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Specific cytogenetic abnormalities are associated with a significantly inferior outcome in children and adolescents with mature B-cell Non-Hodgkin's Lymphoma: Results of the FAB/LMB 96 international study

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A complete list of the participants in the cytogenetics study of the FAB/LMB96 International trial appears in the "Appendix".

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Abstract

Clinical studies showed that advanced stage, high LDH, poor response to reduction therapy and combined bone marrow and central nervous system disease are significantly associated with a decreased event free survival (EFS) in pediatric mature B-NHL treated on FAB/LMB96. Although rearranged MYC/8q24 (R8q24) is characteristic of Burkitt Lymphoma (BL), little information is available on other cytogenetic abnormalities and their prognostic importance. We performed an international review of 238 abnormal karyotypes in childhood mature-B-NHL treated on FAB/LMB96: 76% BL, 8% Burkitt-like lymphoma, 13% diffuse large B-cell lymphoma (DLBCL). The main BL R8q24 associated chromosomal aberrations were +1q [29%], +7q and del(13q) [14% each]. The DLBCL appeared heterogeneous and more complex. Incidence of R8q24 [34%] was higher than reported in adult DLBCL. The prognostic value of cytogenetic abnormalities on EFS was studied by Cox model controlling for the known risk factors: R8q24, +7q and del(13q) were independently associated with a significant inferior EFS [HR: 6.1 (p=0.030), 2.5 (p=0.015), 4.0 (p=0.0003), respectively]. The adverse prognosis of R8q24 was observed only in DLBCL while del(13q) and +7q had a similar effect in DLBCL and BL. These results emphasize the significant biological heterogeneity and the development of cytogenetic risk adapted therapy in childhood mature-B-NHL.

Keywords

Childhood mature B-cell lymphoma; Burkitt lymphoma; DLBCL; cytogenetics; prognosis

Introduction

We recently reported the clinical results of the first international randomized study in children and adolescents with mature B-cell lymphoma (FAB/LMB 96) [1-3]. In children with intermediate risk B-NHL, the 4 year event-free survival (EFS) and overall survival (OS) were 90.2% and 92.7%, respectively[1]. Low stage presentation (non resected stage I/II), normal LDH (< 2 times institutional upper limit) and response to COP (cyclophosphamide, vincristine and prednisone) reduction therapy greater then 20% were associated with higher EFS[1]. In patients with advanced B-NHL (bone marrow involvement ≥ 25% blasts [B-ALL] ± central nervous system involvement), the 4 year EFS and OS were 79 ± 3% and 82 ± 3%, respectively[2]. Poor response to COP (cyclophosphamide, vincristine, prednisone) reduction therapy and combined bone marrow and CNS disease were associated with a significantly poorer EFS[1]. In the low risk patients, with resected localized B-NHL, 4 year EFS and OS of

98.3 % and 99.2 3%, respectively, were obtained with a low intensity treatment without intrathecal chemotherapy[3].

However, little information is available regarding the prognostic value of cytogenetic aberrations in childhood B-NHL, especially in those children treated on a uniform protocol. Mature B-cell lymphoma/leukemia in children are mainly represented by Burkitt lymphoma/leukemia (BL) and to a lesser extent by high grade B-cell (Burkitt-like or atypical Burkitt) lymphoma (BLL) and diffuse large B-cell lymphoma (DLBCL)[4,5]. BL is a pathological entity characterized by chromosomal translocations associating the *MYC* gene (located at 8q24) to one of three immunoglobulin loci[6-9]. These cytogenetic translocations result in deregulated *MYC* expression, a well known oncogene responsible for maintaining the balance of cellular proliferation, differentiation, adhesion and apoptosis[10]. Other genetic changes, such as disruption of the p14ARF-MDM2-p53 pathway, have been identified in more than half of childhood sporadic BL and may provide further growth stimulation and apoptosis protection[11,12]. Some additional chromosomal alterations have been previously described, such as gains of the long arm of chromosomes 1 (+1q) or 7 (+7q) or 12 (+12q), deletion (del)17p13 and abnormalities of band 13q34, usually in adult BL, without or in the setting of an HIV infection[13-18]. Secondary abnormalities are said to be associated with tumor progression[19], but their prognostic value has not been clearly evaluated and few cytogenetic data are available in pediatric BL[20-22].

DLBCL is less common in childhood (10-15%) than in adult patients with B-NHL (30-40%). Involvement of the *BCL6* (3q27), *BCL2* (18q21) and to a lesser extent *MYC* (8q24) loci have been demonstrated in adult DLBCL. Chromosomal alterations associated with childhood DLBCL have not been well described and a study of 7 pediatric cases suggested that they could be distinct from those known to occur in adult DLBCL[23].

We now report the cytogenetic results of 238 children and adolescents with localized, intermediate and advanced B-NHL treated on FAB/LMB 96 in a uniform manner that were reviewed by an international cytogenetic panel of experts and correlated with centrally reviewed pathology. We further characterize the non-random chromosomal alterations and analyze the prognostic significance of specific cytogenetic aberrations on the EFS.

Patient and Methods

FAB/LMB Patients

This study included children and adolescents with mature B-cell NHL registered and treated on the randomized international FAB/LMB 96 therapeutic trial with the collaboration of 3 pediatric cooperative groups: SFOP (Société Française d'Oncologie Pédiatrique), CCG (Children's Cancer Group of the USA, Canada and Australia) and UKCCSG (United Kingdom Children's Cancer Study Group). One thousand one hundred eleven non immunosuppressed patients under 18 (SFOP, UKCCSG) or 21 (CCG5961) years of age with newly diagnosed *de novo* mature B-cell lymphoma enrolled from May 1996 to June 2001 were eligible (SFOP: 385 cases; CCG5961: 531; UKCCSG: 195). International morphologic review and follow-up data were available in 1018 (92%). Patients were stratified into 3 risk groups [24]: A (resected stage I or completely resected abdominal stage II), B (non eligible for

A and C), C (stage IV with CNS involvement and/or B-ALL) with treatment of progressive intensity [1,2].

Pathologic review

The pathological materials for each case were initially reviewed in each national cooperative group by at least two expert hematopathologists. A diagnosis was defined according to the REAL classification[4] which formed the basis of the new WHO classification[5]. All cases were then re-reviewed by the two other national group pathologists at a group review meeting. A consensus diagnosis was established for each case when all three national diagnoses were in agreement or when two of the three national expert groups were in agreement. When none of the three national diagnoses were in agreement a consensus diagnosis was reached following group review on a multi-headed microscope by all members of the reviewing committee[25]. *A posteriori*, due to the high incidence of DLBCL with 8q24/MYC rearrangement, all of the DLBCL with an 8q24/MYC translocation were reviewed again by the panel to exclude any cases of BL or BLL by morphology. Upon subsequent re-review by the international panel, all cases were confirmed histologically to be DLBCL based on morphologic features.

Cytogenetic review

Abnormal karyotypes from 280 children enrolled in the FAB LMB96 study were collected by the cooperative groups. Inclusion criteria for the cytogenetic study were: (i) an abnormal karyotype from an involved tissue obtained at the time of primary diagnosis and before treatment; (ii) for each case, at least two karyograms representative of each abnormal clone reviewed by at least two experienced cancer cytogeneticists, one of whom was not from the submitting institution. The cytogenetic reviews were performed within the framework of each national therapeutic groups. The study was based solely on conventional chromosomal analysis with no FISH input. The karyotypes were described according to the 2005 International System for Human Cytogenetic Nomenclature[26] (Supplementary Table 1). Forty-two cases were excluded: 15 without any morphologic review, 26 without any cytogenetic review and 1 because the karyotype study was performed during treatment. Finally, 238 cases were included in this study, 121 from the SFOP group, 96 from the CCG and 21 from the UKCCSG. In 9 cases, a karyotype of at least 2 different samples from the same patient were available. The most complex karyotype was scored for inclusion in the prognostic analysis. In this study, the presence of more than 3 chromosomal alterations was considered to define a complex karyotype.

Statistics

Comparisons of the distribution of patients' characteristics were performed using either the Chi-squared or Fisher's exact test. The end-point of the prognostic analysis was event-free survival (EFS) which was defined as the minimum time between treatment start and progressive disease or relapse or second malignancy or death from any cause or the last follow-up contact for patients who did not experience any event. EFS was estimated with the Kaplan Meier method. Prognostic impact of each chromosomal abnormality was studied using Cox's model with adjustment for the national cooperative group (SFOP, CCG,

UKCCSG), the therapeutic groups (C standard treatment vs C reduced treatment vs A or B), the morphologic consensus diagnosis (DLBCL vs BL or BLL or not subclassified), the LDH level (>2 times the normal institutional value vs <=2N), CNS involvement and primary mediastinal localization. Individual chromosomal abnormalities with a p value <0.20 in this analysis were studied altogether in a Cox's model in order to identify the independent prognostic factors. The variable "karyotype complexity" was then added in the model to determine whether the effect of the individual chromosomal abnormalities was independent of complexity or was related to their association with the cytogenetic complexity. A test for interaction was used to investigate if the impact on EFS of the significant chromosomal abnormality was substantially different in BL or DLBCL. The reported p-values are two-sided.

Results

Patient Demographics (Table 1)

Median age was 9.1 years (range [2-20]); male / female sex ratio was 3.1. Seventy-six percent of cases were classified as BL, 8% BLL, 13% DLBCL and 3% not sub classified. Five percent were treated according to group A regimen, 55% group B and 40% group C. As compared to the other 780 patients of the FAB/LMB96 study, there was a significant over-representation of group C, especially patients with B-ALL, with LDH level > 2N and with CNS involvement. Otherwise patients in this cytogenetic analysis had an increased frequency of BL compared to the other patients treated on the FAB/LMB 96 study (Table 1). After adjustment for risk group and LDH level, the EFS of patients included in the cytogenetic study did not significantly differ from the EFS of the other patients treated on the FAB/LMB 96 study

Characterization of cytogenetic abnormalities (Figure 1)

Rearrangement of the chromosomal band 8q24 (rearranged 8q24), site of the *MYC* locus, with the different immunoglobulin gene loci was detected in 84% cases: 93% of BL, 83% of BLL and 33% of DLBCL. Rearranged 8q24 was associated with other chromosomal aberrations in 69% of cases [BL: 64%, BLL: 93%, DLBCL: 100%]. The main associated clonal structural alteration was +1q followed by +7q, del(13q) and del(6q). In the absence of rearranged 8q24, karyotypes were more complex (57% versus 33%, p=0.006), there was more aneuploidy (70% versus 30%, p<0.0001), and the pattern of associated abnormalities was quite different with a higher incidence of der(11q), +12q and del(6q) and a lower proportion of +1q. The pattern of chromosomal alterations also varied according to the morphological subtype, except for del(13q) and +7q, which occurred in similar proportions in BL and in DLBCL. The main secondary alteration in BL was +1q (29%). Dup(1q) was only identified in BL while del(6q), der(11q) and +12 were significantly more frequent in DLBCL (43%, 27%, 23% respectively). The DLBCL karyotypes were significantly more complex and more aneuploid than BL (both 80% vs 27%, p<0.0001). The small group of BLL appeared heterogeneous, sharing characteristics of BL as well as of DLBCL (Figure1). Gain of the long arm of chromosome 1 was due to dup(1q) in 43/65 cases (66%). Alterations of chromosome 13q were very heterogeneous. The majority (33/38) resulted in 13q deletions either isolated or due to various unbalanced translocations without obvious recurrent

breakpoints. The most commonly deleted band was 13q34 (82%). Gain of 7q (36 cases) was due to whole chromosome trisomy (19 cases), unbalanced translocations with different partners (12 cases), isochromosome 7q (4 cases), interstitial 7q du-/triplications (3 cases). Coexistence of 2 different mechanisms of +7q was observed in 2 cases leading to 7q tetrasomy. The minimal region of gain was restricted to 7q21q22. The 13q and 7q alterations were frequently encountered in a complex karyotype (88% and 58% respectively). A group of 33 cases had loss of part or all of the long arm of a chromosome 6, del(6q). In 28 of these, there appeared to be a simple deletion; in the remaining 5 the loss occurred as the result of an unbalanced translocation. Two different rearrangements of chromosome 11 were detected: deletions (14 cases) and 11q gains (5 cases). The most frequent breakpoint was 11q23 (63%). Gain of 12q was due to whole chromosome trisomy in 15/16 cases. Lastly, complexity was associated with aneuploidy (65%), del(13q) (34%), del(6q) (28%) and +7q (23%). The aneuploidy was usually due to hyperdiploidy (71%).

Prognostic significance of cytogenetic abnormalities

The median follow-up time of the subset of 238 patients with both cytogenetic and morphologic reviews was 4.5 years [range: 10 months – 8 years]. There were 43 events. The cytogenetic abnormalities associated with a significantly worse EFS were aneuploidy, complexity, rearranged 8q24, del(13q), +7q and der(3q) (Table 2).

The combined analysis of the different cytogenetic abnormalities showed that rearranged 8q24, del(13q) and +7q were independently associated with a worse EFS: their respective hazard ratios (HR) [95%CI] were 6.1 [1.2-31] (p=0.028), 4.0 [1.9-8.6] (p=0.0003) and 2.5 [1.2-5.2] (p=0.015), respectively. The 4-year EFS of patients with rearranged 8q24 was 79.6% versus 94.6% in the other patients (Figure 2A). In patients with a +7q abnormality, the EFS was 72.2% versus 83.6% in patients without this abnormality. Similarly in patients with a del(13q) the EFS was 63.6% versus 84.9% in the rest of the group. Furthermore, patients with del(13q) had a significantly inferior response to COP reduction therapy after one week of therapy (15% vs 2%, $p<0.004$). Complexity of the karyotype was associated with a significantly worse EFS (HR=3.2, p=0.0005) (Table 2): the EFS of patients with a complex karyotype was 72.1 vs 87.4% without (Figures 2). However, when complexity was added to the model including these 3 chromosomal alterations, the prognostic effect of each of them remained significantly associated with EFS (respective HR were 5.8, 2.5 and 2.5), and the hazard ratio of complexity decreased to 2.0 [95%CI=0.92-4.3] (p=0.08).

The prognostic effect of del(13q), +7q and karyotype complexity did not differ between BL and DLBCL, whereas the adverse prognostic effect of rearranged 8q24 was only observed in DLBCL (interaction test, p=0.19). In BL, the 4 year EFS was 83.4 and 84.6% with and without rearranged 8q24. Although the numbers were very small, the EFS in DLBCL with and without rearranged 8q24 was 50% (5 events /10 patients) vs 100% (0 event /20 patients) (Figures 3).

Discussion

Childhood mature B-cell lymphomas currently have a favorable outcome with present therapeutic strategies, but intensive chemotherapy is associated with significant

morbidity[1-3,24,27]. The principal objective of the international randomized FAB LMB96 study was to try to diminish treatment intensity without jeopardizing survival[1-3]. Among the secondary aims of the study was to identify prognostic factors to tailor further treatment and develop more risk adaptive therapy.

This is the first large cytogenetic study performed on such an international randomized trial in children and adolescents with mature B-cell lymphoma treated in a uniform manner. The multivariate analysis showed that specific karyotype abnormalities, rearranged 8q24, +7q, del(13q) have an independent prognostic significance in childhood mature B-cell lymphoma. Their hazard ratios of greater than 2.5 were in the same range as some other clinical and biological prognostic risk factors that we have previously identified such as CNS disease, COP response, risk groups and initial LDH level[1-3]. Further, the complete cytogenetic characterization in the subgroup of children with B-NHL contributed to the identification of distinctive patterns of chromosomal alterations that provide additional diagnostic information to the morphologic classification.

We did not detect any prognostic value of 1q gain, though the size of the series was sufficient to detect any significant effect of this common chromosomal abnormality. This is in contrast to a smaller study of 46 sporadic BL that had previously identified +1q to be a poor risk factor but treated with heterogeneous therapeutic schemes[20]. This discrepancy may be due to improvement in the recent development of short intensive chemotherapy utilizing fractionated cyclophosphamide, higher doses of methotrexate and in more advanced patients high dose fractionated and continuous infusion ARA-C, which could have abolished the effect of this chromosomal abnormality.

Complexity of the karyotype could be a measure of the number of the oncogenetic steps but also could reflect the genetic instability of tumors. In our series, the prognostic effect of complexity was partly explained by the role of del(13q) and to a lesser extent of +7q. Both of these alterations were detected in BL and DLBCL in similar proportions and were usually associated with complexity. These observations suggest that del(13q) and +7q could be secondary events associated with tumor progression of childhood B-cell mature lymphomas regardless of the morphologic subclassification.

Although we detected two partial 13q duplications leading to 13q11q22 trisomy as reported in Barin C *et al.*[28], most of the 13q alterations resulted in a del(13q) involving chromosomal band 13q34 and to a lesser extent 13q14. Chromosome 13 candidate genes include *BAFF* (13q32q34), which recently has been shown to be involved in BL apoptosis[29], and a new family of regulatory micro-RNA genes (miR genes), which have been identified at different genomic regions involved in cancers and specifically on 13q14[30].

As expected, rearranged 8q24 was cytogenetically detected in 93% of BL, most of them resulting from a t(8;14) translocation. The incidence rates of variant translocations t(8;22) and t(2;8) were lower than previously reported (11% and 5.6% respectively)[13]. The 13 cases classified as BL without an obvious *MYC* locus rearrangement (7% in this series) shared a similar pattern of chromosomal alterations with the 169 BL with rearranged 8q24, except for more frequent aneuploidy and presence of der(11q), although not significant. This

observation raises the question if the BL without rearranged 8q24 truly belong to the Burkitt entity (with possible cryptic *MYC* rearrangement potentially detectable by FISH) or if they are actually some other aggressive mature B-cell proliferations sharing morphologic similarities with BL. It is noteworthy that a recent gene expression profiling study confirmed the existence of lymphomas with the molecular signature of BL without cytogenetically detectable *MYC* rearrangement[31] The significant difference in EFS associated with a rearranged 8q24 occurred in the small number of patients in the DLBCL subgroup where presumably it may represent a secondary event in contrast to likely being a primary event in the Burkitt subgroup. This assumption is also supported by the detection of a different molecular signature between BL and DLBCL with *MYC* rearrangement[32]. This needs to be confirmed in a large series and analyzed by DLBCL subtypes including germinal center (GC) and activated B-cell like (ABC).

The pattern of chromosomal alterations in this childhood DLBCL series was quite distinct from those reported in adult patients. Alterations of loci containing oncogenes known to play a major role in adult DLBCL lymphomagenesis, such as *BCL6* (3q27) and *BCL2* (18q21), were very rare (each < 7%) in this childhood series. In particular, no concurrent t(14;18) and R8q24 were detected, which is known to be a poor-outlook combination in DLBCL. Conversely, involvement of the *MYC* (8q24) locus was much more frequent (33%) than the 5-10% reported in adult DLBCL[33],[34]. We and others have recently reported an increase in frequency of the GC vs ABC subtype of DLBCL in children and adolescents compared to previous reports in adults[35]-[37].

Our data showed that specific cytogenetic findings at diagnosis are useful for improving sub-classification of childhood mature B-cell lymphomas, in conjunction with morphology and immunophenotyping. Furthermore, we have found that cytogenetic aberrations are independent prognostic variables in childhood mature B-cell NHL. In particular, we showed the independent importance of rearranged 8q24, +7q, del(13)(q34). The prognostic effect of complexity was partly explained by the role of del(13q) and to a lesser extent of +7q. These results emphasize the biological heterogeneity of childhood mature B-cell NHL and the impact of cytogenetics in prognostic stratification. In this latter purpose, conventional cytogenetics can be supplemented by interphase FISH to enhance detection of relevant chromosomal alterations (such as 8q24 translocations and +7q). High resolution genome-wide array in parallel with gene expression profiling should allow more precise characterization of heterogeneous chromosomal abnormalities, especially complexity and del(13q), in order to search for candidate genes and deregulated cellular pathways. If other studies confirm these results, future therapeutic strategies could incorporate the results of these cytogenetic findings and investigate whether alternative treatment strategies would improve the prognosis in subgroups of patients with poor risk cytogenetic factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Appendix: contributing cytogeneticists and their institutions by alphabetic order (* cytogeneticists who participated on the panel of reviewers)

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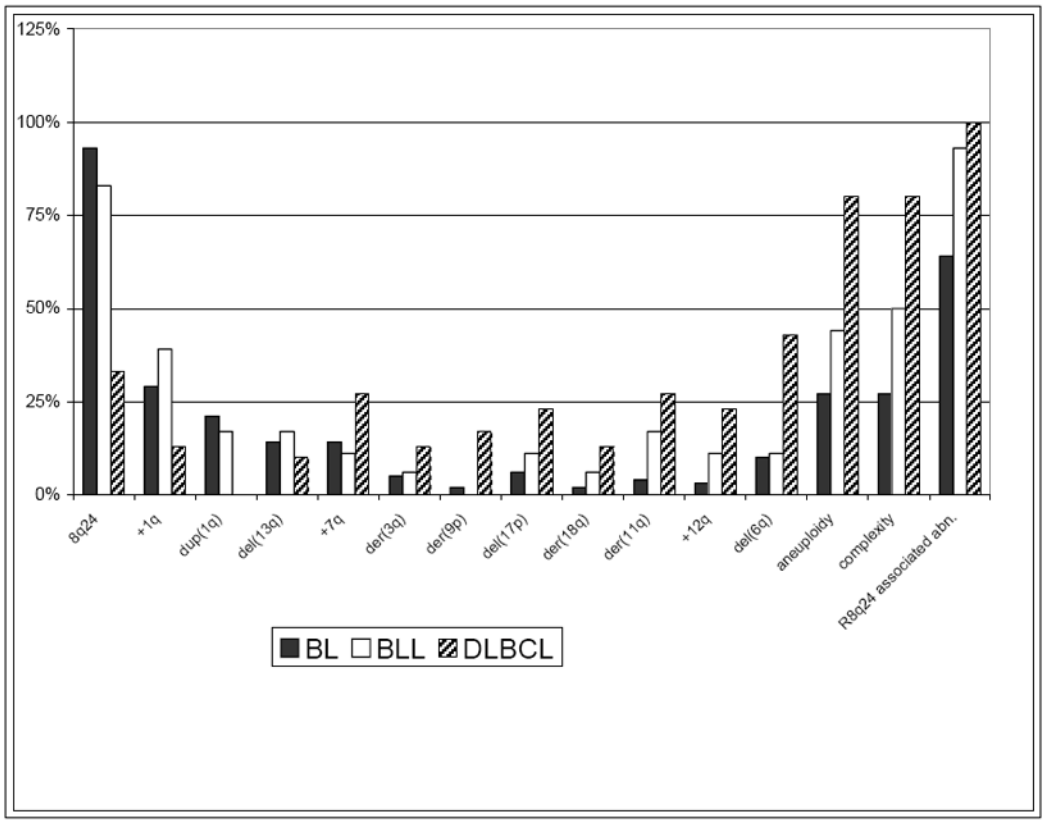

Figure 1. Distribution of cytogenetic abnormalities in FAB/LMB 96 Study stratified by histological subtypes Burkitt Lymphoma (BL), Burkitt Like Lymphoma (BLL) and Diffuse Large B-Cell Lymphoma (DLBCL)

R8q24, dup(1q), del(6q), der(11q), +12, ploidy and complexity are helpful in the discrimination between BL and DLBCL. BLL exhibit an intermediary pattern.

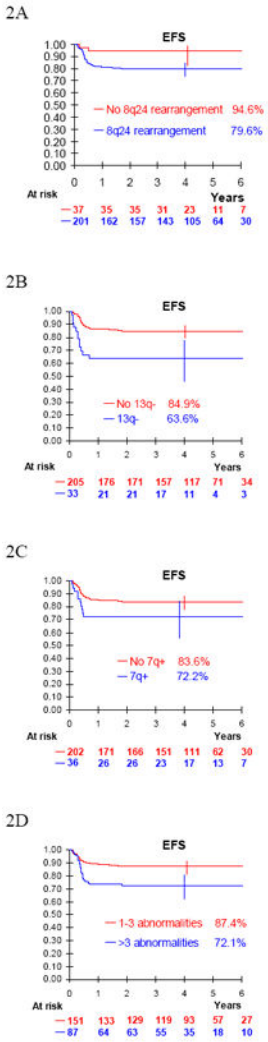

Figure 2. Probability of EFS by Kaplan-Meier method in children with B-NHL treated on FAB/LMB 96 on the whole population (N=238)

Figure 2A: EFS with and without rearranged 8q24 cytogenetic abnormality

Figure 2B: EFS with and without del(13q) cytogenetic abnormality

Figure 2C: EFS with and without +7q cytogenetic abnormality

Figure 2D: EFS with and without a complex karyotype (>3 cytogenetic abnormalities)

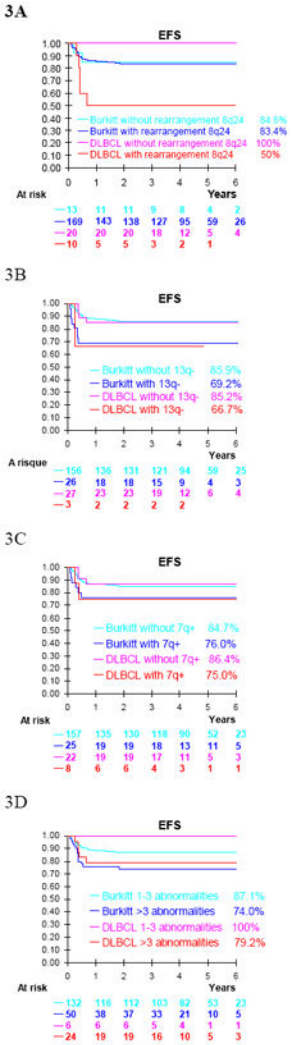

Figure 3. Probability of EFS by Kaplen-Meier method in children with B-NHL treated on FAB/LMB 96 according to the main morphologic entities BL (N=182) and DLBCL (N=30)

Figure 3A: EFS with and without rearranged 8q24 cytogenetic abnormality

Figure 3B: EFS with and without del(13q) cytogenetic abnormality

Figure 3C: EFS with and without +7q cytogenetic abnormality

Figure 3D: EFS with and without a complex karyotype (>3 cytogenetic abnormalities)

While del(13q), +7q and the complexity altered the prognosis of BL and DLBCL in the same proportion, the adverse effect of R8q24 is only detected in DLBCL.

Table 1

Initial patient characteristics of the 238 cases with cytogenetics Comparison with the other cases without cytogenetics of FAB/LMB96

	With cytogenetics (N=238)		Without cytogenetics (N=780)		p*
M/F Sex ratio	180/58 (3.1)		603/177 (3.4)		0.59
Median age, years [range]	9.1 [2-20]		10.1 [1-20]		0.03°
Therapeutic group					0.0001
A	11	(5%)	119	(15%)	
B	132	(55%)	550	(71%)	
C	95	(40%)	111	(14%)	
Stage					0.0001
I	11	(5%)	104	(13%)	
II	26	(11%)	187	(24%)	
III	88	(37%)	358	(46%)	
IV	33	(14%)	61	(8%)	
Leukemia	80	(34%)	70	(9%)	
LDH > 2N	167	(71%)	244	(33%)	0.0001
CNS disease	42	(18%)	65	(8%)	0.0001
COP response <20%	9/227	(4%)	31/658	(5%)	0.64
Morphologic group					0.0001
BL	182	(76%)	468	(60%)	
BLL	18	(8%)	58	(7%)	
DLBCL	30	(13%)	208	(26%)	
Not sub classified	8	(3%)	46	(6%)	

M/F : Male/Female

CNS : central nervous system

BL : Burkitt lymphoma, BLL : Burkitt-like lymphoma, DLBCL : diffuse large B-cell lymphoma

* chi-square test except for

° Kruskal-Wallis test

Table 2

Prognostic significance of individual cytogenetic abnormalities (analysis of each abnormality separately)

	Whole population			Burkitt lymphoma			DLBCL	
	EFS (43 events / 238 patients)			EFS (30 events / 182 patients)			EFS (5 events / 30 patients)	
	Event / Patient	HR [IC95%]	p	Event / Patient	HR [IC95%]	p	Event / Patient	p
R8q24	41 / 201	5.4 [1.2-25]	0.03*	28 / 169	1.2 [0.26-5.2]	0.84$	5 / 10	0.0004£
N8q24	2 / 37	1						
R8q24 alone	10 / 62	4.0 [0.75-21]						
R8q24 associated	31 / 139	5.7 [1.2-26]	0.06*					
del(13q)	12 / 33	4.3 [2.0-9.1]	0.0002*	8 / 26	4.8 [1.9-12]	0.001$	1 / 3	0.31£
der(3q)	5 / 13	3.1 [1.1-8.4]	0.03*	2 / 8	2.8 [0.60-12.8]	0.19$	2 / 4	0.02£
+7q	10 / 36	2.8 [1.4-5.9]	0.005*	6 / 25	2.6 [1.01-6.5]	0.047$	2 / 8	0.44£
complexity	24 /87	3.2 [1.7-6.1]	0.0005*	13 / 50	2.5 [1.2-5.2]	0.02$	5 / 24	0.24£
aneuploidy	21 / 86	2.1 [1.1-4.0]	0.02*	13 / 49	2.5 [1.2-5.4]	0.02$	3 / 24	0.19£
+1q	8 / 65	0.53 [0.24-1.2]	0.11*	4 / 52	0.37 [0.13-1.1]	0.065$	1 / 4	0.63£
del(6q)	6 / 33	0.97 [0.35-2.6]	0.95*	3 / 18	1.1 [0.32-3.7]	0.90$	3 / 13	0.38£
der(9p)	0 / 7	/	0.37°	0 / 5	/	0.48°	0 / 2	0.53£
der(11q)	3 / 19	0.96 [0.28-3.3]	0.95*	0 / 8	/	0.23°	2 / 8	0.43£
+12q	1 / 16	0.24 [0.03-1.9]	0.18*	0 / 6	/	0.28°	0 / 7	0.20£
del(17p)	6 / 21	1.4 [0.56-3.7]	0.45*	4 / 11	1.8 [0.63-5.4]	0.27$	1 / 7	0.85£
der(18q)	3 / 10	2.1 [0.57-7.8]	0.27*	0 / 4	/	0.52°	1 / 4	0.63£

*Adjusted on

- national cooperative group (SFOP vs CCG vs UKCCSG)
- therapeutic stratification group (C vs A / B)
- pathology (DLBCL vs BL / BLL / not sub classified)
- LDH level (>2N vs <=2N)
- CNS disease (yes vs no)

- primary mediastinal localisation (yes vs no)

$ Adjusted on

- national cooperative group (SFOP vs CCG vs UKCCSG)
- therapeutic stratification group (C vs A / B)
- LDH level (>2N vs <=2N)
- CNS disease (yes vs no)

° Logrank test adjusted on LDH level and CNS disease

£ Logrank test without any adjustment (due to the small number of events)

HR : hazard ratio