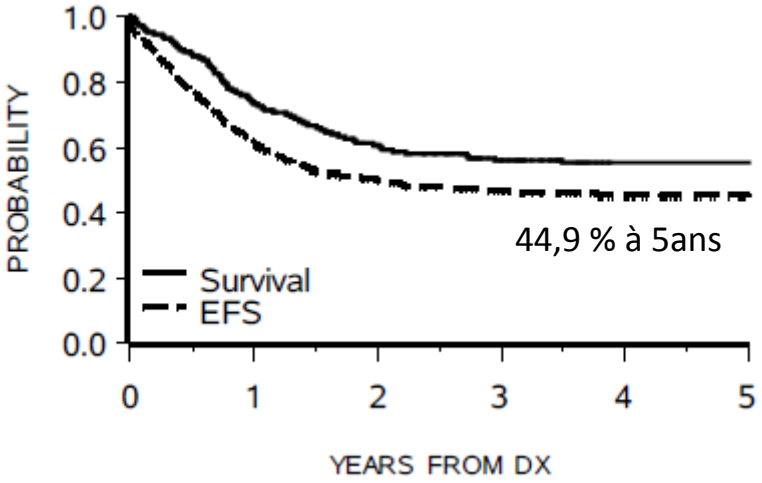
- Sujet difficile car âge a un **pronostic différent selon lignée**

LAL : ↘↘



CCG 1953 and CCG 1883.

Hilden JM, Blood 2006



Interfant 2006 , non publié

1. Introduction

- Sujet difficile car âge a un **pronostic différent selon lignée**

LAL : ↘↘

LAL	N=4624	OS 5 ans% [95% CI]
0-1 an	136	**53.8** [44.8-61.9]
1-14 ans	4488	**90.6** [89.7-91.5]

J Clavel, Registre national des LA de l'enfant 2000-2011

2. Pathogénie moléculaire

Réarrangement du gène MLL 11q2.3

- 5% des LAL de l'enfant mais **70-80% des NRS**

  Hilden JM, Blood 2006(COG)
  Pieters R, Lancet 2007 (Interfant-99)

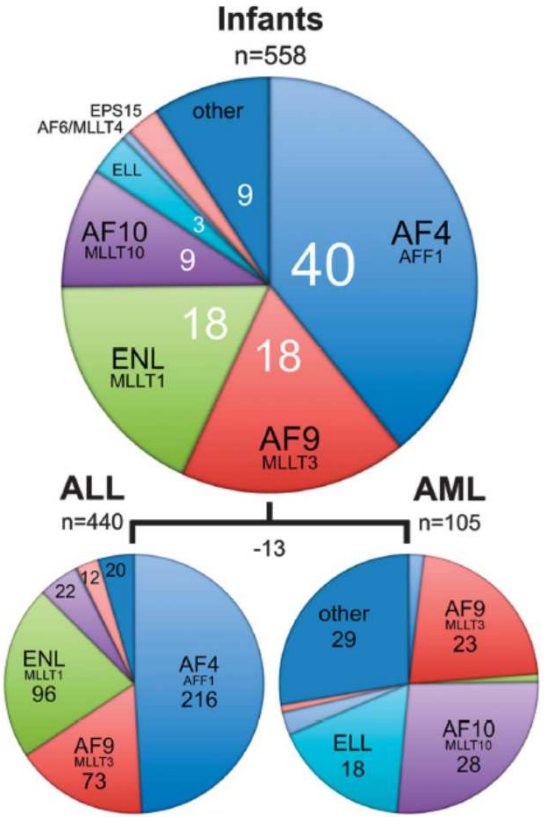
- 15-20% des LAM de l'enfant et **50% des NRS**

  Harrison CJ, JCO 2010
  Le Mouël L, SFH 2015

	LAME 89/91		LAME 89/93		ELAM02		ELAM02 sans M0, M7, inclassable, chlorome isolé	
	n	%	n	%	n	%	n	%
Nombre de patients	17		27		54		38	
Réarrangement MLL	8	61,5	12	54,5	29	55,8	26	70,3
dont MLL AF9	1		4		8		7	

2. Pathogénie moléculaire: MLL-r

- Au moins 79 partenaires différents à MLL



NRS	LAL	LAM
AF4 t(4;11)	49%	2%
AF9 t(9;11)	17%	22%
ENL t(11;19)(q23;p13.3)	22%	1%
AF10 t(10;11)	5%	27%
ELL t(11;19)(q23;p13.1)	0	17%

Meyer C, Leukemia 2013

2. Pathogénie moléculaire: MLL-r

- Origine *in utero* (Guthrie et jumeaux) (Ford AM, Nature 1993, Gale KB, PNAS 1997)

- Pouvoir leucémogène majeur

Table 1 Copy number abnormalities (CNAs) detected by SNP arrays in B-cell precursor ALL

Authors	*SNP array*	*Age of patients*	*BCP-ALL patients*		*MLL rearranged patients*	
			Number of patients	*CNA mean (range)*	*Number of patients*	*CNA mean (range)*
Mullighan *et al.*[13]	350K	Pediatric[a]	192	6.6 (0–27)	11	1.0 (0–6)
Kuiper *et al.*[14]	250K	Pediatric >1 year	33	4.2 (range NA)	1	NA
Kawamata *et al.*[15]	300K	Pediatric >1 year	399	Similar to Mullighan *et al.*[b]	0	NA
Paulsson *et al.*[16]	500K	Adult and adolescent	45	7.8 (0–40)	2	0, 12[c]
Bardini *et al.* (this study)	100K[d]	Infant	0	NA	28	0.2 (0–2)

Bardini M, Leukemia 2010

2. Pathogénie moléculaire: MLL-r

- Pouvoir leucémogène majeur

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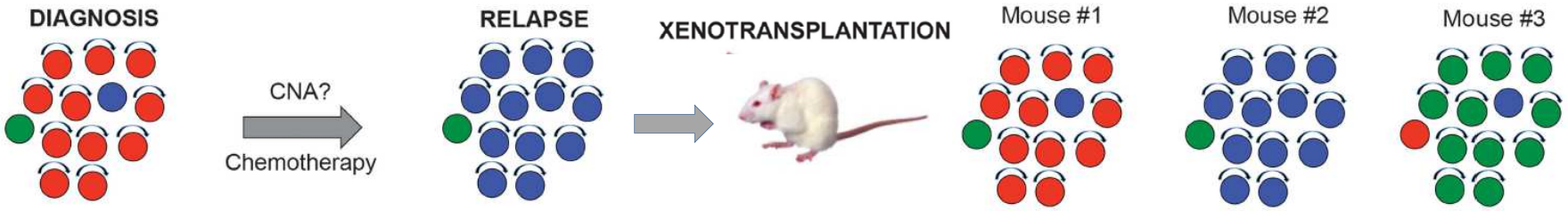
Bardini M, Leukemia 2010, 2011, 2015

- Sous clones IgH/TCR réarrangés dès le dg (présents à rechute)



3. Facteurs étiologiques

- **Facteurs prénataux?**
  - Pas de association avec anomalies congénitales selon étude COG 1998-2006 (Johnson KJ, PBC 2010)
  - Exposition gestationnelle aux toxiques ménagers : benzène

Adjusted associations between maternal household chemical exposure and infant acute leukemia

	Controls	ALL		AML		*MLL+*		*MLL−*	
	($n = 324$)	($n = 264$)		($n = 172$)		($n = 228$)		($n = 146$)	
	n	*n*	OR[a] (95% CI)	*n*	OR[a] (95% CI)	*n*	OR[a] (95% CI)	*n*	OR[a] (95% CI)
Petroleum products									
Any	29	33	1.56 (0.90–2.70)	29	**2.33 (1.30–4.18)**	28	1.38 (0.77–2.48)	27	**2.48 (1.37–4.48)**
Month before pregnancy	25	24	1.31 (0.71–2.41)	16	1.42 (0.71–2.83)	19	1.14 (0.58–2.21)	16	1.65 (0.83–3.28)
During pregnancy	26	31	1.60 (0.90–2.83)	29	**2.54 (1.40–4.62)**	26	1.37 (0.74–2.51)	27	**2.69 (1.47–4.93)**

Slater M, Cancer Causes control 2011

3. Facteurs étiologiques

- **Facteurs prénataux?**
  - Exposition transplacentaire aux toxiques et LA MLLr

Table 2 *In utero chemical exposures and infant leukemia (OR,*[a] 95% CI)

Exposure[b]	Total series	MLL^{+ve} subgroup	MLL^{-ve} subgroup	ALL	AML
Smoking	1.43 (0.86–2.39)	0.98 (0.46–2.09)	1.72 (0.74–3.99)	1.59 (0.82–3.07)	1.33 (0.63–2.80)
(ca = 36, ct = 53)	$P = 0.17$	$P = 0.97$	$P = 0.21$	$P = 0.17$	$P = 0.45$
Alcohol	1.23 (0.68–2.23)	0.74 (0.29–1.90)	2.09 (0.91–4.84)	0.63 (0.25–1.60)	1.92 (0.90–4.10)
(ca = 21, ct = 33)	$P = 0.50$	$P = 0.54$	$P = 0.08$	$P = 0.33$	$P = 0.09$
DNA damaging drugs	1.71 (1.03–2.84)	2.31 (1.06–5.06)	0.56 (0.18–1.80)	1.78 (0.95–3.34)	2.28 (1.10–4.71)
(ca = 37, ct = 47)	$P = 0.039$	$P = 0.036$	$P = 0.33$	$P = 0.07$	$P = 0.026$
Herbal medicines	2.93 (1.57–5.48)	3.00 (1.38–6.54)	2.64 (1.04–6.67)	4.45 (2.06–9.63)	2.09 (0.89–4.92)
(ca = 27, ct = 22)	$P = 0.001$	$P = 0.006$	$P = 0.04$	$P < 0.001$	$P = 0.09$
Maternal pesticide	3.67 (1.54–8.74)	4.96 (1.71–14.43)	1.87 (0.36–9.61)	2.53 (0.71–8.97)	5.08 (1.84–14.04)
(ca = 15, ct = 10)	$P = 0.003$	$P = 0.003$	$P = 0.45$	$P = 0.15$	$P = 0.002$
Dipyrone	2.83 (1.15–6.99)	5.84 (2.09–16.30)	0.64 (0.08–5.41)	3.13 (1.02–9.57)	3.01 (0.93–9.79)
(ca = 12, ct = 9)	$P = 0.02$	$P = 0.001$	$P = 0.68$	$P = 0.046$	$P = 0.07$
Baygon/mosquitocidal	5.14 (1.27–20.85)	9.68 (2.11–44.40)	0 (0–15.19)	4.30 (0.66–28.08)	7.82 (1.73–35.39)
(ca = 7, ct = 3)	$P = 0.02$	$P = 0.003$	$P = 1.0$	$P = 0.13$	$P = 0.008$

[a] ORs are for exposed compared with nonexposed.
[b] Numbers are for cases (ca) and controls (ct) exposed in the total series.

Alexander F, Cancer Res 2001

  - Flavonoides : ingestion induit clivage MLL *in utero*

Strick R, PNAS 2000

4. Les LA Lymphoblastiques

- **Présentation clinique**

Interfant-06
Characteristics by risk group

	LR		MR		HR		total	
	N	%	N	%	N	%	N	%
553 on study patients	139	*25.1*	273	*49.4*	141	*25.5*	553	*100.0*
Gender								
Male	80	*57.6*	113	*41.4*	57	*40.4*	250	*45.2*
Female	59	*42.4*	160	*58.6*	84	*59.6*	303	*54.8*
Age								
< 3 months	9	*6.5*	41	*15.0*	71	*50.3*	121	*21.9*
3 - 6 months	23	*16.6*	65	*23.8*	70	*49.7*	158	*28.6*
6 - 9 months	43	*30.9*	106	*38.9*	0	*0.0*	149	*26.9*
9-12 months	64	*46.0*	61	*22.3*	0	*0.0*	125	*22.6*
WBC								
< 100000	103	*74.1*	139	*50.9*	7	*5.0*	249	*45.0*
100-300000	24	*17.3*	93	*34.1*	19	*13.5*	136	*24.6*
≥300000	12	*8.6*	*40*	*14.6*	*114*	*80.8*	166	*30.0*
NK	0	*0.0*	1	*0.4*	1	*0.7*	2	*0.4*
Immunophenotype								
B-lineage - CD10 neg.	23	*16.5*	201	*73.7*	99	*70.2*	323	*58.4*
B-lineage - CD10 pos.	102	*73.4*	47	*17.2*	21	*14.9*	170	*30.8*
B-lineage - CD10 NK	5	*3.6*	8	*2.9*	13	*9.2*	26	*4.7*
T	6	*4.3*	3	*1.1*	0	*0.0*	9	*1.6*
Biphenotypic	3	*2.2*	11	*4.0*	6	*4.3*	20	*3.6*
NK	0	*0.0*	3	*1.1*	2	*1.4*	5	*0.9*
CNS-Involvement								
Yes	14	*10.0*	24	*8.8*	29	*20.6*	67	*12.1*
No	102	*73.4*	198	*72.5*	66	*46.8*	366	*66.2*
Not evaluable	20	*14.4*	41	*15.0*	40	*28.3*	101	*18.3*
NK	3	*2.2*	10	*3.7*	6	*4.3*	19	*3.4*

Moitié< 6 mois ←

55% >100.000 GB ←

≈60% CD 10 neg ←

LR: germline
MR: otherwise
HR: MLL rearranged and age <6 months and
WBC ≥300x10^9 *or* PDN Poor Response

4. Les LA Lymphoblastiques

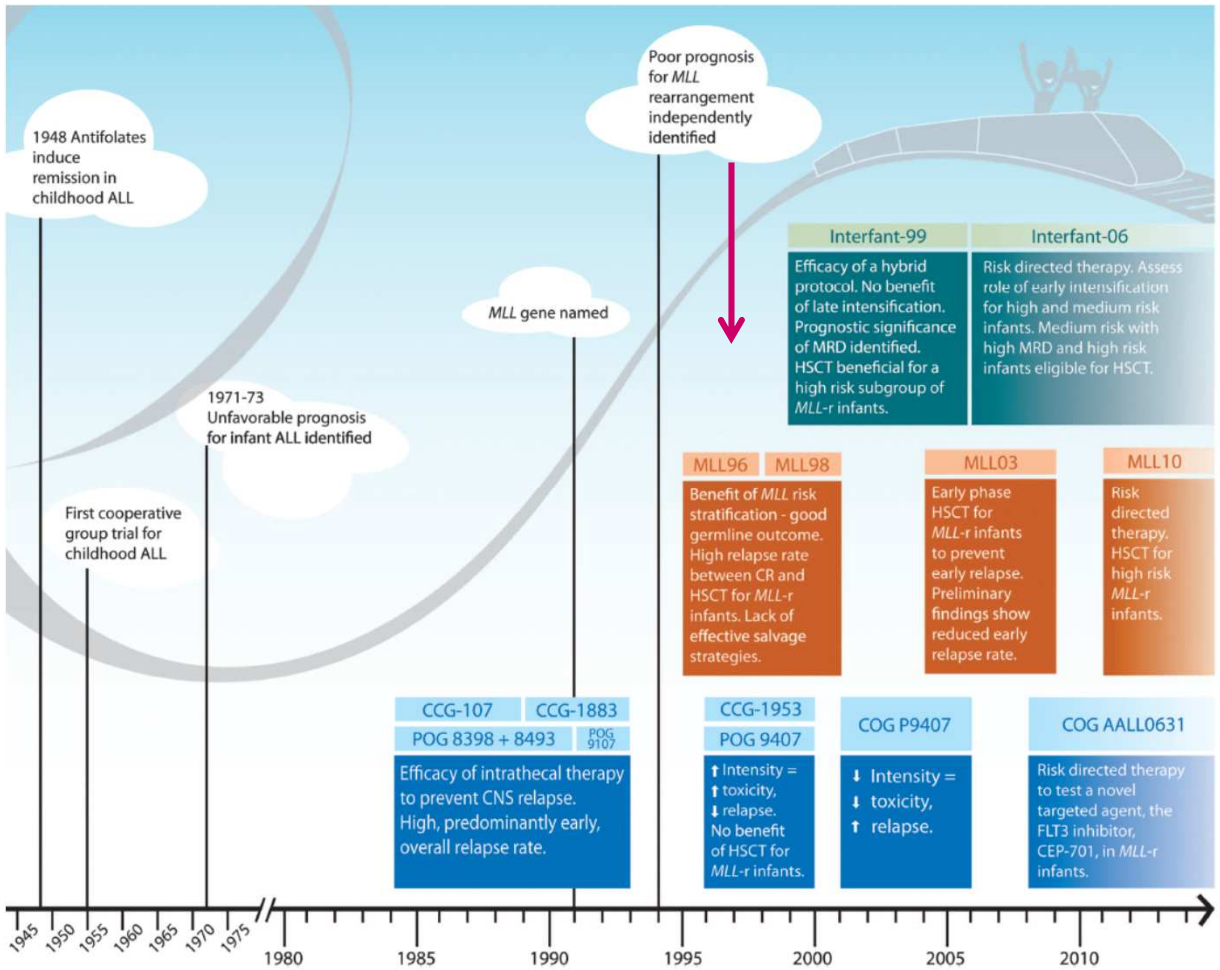
- **Présentation clinique**

Interfant-06
MLL status by risk group

	LR		MR		HR		total	
	N	%	N	%	N	%	N	%
553 on study patients	139	*25.1*	273	*49.4*	141	*25.5*	553	*100.0*
MLL Status								
Rearranged	0	*0.0*	267	*97.8*	141	*100.0*	408	*73.8*
Germline	139	*100.0*	0	*0.0*	0	*0.0*	139	*25.1*
Not evaluable	0	*0.0*	6^	*2.2*	0	*0.0*	6	*1.1*
MLL rearranged (% on rearranged)								
t(4;11)	0	*0.0*	125	*46.8*	60	*42.6*	185	*45.3*
t(9;11)	0	*0.0*	33	*12.4*	12	*8.5*	45	*11.0*
t(11;19)	0	*0.0*	51	*19.1*	36	*25.5*	87	*21.3*
other pos., defined	0	*0.0*	23	*8.6*	9	*6.4*	32	*7.9*
other pos., undefined	0	*0.0*	35	*13.1*	24	*17.0*	59	*14.5*

4. Les LA Lymphoblastiques

- **Evolution des essais cliniques**



Points clés:

- Mauvaise EFS dans les HR
- Toxicité particulière des NRS

↓

Protocoles spécifiques pour NRS

Kotecha Rs,Blood Cancer Journal 2014

4. Les LA Lymphoblastiques

- **3 cohortes principales actuelles**

Table 2. Summary of results for infant-specific collaborative group ALL protocols

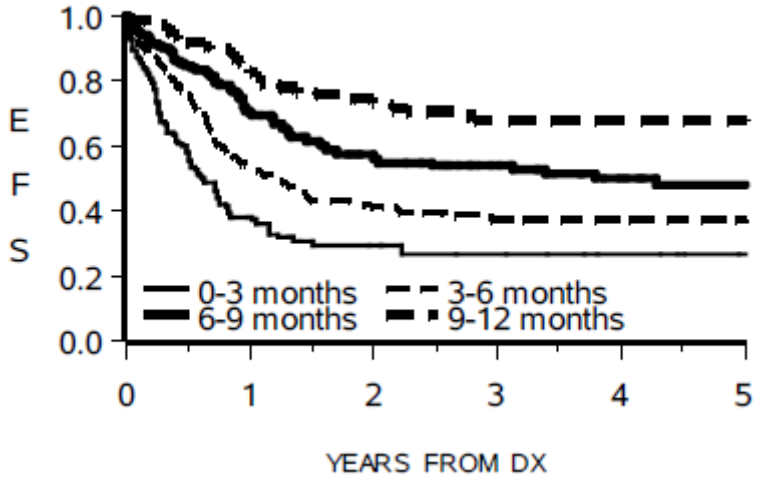
Group	*Study*	*Year*	*Number analyzed*	*CR (%)*	*5-Year EFS (%)*	*5-Year OS (%)*	*Key conclusions*
COG	P9407 (cohort 3)	2001–2006	141	—	42.3	53.0	• Therapeutic modifications reduced toxicity but increased relapse rate compared with cohorts 1 and 2
JILSG	MLL96	1995–1998	55	94.1	50.9	60.5	• Infants with germline *MLL* highly curable with chemotherapy alone (95.5% 5-year EFS and OS) showing benefit of risk-stratification by *MLL* status
	MLL98	1998–2001	47				• High proportion of relapses between first CR and HSCT in *MLL*-rearranged infants suggesting need for more effective postremission therapy • Age <6 months at diagnosis identified as an independent adverse prognostic factor for *MLL*-rearranged infants • Failure to achieve remission following salvage therapy identified as an independent adverse prognostic factor for recurrent/refractory *MLL*-rearranged disease
Interfant	Interfant-99	1999–2005	483	93.9	46.1	55.2	• Efficacy of a hybrid protocol demonstrated • *MLL* rearrangement, age <6 months at diagnosis and poor day 8 prednisone response identified as independent adverse prognostic factors • No benefit from adding a late intensification course • Prognostic impact of MRD following induction and consolidation identified • Risk of relapse significantly higher for congenital ALL • HSCT beneficial for MLL-rearranged infants aged <6 months and poor day 8 prednisone response or WBC ≥300 g/l at diagnosis

4. Les LA Lymphoblastiques

- **Facteurs pronostiques et résultats**

Interfant-06

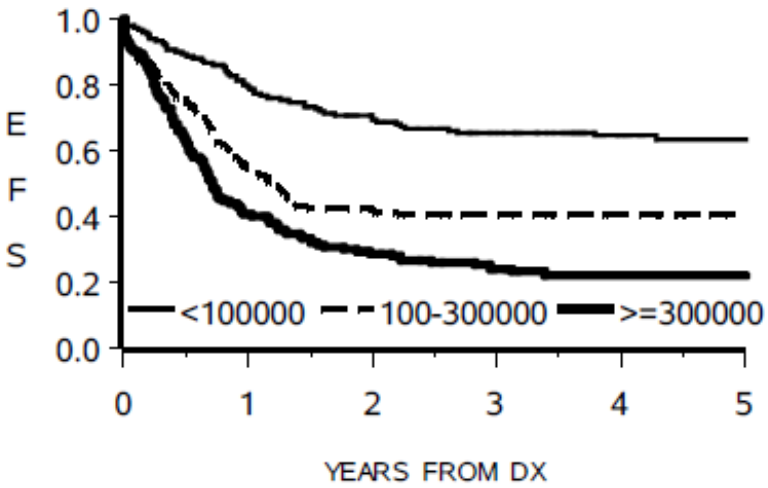
âge



68 % à 4 ans

26,4 %

leucocytose



64,4 % à 4 ans

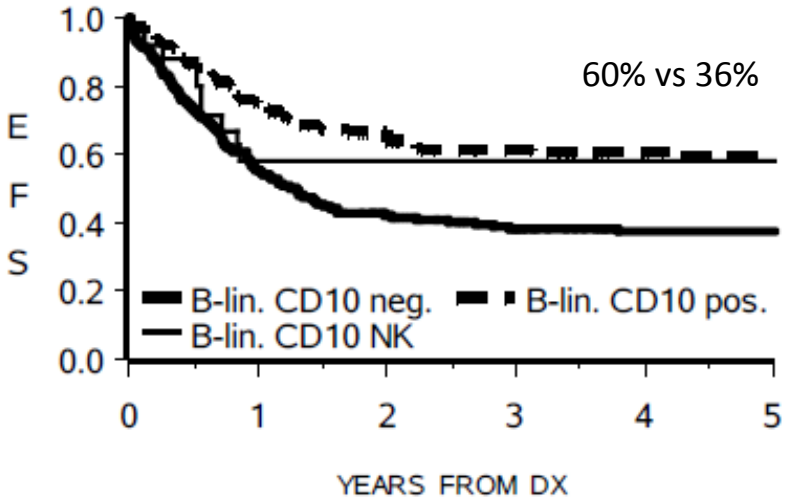
21,9 %

4. Les LA Lymphoblastiques

- **Facteurs pronostiques et résultats**

Interfant-06

CD10



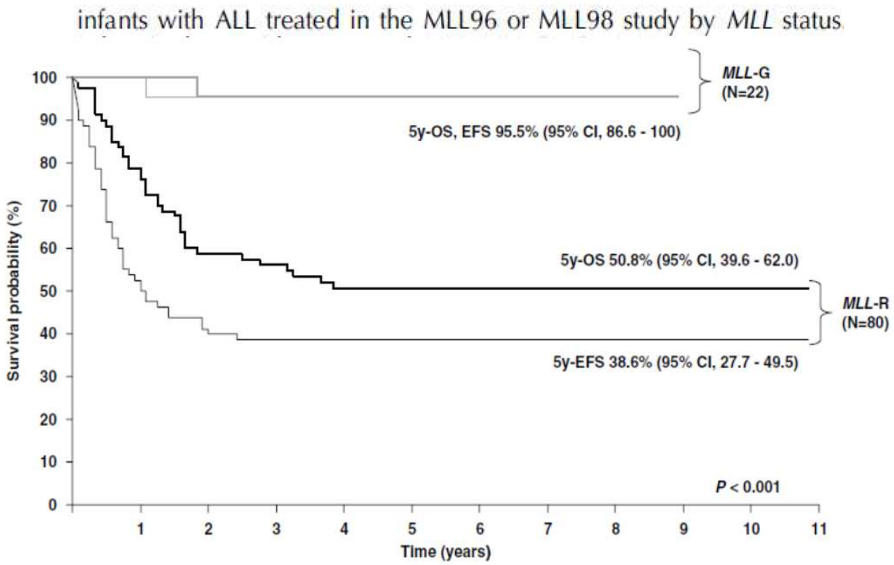
60% vs 36%

CCG 1953 and CCG 1883: five-year EFS according to prognostic factors

Variable	CCG 1883 No. of patients	CCG 1883 5-year EFS, %	*P*
Age			< .001
Less than 3 mo	21	9.5	
3 to less than 6 mo	36	27.8	
At least 6 mo	78	49.7	
CD10			.002
$CD10^+$	41	55.3	
$CD10^-$	56	28.6	
WBC count			< .001
Less than 50×10^9/L	52	57.6	
50×10^9/L to 199×10^9/L	37	34.8	
At least 200×10^9/L	46	17.4	

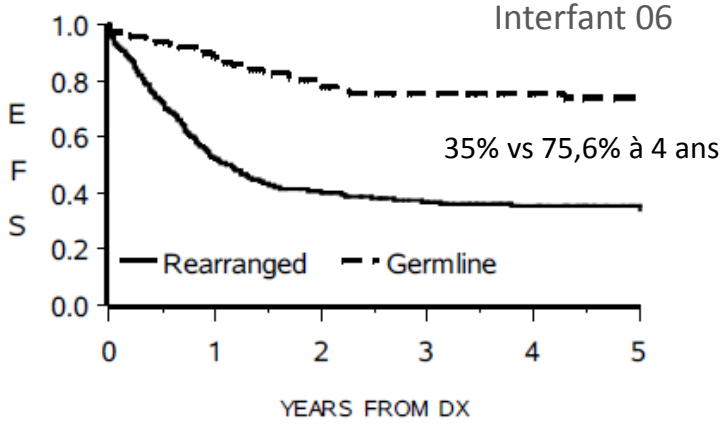
4. Les LA Lymphoblastiques

- **Facteurs pronostiques et résultats**: MLLr
  - les 1ers : JILSG n=102

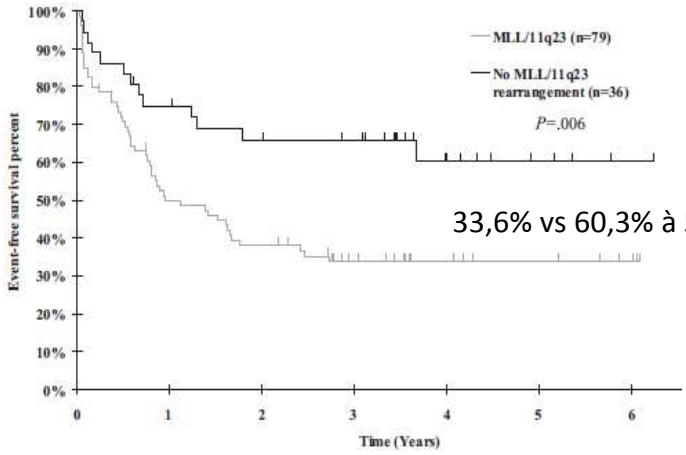


Tomizawa D, Leukemia 2007

Interfant 06



35% vs 75,6% à 4 ans



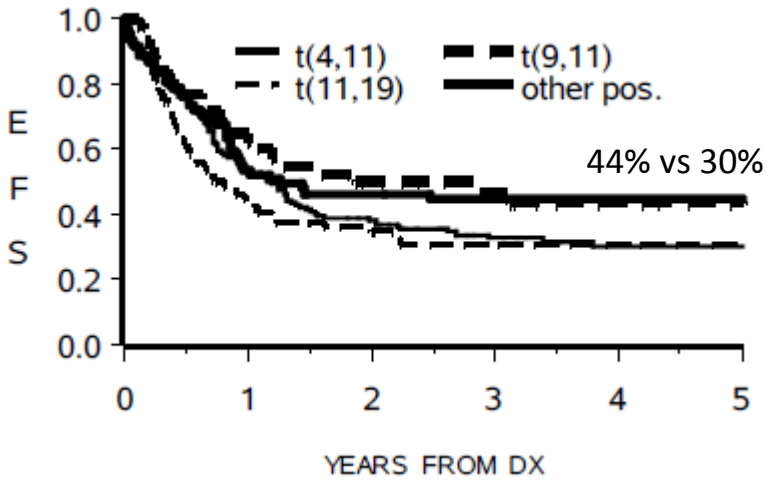
33,6% vs 60,3% à 5 ans

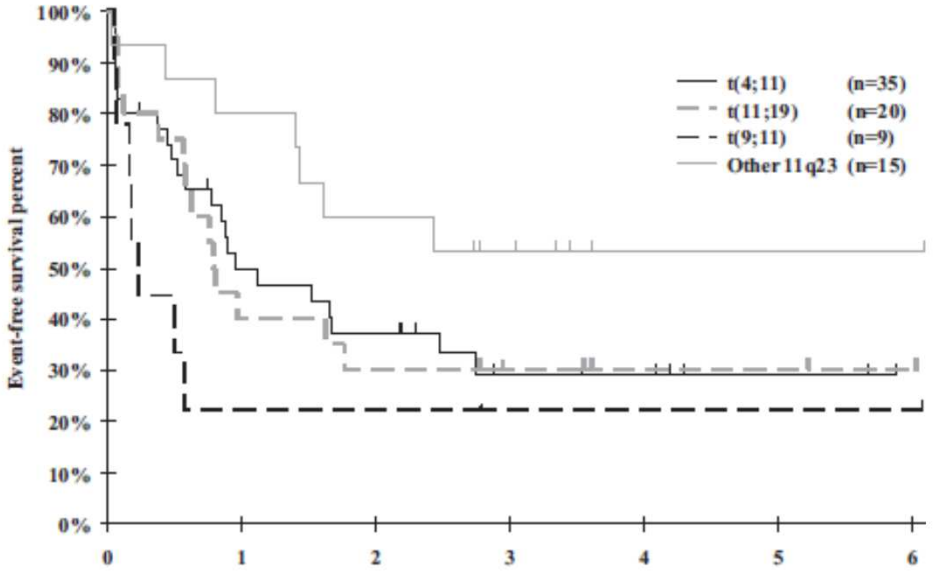
COG, Blood 2006

4. Les LA Lymphoblastiques

- **Facteurs pronostiques et résultats**: MLLr

Interfant-06





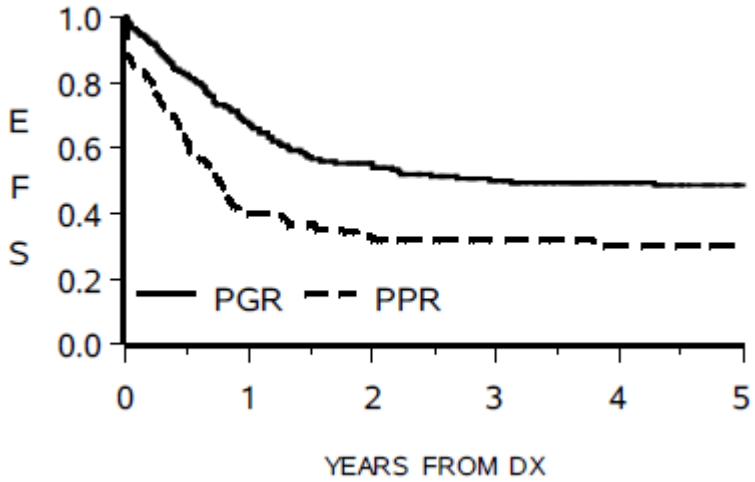
Analysis of prognostic factors of acute lymphoblastic leukemia in infants: report on CCG 1953 from the Children's Oncology Group

Joanne M. Hilden, Patricia A. Dinndorf, Sharon O. Meerbaum, Harland Sather, Doojduen Villaluna, Nyla A. Heerema, Ron McGlennen, Franklin O. Smith, William G. Woods, Wanda L. Salzer, Helen S. Johnstone, Zoann Dreyer, and Gregory H. Reaman

4. Les LA Lymphoblastiques

- **Facteurs pronostiques et résultats**: réponse à la préphase

Interfant-06



PDN Response	N. pts.	N. events	4-year EFS (SE)	p-value
PGR	414	188	49.0 (2.7)	<0.0001
PPR	116	74	30.1 (4.7)	

4. Les LA Lymphoblastiques

- **Résultats et toxicité aigue**:
  - Pronostic reste inférieur aux autres LAL
  - Rechute souvent précoce et faible taux de RC2 (JILSG-Tomizawa D, PBC 2009)

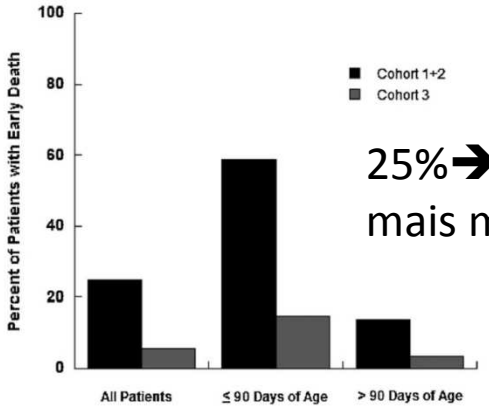
  - **et vulnérabilité particulière** !
    - Masse corporelle et volume de distribution
    - Maturité système enzymatique (CP450 …) et liaison aux protéines plasmatiques
    - Fonction rénale
    - Immunocompétence

4. Les LA Lymphoblastiques

- **Résultats et toxicité aigue**:
  - DC précoces (+ en induction et intensification): 80% infectieux et surtout les <3 mois
    - COG

DXM 10 mg/m² vs PDN 40 mg/m²
DNR sur 48h vs 30 min

Salzer W, PBC 2012



25%➔5,7%
mais même OS=53%

Fig. 1.
Early death rate (death within 90 days of enrollment) in Cohorts 1 + 2 and Cohort 3 for all patients, those ≤90 days of age at diagnosis, and those >90 days of age at diagnosis.

    - Interfant 06

	total
On study pts.	**553**
Deaths in Induct (%)	**23 (4.2)**
Deaths in CCR (%)	**43 (7.8)**

Seuil d'arrêt =28 DC

4. Les LA Lymphoblastiques

- **Greffe**:
  - objectifs: diminuer recours /toxicité aigue et tardive
    - COG P9407 cohort 3 (Dreyer ZE, PBC 2015)
    - Interfant-06

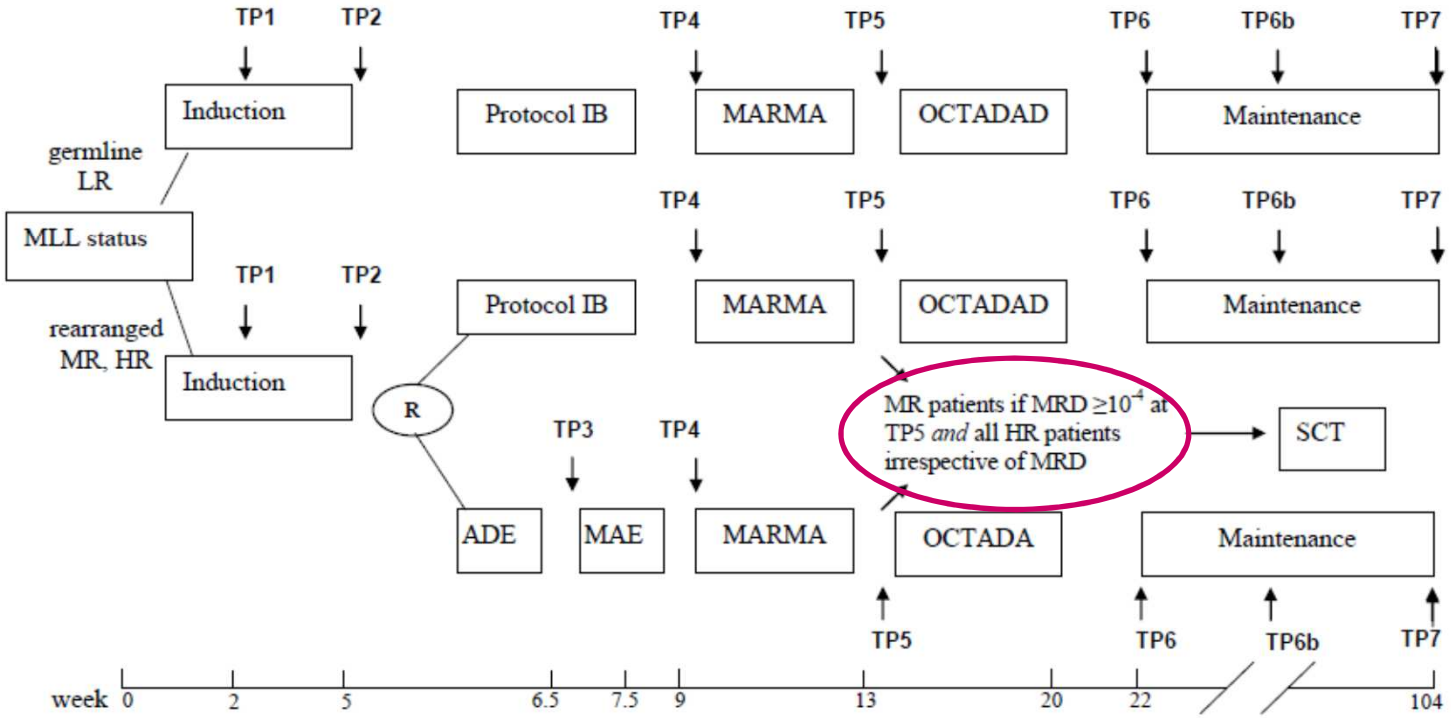
16% des patients

- ***From 1st CR***

	total		Interfant-06 553 pts.	*Interfant99 478 pts.*
	Chemo	SCT CR1		
CR	428	79	507 *(91.7%)*	*448 (93.7%)*
Relapses (deaths)	51 (110)	30 (19)	181 *(32.7%)*	*193 (40.4%)*
BM	*96*	*26*	122	
CNS	*21*	*0*	21	
Testis	*3*	*0*	3	
BM+CNS	*23*	*0*	23	
BM+Testis	*1*	*1*	2	
Other	*7*	*3*	10	
Deaths in CCR (%)	28 (6.5)	15 (19.0)	43 *(7.8%)*	*25 (5.2%)*
Sepsis	*15*	*0*	*15*	
Pneumonia	*3*	*0*	*3*	
Other (infections)	*4*	*0*	*4*	
Haemorrhage	*4*	*0*	*4*	
SCT-related/MOF	*-*	*15*	*15*	
NK	*2*	*0*	*2*	
Second tumors (deaths)	1 (0)	1 (0)	2 *(0.4%)*	*1 (0.2%)*
CCR	248	33	281 *(50.8%)*	*229 (48.1%)*

→ Sur 79 greffes: 19%

Treatment schedule and MRD time-points



LR: germline
MR: otherwise
HR: MLL rearranged and age <6 months and WBC ≥300x10^9 *or* PDN Poor Response

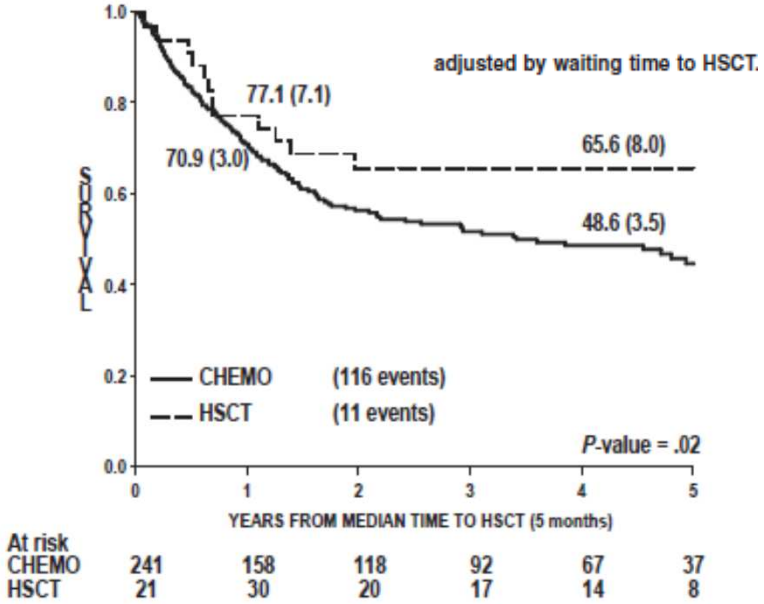
TP1	day 15
TP2	day 33 (or before IB/ADE, as per protocol)
TP3	before MAE
TP4	before MARMA
TP5	before OCTADA(D)
TP6	before Maintenance
TP6b	week 65 (week 43 in Maintenance)
TP7	at end of therapy

4. Les LA Lymphoblastiques

- **Greffe**:
  - objectifs: améliorer survie mais limiter recours /toxicité (tardive)

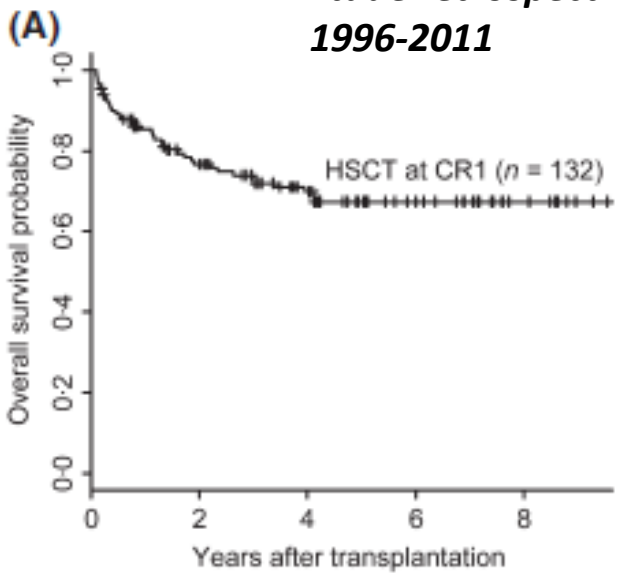
Interfant-99

Tous MLL r



Mann G, Blood 2010

Étude rétrospective JSHCT 1996-2011



Kato M, BJH 2014

5. Les LA Myéloblastiques

- **Présentation clinique**

Table 1a Initial patient data in infants from studies AML-BFM-98 and -2004 compared with older patients

Age groups	*Infants 0–<1 year*	*1–<2 years*	*2–<10 years*	*P-value*
No. of patients	125	136	354	
Leukocytes ($\times 10^3/\mu l$), median (Q1–Q3)	29 080 (8800–120 000)	17 445 (6950–58 950)	17 100 (5700–54 200)	0.004
	N *(%)*	N *(%)*	N *(%)*	
Leukocytes ⩾ 100 000/μl	35 (28)	25 (18)	51 (14)	0.003
Gender: male	61 (49)	68 (50)	190 (54)	0.57
CNS leukemia[a]	27/114 (24)	17/127 (13)	25/342 (7)	0.00003
Extramedullary organ involvement	44 (36)	41 (31)	72 (21)	0.0015
FAB types				<0.00001
M0	9 (7)	2 (2)	11 (3)	
M1	7 (6)	4 (3)	61 (17)	
M2	4 (3)	12 (9)	106 (30)	
M3	1 (1)	3 (2)	20 (6)	
M4	27 (22)	26 (19)	67 (19)	
M5	53 (42)	52 (38)	59 (17)	
M6	2 (2)	4 (3)	7 (2)	
M7	21 (17)	32 (24)	20 (6)	
Other	1 (1)	1 (1)	3 (1)	
BM blasts day 15 > 5%[a]	12/104 (12)	12/119 (10)	55/314 (18)	0.089

Creutzig U, leukemia 2012

5. Les LA Myéloblastiques

- **Présentation clinique**

	LAME 89/91 n = 17	LAME 89/93 n= 27	ELAM02 n = 54
Sexe masculin	6 (35,3%)	10 (37%)	31 (57,4%)
Age médian (années)	0,6	0,61	0,56
GB médian G/L	**86** (1,3-480)	49,5 (4,9-256)	**14,2** (3,7-575)
Classification FAB			
M0			2 (3,7%)
M1	1 (5,9%)	2 (7,4%)	0
M2	0	2 (7,4%)	1 (1,9%)
M3	0	0	
M4	4 (**23,5%**)	6 (**22,2%**)	5 (**9,3%**)
M5	12 (**70,6%**)	17 (**63%**)	30 (**55,6%**)
M6	0	0	2 (3,7%)
M7			9 (16,7%)
Inclassable et autre			5 (9,3%)

Le Mouël L, SFH 2015

5. Les LA Myéloblastiques

- **Présentation clinique** : >50% de MLLr

Table 1b Cytogenetic subgroups in infants of study AML-BFM-98 and -2004 compared with older age groups

Cytogenetic aberration	*Age, n (%)*		
	<1 year	*1–⩽2 years*	*2–⩽10 years*
Patients with MLL rearrangement	62 (56)	51 (40)	57 (18)
t(9;11) and/or MLL/AF9	20 (18)	30 (23)	25 (8)
t(11;19) (q23;p13)	4 (4)	1 (1)	3 (1)
t(10;11) and/or MLL/AF10	10 (9)	7 (6)	5 (2)
t(1;11) (variable;q23)	6 (5)	3 (2)	2 (1)
MLL rearrangement with other translocation partner	17 (15)	7 (6)	19 (6)
MLL rearrangement with unknown translocation partner	5 (5)	3 (2)	3 (1)

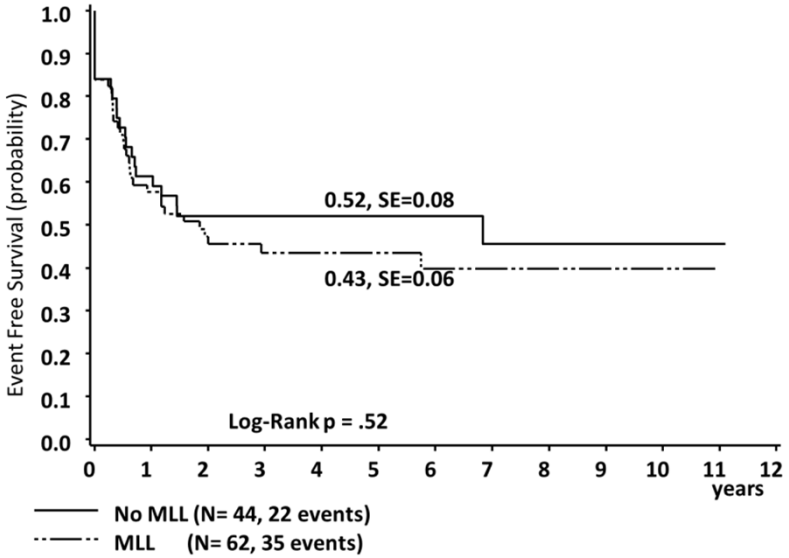
Creutzig U, leukemia 2012

	ELAM02				
	moins de 1 an		plus de 1 an		
	n	%	n	%	p values
Nombre de patients	54		384		
Cytogénétique [1]					
CBF	0	0	97	25,4	<0,0001
dont t(8;21)	0		61		
dont inv16	0		36		
Réarrangement MLL	29	55,8	66	17,3	<0,0001
dont MLL AF9	8		31		
Caryotypes normaux	6	11,5	104	27,2	0,016
Reste	17	32,7	115	30,1	0,75
Echec	2		2		
Non fait ou non renseigné	0		0		

Le Mouël L, SFH 2015

5. Les LA Myéloblastiques

- **Facteurs pronostiques** : pas d'impact de MLL



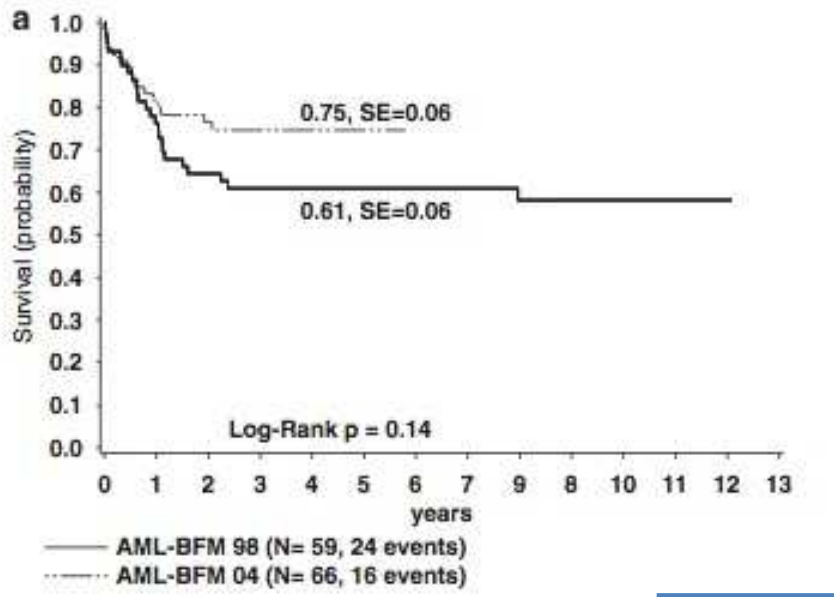
Creutzig U, leukemia 2012 (BFM)

	n	%	Survie globale à 5 ans (s.e)	p value
Nombre de patients	54			
Cytogénétique				
Réarrangement MLL	29	53,7	75% (8%)	0,4381
Pas de réarrangement MLL	25	46,3	68% (9%)	

L LeMouël, G Leverger, non publié (ELAM02)

5. Les LA Myéloblastiques

- **Résultats** : ceux des LAM



Un peu plus de rechute neuroméningée chez les <2 ans/>2 ans

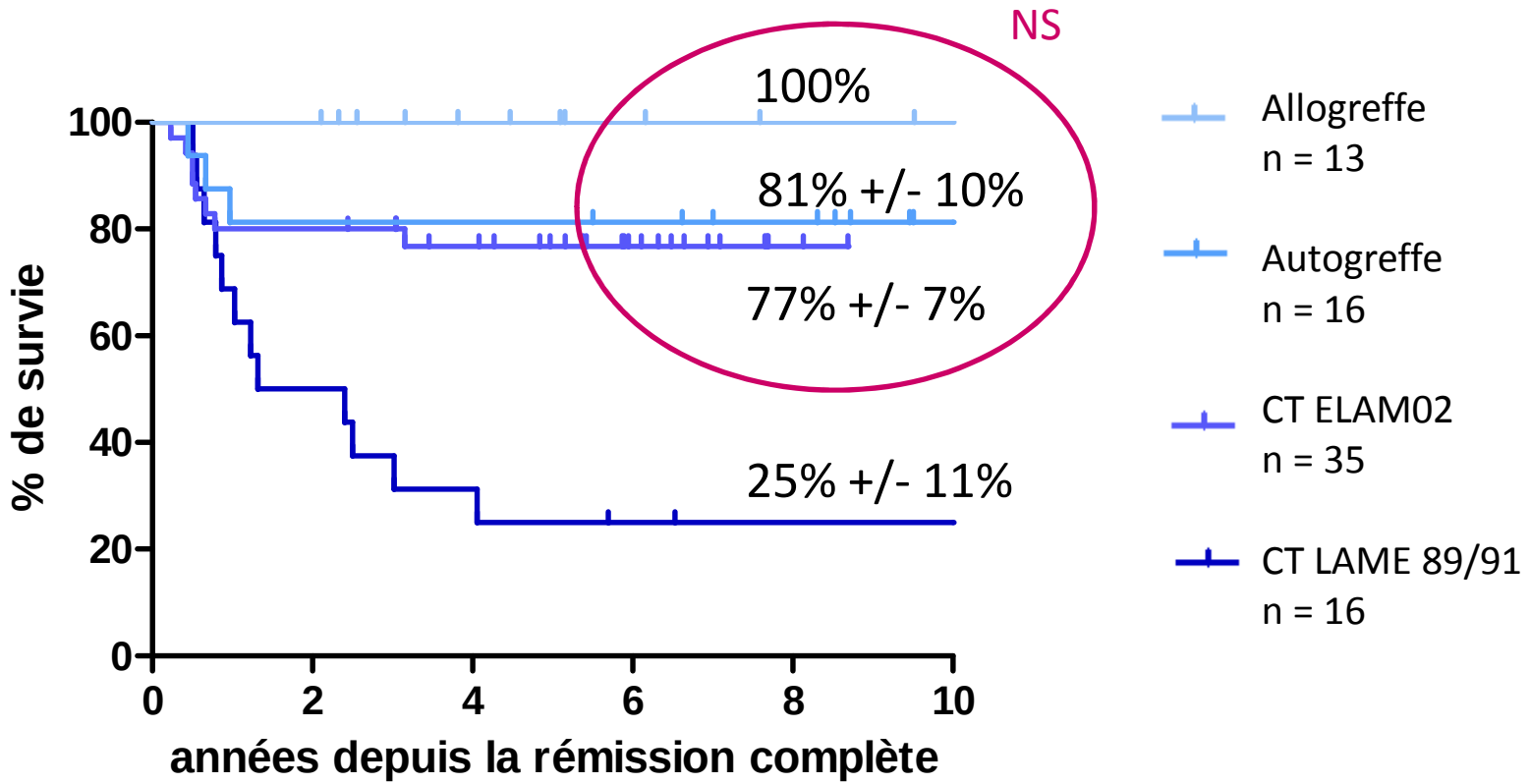
Creutzig U, leukemia 2012

	< 1 an		> 1 an	
	n	OS 5ans (se)	n	OS 5ans (se)
LAME 89/93	27	66% +/- 9%	188	68% +/- 4%
ELAM02	54	72% +/- 6%	384	71% +/- 2%

Le Mouël L, SFH 2015

5. Les LA Myéloblastiques

- **Résultats :** pas de bénéfice de la greffe



Le Mouël L, SFH2015
Kawasaki H, Blood 2001

5. Les LA Myéloblastiques

- **Vulnérabilité comme pour les LAL de < 1an**
  - MRC AML10 et AML12 : Dc en induction

    <1 an : 12 % vs 3% > 1 an p =0.0008

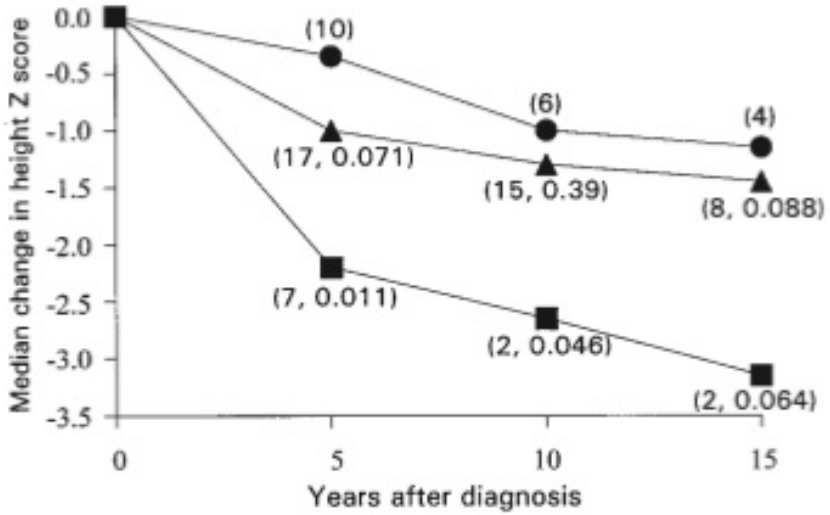
Gibson BE, leukemia 2005
Kawasaki H, Blood 2001

Table 3 Toxicity after Induction in high-risk infants compared with older high-risk patients — Creutzig U, leukemia 2012

Tox. gr. 3/4	*Infants, n/total*	*%*	*1–2 years, n/total*	*%*	*<2–10 years, n/total*	*%*	*P-value*
General condition	49/99	50	44/102	43	52/168	31	**0.007**
S-GOT/s-GPT	4/97	4	12/100	12	14/168	8	0.12
Arrhythmia	3/94	3	2/98	2	4/154	3	0.92
Cardiac function (CHF)	1/83	1	4/86	5	3/137	3	0.42
Echocardiography	0/79	0	0/81	0	2/138	1	0.50
Cardiac total	3/97	3	4/100	4	4/158	3	0.80
Central neurotoxicity	3/99	3	6/103	6	3/166	2	0.18
Infection	42/101	42	36/100	36	48/168	29	0.08
Pulmonary problems	19/56	34	13/55	24	13/96	14	**0.01**
Mucositis	14/97	14	23/102	23	39/168	23	0.20

6. Toxicité et complications à long terme

- **Problème crucial dans cette population**
  - Croissance
  - Développement neurocognitif
  - etc…



34 LA du NRS, recul 13 ans en médiane

- Group A *CT* (n=10): 40% ont ≥1 séquelle
- ⏏ Groupe B *CT+RxT* (n=17): 88%
- ■ Groupe C *CT+Greffe+RxT* (n=7): 100%

Leung w, leukemia 2000

7. Conclusion

- Biologie complexe imparfaitement comprise
- Balance efficacité /toxicité
- Pronostic reste mauvais : formes résistantes fréquentes

- Perspectives thérapeutiques/formes résistantes
  - Inhibiteurs de FLT3 (essai du COG AALL0631)
  - HDAC et hypométhylants
  - Inhibiteurs de CXCR4/ niche stromale et résistance
  - DOTL1 inh…

Nécessité de groupes coopérateurs internationaux et suivi à long terme

Table 1. CCG 1953 therapy detail

Phase	Treatment regimen
Induction, 4 wk	
CPM	250 mg/m² every 12 h × 4 doses, days 2, 3
DXM	10 mg/m² orally 3 times daily, days 0-20, no taper
VCR	0.05 mg/kg, days 0, 14; 0.03 mg/kg day 7
DNM	2 mg/kg/dose intravenously over 30 min for patients age ≤ 90 d
	2 mg/kg/d; 4 mg/kg over 48 h, age > 90 d to < 6 mo
	2.5 mg/kg/d; 5 mg/kg over 48 h, age 6 to < 9 mo
	3 mg/kg/d; 6 mg/kg over 48 h, age ≥ 9 mo, as a 48-h continuous infusion through central venous catheter, days 0, 1
L-ASP	6000 IU/m² × 8 doses, 3 times weekly
ITT	Intrathecal triple therapy (methotrexate 7.5 mg; hydrocortisone 7.5 mg; ARA-C 15 mg), days 0, 7, 14, 21, 28
MTX	4 g/m², days 21, 28
CF rescue	10 mg/m² orally or intravenously every 6 h × ≥ 5 doses, start 18 h after MTX completion
VCR	0.05 mg/kg intravenous push
Intensification, 4 wk	
VP-16	100 mg/m², days 36-40
DXM	10 mg/m² orally 3 times daily, days 0-20, no taper
CPM	300 mg/m²/day intravenously, days 36-40
Reinduction, 4 wk	
CPM	250 mg/m² every 12 h × 4 doses, days 2, 3
VCR	0.05 mg/kg days 0, 14; 0.03 mg/kg day 7
DNM	45 mg/m²/d × 2 days
DXM	10 mg/m² divided 3 times daily, days 0-20, no taper
L-ASP	6000 IU/m² intramuscularly × 8 doses, 3 times daily, days 0-20
ITT	Days 0, 14
BMT for 11q23/MLL	
Reintensification, 6 wk	
VCR	0.75 mg/m² intravenously, days 0, 7
VHMTX	6000 mg/m² in 1 h, followed by 1200 mg/m²/h × 23 hours × 2 doses, days 0, 14
CF rescue	200 mg/m² intravenously over 1 h, then 12 mg/m² intravenous push every 3 h × 6 doses, then 12 mg/m² intravenously or orally every 6 h until plasma MTX level < 0.1 μM; start 12 h following MTX completion (36 h after start)
VP-16	100 mg/m²/d intravenously, days 29-32
CPM	300 mg/m²/d intravenously over 30 min, days 29-32
IT ARA-C	15 mg intrathecally, days 7, 21
Consolidation, 9 wk	
VHMTX	6000 mg/m² intravenously in 1 h, followed by 1200 mg/m²/h intravenously for 23 h, days 28, 42
CF rescue	10 mg/m² orally or intravenously every 6 h × ≥ 5 doses, start 18 h after MTX completion
IT ARA-C	15 mg intrathecally, days 35, 49
VCR	0.75 mg/m² intravenously, days 28, 42
IV ARA-C	3000 mg/m² intravenous 3 h infusion every 12 h, days 0, 2, 7, 8 for total of 8 doses
L-ASP	6000 IU/m² intramuscularly 3 h after intravenous ARA-C on days 1, 8
Intensified maintenance, 72 d × 3	
VCR	0.75 mg/m² intravenously, days 0, 28
DXM	10 mg/m² divided orally 3 times daily, days 1-4 and 28-32
6-MP	75 mg/m² orally, days 0-48
MTX	20 mg/m² intramuscularly every week, days 0, 7, 14, 21, 28, 35, 42
VP-16	100 mg/m²/d, days 49-53
CPM	300 mg/m²/d intravenously over 30 min, days 49-53
IT ARA-C	15 mg intrathecally, days 0, 28
Routine maintenance, 4 cycles, 1 y	
VCR	1.5 mg/m² intravenously every 4 wk × 12 doses, days 0, 28, 56
PRED	40 mg/m² orally divided in 3 doses for 5 d with each VCR dose
MTX	20 mg/m² orally weekly, days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77
6-MP	75 mg/m² orally daily for 12 weeks per cycle
IT MTX	8 mg age 12-23 mo, 10 mg age 24-35 mo, day 0

COG P9407 Induction and Induction Intensification Therapy and Modifications

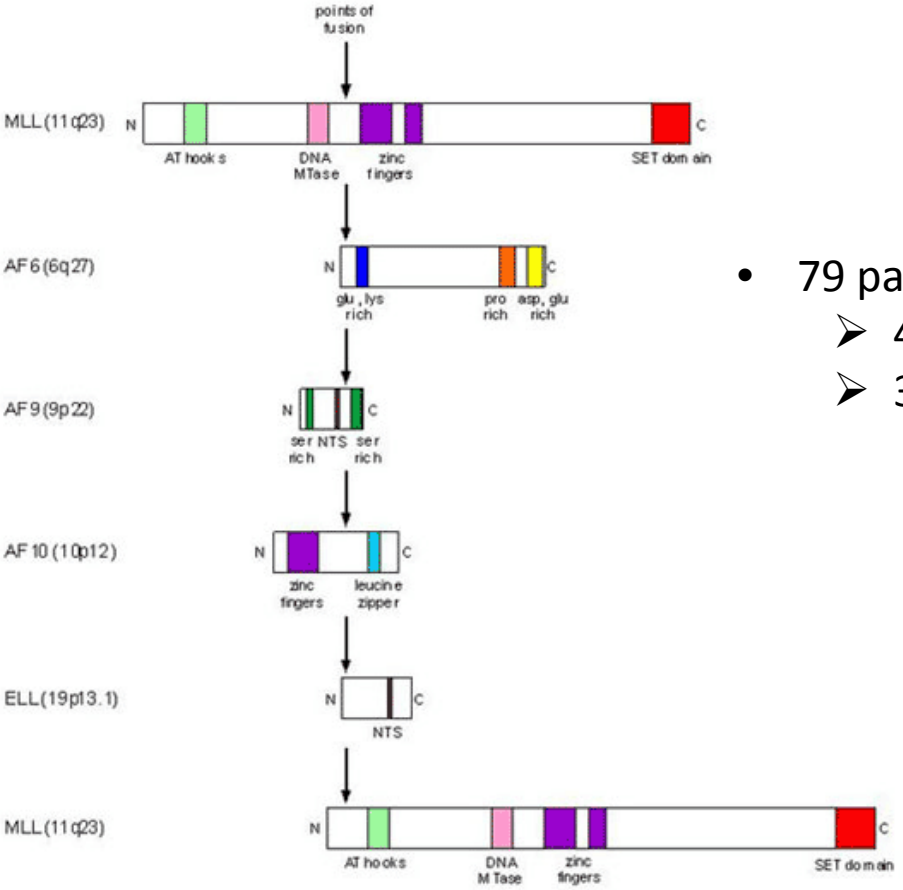
Cohort 1 (1996–1997)	Cohort 2 (1997–2000)		Cohort 3 (2001–2006)
June 1996	**November 1997**	**July 1998**	**Jan 2001**
TIT[a] days 1, 8, 15, 22, 29			
VCR 0.05 mg/kg, days 1, 15; VCR 0.03 mg/kg, day 8			
Dex 10 mg/m^2/day div TID, days 1–21			PDN 40 mg/m^2/day div TID, days 1–21
Daun days 1, 2	Daun days 1, 2	Daun days 1, 2	Daun days 1, 2
All ages—120 mg/m^2 CI over 48 hours		≤90 days 2 mg/kg/day IV over 30 minutes	
	<6 months at diagnosis 2 mg/kg/day CI	>90 days to <6 months 2 mg/kg/day CI	<6 months 2 mg/kg/day IV over 30 minutes
	6 to <9 months 2.5 mg/kg/day CI	6 to <9 months 2.5 mg/kg/day CI	6 to <9 months 2.5 mg/kg/day IV over 30 minutes
	≥9 months 3 mg/kg/day CI	≥9 months 3 mg/kg/day CI	≥9 months 3 mg/kg/day IV over 30 minutes
Cy 250 mg/m^2 every 12 hours × 4 doses, days 3, 4 (with MESNA)			
Asp 6,000 U/m^2 IM days 4, 6, 8, 10, 12, 15, 17, 19			
HD MTX 4 g/m^2 over 24 hours days 22, 29 (followed by leucovorin rescue)			
VP-I6 100 mg/m^2/day days 36–40			
Cy 300 mg/m^2/day days 36–40 (with MESNA)			

[a] TIT to <365 days of age—intrathecal methotrexate 7.5 mg, hydrocortisone 7.5 mg, cytosine arabinoside 15 mg; >365 days of age—intrathecal methotrexate 8 mg, hydrocortisone 8 mg, cytosine arabinoside 16 mg; VCR—vincristine; Dex—dexamethasone; Daun—daunorubicin; Cy—cyclophosphamide; Asp—native L-asparaginase; HD MTX—high dose methotrexate; VP-16—etoposide; PDN—prednisone; TID—three times daily; CI—continuous infusion; Leucovorin rescue beginning 42 hours after start of HD MTX infusion—10 mg/m^2 every 6 hours for five doses.

Leucémies aiguës du nourrisson

3. Pathogénie moléculaire

Réarrangement du gène MLL 11q2.3

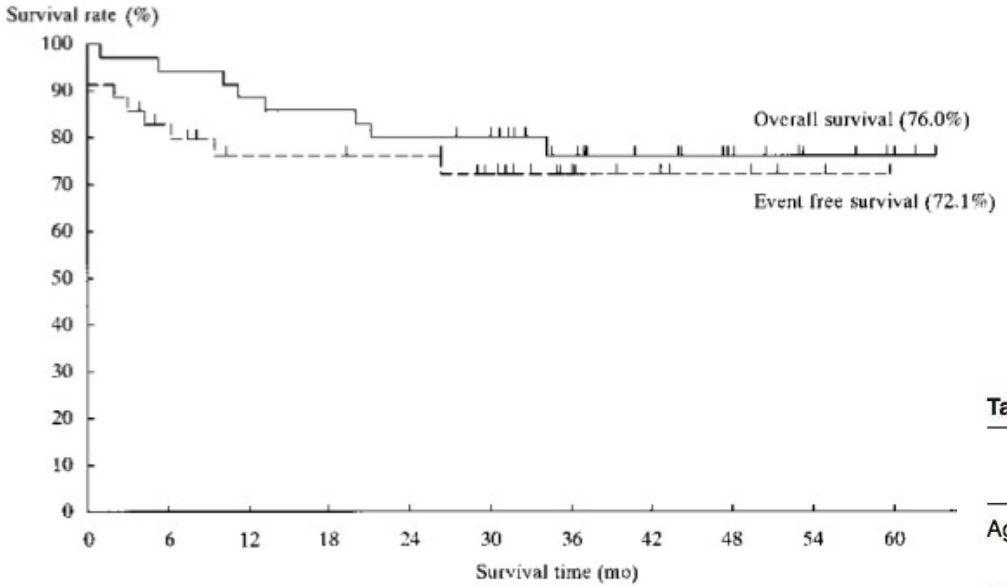


- 79 partenaires différents à MLL:
  - 4 réarr expliquent 93% des LAL-MMLr du NRS
  - 3 réarr expliquent 66% des LAM-MMLr du NRS

Meyer C, Leukemia 2013

5. Les LAM du NRS

- **Résultats et facteurs pronostiques** : ceux des LAM



Kawasaki H, Blood 2001

Table 2. Comparison of EFS between two subgroups divided by risk factors

Risk factor	Subgroup	No. of patients	EFS (%)	*P*
Age	< 6 mo	12	72.9	.379
	≥ 6 mo	23	69.1	
Gender	Boys	22	66.6	.362
	Girls	13	83.1	
WBC	< 100 000/μL	23	72.0	.843
	≥ 100 000/μL	12	74.1	
WBC	< 200 000/μL	28	70.1	.382
	≥ 200 000/μL	7	83.3	
FAB subtype	M4/M5	23	80.8	.105
	non-M4/M5	12	56.1	
MLL rearrangements	Positive	17	74.1	.961
	Negative	18	73.4	