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ORIGINAL ARTICLE

Chromosomal aberrations in childhood acute lymphoblastic leukemia: 15-year single center experience

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Genetic analysis of leukemic cells significantly impacts prognosis and treatment stratification in childhood acute lymphoblastic leukemia (ALL). Our retrospective single center study of 86 children with ALL enrolled into three consecutive treatment protocols (ALL-BFM 90, ALL-BFM 95 and ALL IC-BFM 2002) between 1991 and 2007 demonstrates the importance of conventional cytogenetics and fluorescence in situ hybridization (FISH). Cytogenetic and FISH examinations were performed successfully in 82/86 (95.3%) patients and chromosomal changes were detected in 78 of the 82 (95.1%) patients: in 69/73 patients with B-cell precursor (BCP)-ALL and in 9/9 patients with T-lineage ALL (T-ALL). The most frequent chromosomal changes in subgroups divided according to WHO classification independent of treatment protocol and leukemia subtype were hyperdiploidy in 36 patients (with ≥50 chromosomes in 23 patients, with 47–49 chromosomes 13 patients) followed by translocation t(12;21) with *ETV6/RUNX1* fusion detected by FISH in 18 (22%) patients. Additional changes were detected in 16/18 (88.8%) *ETV6/RUNX1*-positive ALL patients with predominant deletion or rearrangement of untranslocated *ETV6* allele. Unique aberrations were detected in 4 patients and dicentric chromosomes in 8 patients, one with T-ALL. These results demonstrate that cytogenetics and FISH successfully provided important prognostic information and revealed not only recurrent but also new and rare rearrangements requiring further investigation in terms of prognostic significance.

Keywords Childhood acute lymphoblastic leukemia, cytogenetics, fluorescence in situ hybridization (FISH), chromosomal aberration, dicentric chromosome

Introduction

Advances in cytogenetics and molecular cytogenetics over the last 20 years as well as our understanding of the numerous pathways and regulation mechanisms including epigenetics in tumorigenesis have led to significant progress in the field of childhood acute lymphoblastic leukemia (ALL) (1,2). Primary genetic abnormalities can be identified in 75% to 80% of childhood ALL by standard chromosomal and molecular genetic analyses, but in virtually all cases after the addition of genome-wide analyses (3). Recent insights gained from genome-wide analyses have identified novel genetic alterations, including *IKZF1*, *CRLF2*, *PAX5* and *FLT3*, some of which have clinical relevance and could also serve as therapeutic targets in childhood ALL (4–11). These gene mutations coexist and cooperate with chromosomal alterations and together perturb multiple key cellular pathways including hematopoiesis, cell signaling, tumor suppression, apoptosis and cell cycle regulation. For example, a new subgroup of high risk patients with *BCR/ABL1*-like gene expression signature has been identi-

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fied, representing approximately 15% of B-precursor (BCP)-ALL (5,11).

Cytogenetics and molecular cytogenetics (fluorescence in situ hybridization, FISH) complemented by molecular genetics have been commonly used to detect chromosomal and genetic changes in childhood ALL in everyday clinical practice. Such an approach stratifies patients into favorable (hyperdiploidy ≥50 chromosomes, t(12;21)(p13;q22) leading to *ETV6(TEL)/RUNX1(AML1)* translocation) and unfavorable (hypodiploidy < 44 chromosomes, intrachromosomal amplification of chromosome 21, t(9;22)(q34;q11) leading to *BCR/ABL1* translocation, t(4;11)(q21;q23) leading to *KMT2A*(*MLL*)/*AFF1*(*AF4*) and other *MLL(KMT2A*) rearrangements) prognostic subgroups, and this is highly successful with survival rates approaching 90% in the best performing international trials (12–14). The superiority of minimal residual disease (MRD) over other risk factors has been emphasized in recent large studies (13).

Here we retrospectively review the results of cytogenetics and molecular cytogenetics in children with ALL treated in a single center in the Czech Republic between 1991 and 2007. Our aim was to demonstrate the importance of successful cytogenetic examination in childhood ALL.

Patients and methods

Patients

In total, 86 ALL children (46 girls and 40 boys; age 1 to 18 years, median 6.2 years) diagnosed after full examination at the Department of Pediatrics of the University Hospital Olomouc between January 1991 and October 2007 were included in the study.

The characteristics of the patients treated with the successive ALL-BFM 90, ALL-BFM 95 and ALL IC-BFM 2002 protocols are depicted in Table 1—distribution of patients according to the major clinical features did not differ significantly among the respective trials. Risk group stratification and therapy elements of the treatment protocols have been described in detail elsewhere (15–18). The median follow-up period of the study group was 15.6, 12.9 and 8.6 years for ALL-BFM 90, ALL-BFM 95 and ALL IC-BFM 2002, respectively. The research was approved by the relevant institutional ethics committee. All patients or their parents or guardians gave informed consent to participate in the study.

Table 1 Characteristics of the cohort of ALL patients in three consecutive protocols

	ALL-BFM 90	ALL-BFM 95	ALL IC-BFM 2002	p
Patients total	29	34	23	—
Gender				
Male	13	13	14	0.24
Female	16	21	9	
Age at diagnosis				
<6 years	13	16	11	0.97
≥6 years	16	18	12	
WBC at diagnosis (μl^{-1})				
<20,000	20	24	14	0.73
≥20,000	9	10	9	
Immunophenotype				
BCP-ALL	27	31	19	0.55
T-ALL	2	3	4	
Molecular genetics				
BCR/ABL1	0	2	1	ND
MLL (KMT2A) translocations	2	0	0	
TEL/AML1	1	10	7	
None of the above	26	22	15	
Risk group				
SR	12	11[a]	6	0.39
IR	13	19[a]	14	
HR	4	1[a]	3	
Relapse				
No	24	29	19	1.0
Yes	5	5	4	
Other event				
No	27	32	23	0.56
Yes	2	2	0	

Abbreviations: WBC, white blood cell count; BCP-ALL, B-cell precursor ALL; T-ALL, T-lineage ALL; MPAL, mixed phenotype acute leukemia; ND, not performed; SR, standard risk; IR, intermediate risk; HR, high risk.

[a] BFM 95: 3 patients excluded—2 *BCR/ABL1*+ and 1 incorrect risk group assignment.