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Genes and childhood leukemia

Geny a białaczki dziecięce

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Summary

Leukemia is a heterogeneous hematologic malignancy originating from a multipotent hematopoietic stem cell. It ranks among the commonest cancers in childhood and is characterized by excessive proliferation and differentiation block. The process of leukemogenesis is governed by genetic changes at both the cytogenetic and molecular level. According to numerous analyses, a large spectrum of mutations and rearrangements underlying the disease affect essential cellular transduction pathways, genes ensuring proper course of hematopoiesis, oncogenes, tumor suppressors and apoptosis regulators. Common lesions include translocations to T cell receptor (TCR) loci in T-lineage acute lymphoblastic leukemia (T-ALL), mutations of transcription factors regulating B-lineage development and cell maturation in B-lineage acute lymphoblastic leukemia (B-ALL) (PAX5, TCF3, EBF1, etc.), aberrational disruption of genes coding for transcription factors and coactivators in acute myeloid leukemia (AML) (e.g. CBF) or BCR-ABL1 fusion and activation of multiple kinases in chronic myeloid leukemia (CML). These alterations severely impair cell function. Broadening knowledge of the genetic background gives an insight into the pathobiology of a disease and allows for a better understanding of it. An appropriate investigation of genomic events yields diagnostic, prognostic and therapeutic implications. Broadening knowledge of the pathogenesis of leukemia seems to be a promising contribution to precise stratification of patients, reducing the toxicity and adverse effects caused by medical intervention, treatment personalization and introduction of targeted therapy accessible to a wide range of patients.

Keywords: **childhood leukemia • lymphoblastic • myeloid • myelodysplastic syndrome**

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Introduction

Leukemia is known as a group of malignant hematopoietic disorders and the most common type of childhood cancer. It represents an internally diverse collection of abnormalities with a heterogeneous profile. They are characterized by disruption of proliferation, differentiation and maturation of cells originating from a multipotent hematopoietic stem cell. The biological mechanisms mentioned above go beyond regular control, may be arrested at several stages of progression or fail to proceed. The pathological condition arises from changes in cells' genome, particularly in genes involved in physiological hematopoiesis. Abnormal cells, which successfully undergo the transformation process, then efficiently settle in bone marrow and peripheral blood, gradually displacing normal cells on account of their exceptional phenotype manifested by e.g. excessive proliferation or resistance to apoptosis. This phenomenon is initiated in a single cell and is followed by acquisition of additional mutations and rearrangements during cell division [9,16,20]. Although genetic alterations in this group of disorders may seem a well-addressed issue, successfully explored for years, they still remain a hot topic research. Owing to modern technologies, each year new reports are available concerning recently discovered correlations at the cytogenetic and molecular level which accompany leukemia. Analyses provide information on the accurate course of leukemogenesis, and produce diagnostic, prognostic, therapeutic implications. Separate subtypes of leukemia originating from the lymphoid and myeloid progenitors are characterized by distinctive genetic abnormalities, which may affect the clinical and biological properties of the disease [20,21,22,24].

Classification of leukemia

Due to the high biological diversity of leukemia there is a need for classification according to standardized diagnostic criteria, which will find application in clinical practice. From a few existing systems of division there are two that deserve special attention: FAB (French-American-British) and WHO (World Health Organization). In practice, for years the one commonly used has been the FAB classification, based on morphology, cytochemistry and blast immunophenotyping. The system distinguishes three major groups: lymphoblastic leukemia, myeloid leukemia and myelodysplastic syndromes (MDS) [14,16]. Furthermore, there are also three subtypes of acute lymphoblastic leukemia (ALL) – L1, L2, L3. Features considered for its diversification are as follows: cell size, nuclear chromatin, nuclear shape, nucleoli, amount and basophilia of cytoplasm. From myeloid leukemia eight subtypes were singled out (M0-M7), which display divergent differentiation to particular cell lines originating from a common myeloid progenitor, different degrees of maturity, and different amounts of cells of the predominating type [3,4,14]. There are also five morphological subtypes of MDS. The diagnostic criteria are mainly based on the proportion of blasts in peripheral blood, bone marrow and peripheral blood monocytosis. Evidence suggests that particular MDS subtypes illustrate gradual transformation to acute myeloid leukemia (AML), and there are similar genetic abnormalities underlying these two conditions. They seldom affect children, but it is estimated that a substantial proportion of pediatric AML cases begin as MDS, a preleukemic state [3,17].

The second classification proposed by WHO aspires to interpret a broad range of accessible information on morphology, immunophenotype, biology, genetics and clinical data referring to leukemia, partially taking into consideration previous FAB criteria. It should be emphasized that finally a role of genetic factors is appreciated. AML gains the new subtype "AML with recurring genetic translocations", which becomes an important component of partition. Due to reduction of the blast threshold for AML diagnosis (20%) in the WHO classification, an MDS division made by FAB undergoes substantial changes. Patients with resistant cytopenia in which the characteristic morphological blast features were not detected may be diagnosed by presence of the following genetic abnormalities: t(11;16)(q23;p13.3), t(3;21)(q26.2;q22.1), t(1;3)(p36.3;q21.2), t(2;11)(p21;q23), inv(3)(q21q26.2), t(6;9)(p23;q34), -7 or del(7q), -5 or del(5q), i(17q) or t(17p), -13 or del(13q), del(11q), del(12p) or t(12p), del(9q), idic(X)(q13) [28]. Classification is extended by pediatric MDS included in a separate category – refractory cytopenia of childhood (RCC). It is assumed that children with the amount of blasts in peripheral blood about 2-19% and in bone marrow 5-19% should be diagnosed according to the same criteria as adult patients. Clonal malignancies of lymphoid precursors include B- and T-cell lymphoblastic leukemia and lymphoma. They are often associated with recurring genetic abnormalities, but distinctive subgroups were only distinguished for B-cell malignancy [13,17,25,28].

Table 1. WHO classification of myeloid neoplasms and acute leukemia

AML with recurrent genetic abnormalities:
AML t(8;21)(q22;q22); *RUNX1-RUNX1T1*
AML inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
APL t(15;17)(q22;q12); *PML-RARA*
AML t(9;11)(p22;q23); *MLLT3-MLL*
AML t(6;9)(p23;q34); *DEK-NUP214*
AML inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
AML (megakaryoblastic) t(1;22)(p13;q13); *RBM15-MKL1*
Provisional entity: AML with mutated *NPM1*
Provisional entity: AML with mutated *CEBPA*
B lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities:
t(9;22)(q34;q11.2) *BCR-ABL1*
t(v;11q23) *MLL* rearrangement
t(12;21)(p13;q22) *TEL-AML1* (*ETV6-RUNX1*)
hyperdiploidy
hypodiploidy
t(5;14)(q31;q32) *IL3-IGH*
t(1;19)(q23;p13.3) *TCF3-PBX1*

Genes involved in the pathogenesis of leukemia

Analysis of pathways involved in leukemogenesis showed that mutations and rearrangements concern genes which may be divided on the basis of their general characteristics into two major groups: promoting unrestrained proliferation and advantage of hematopoietic progenitors over normal cells (class I mutations), differentiation block and resistance to apoptosis (class II mutations). Simultaneous occurrence of these two mutation classes is required to diagnose full-blown leukemia. The rule above-mentioned called the "two-hit model" is not applicable to leukemia associated with *MLL* gene rearrangements, which is seldom accompanied by other mutations [9,26].

Genetic disruptions may occur on several levels; among them, molecular abnormalities such as point mutations, amplifications, deletions, and cytogenetic abnormalities are worth mentioning. Karyotype changes include structural aberrations, caused mostly by double-strand DNA fractures, which fail to be fixed, subsequently creating chromosomal translocations, deletions, duplications, inversions, and numerical aberrations – changes in ploidy. Most often they appear in genes encoding components of key cellular pathways regulating lymphoid development and DNA repair, suppressor genes, apoptosis regulators and oncogenes [9,20]. Commonly they influence the whole cascade of signal transduction and successive changes in the particular cell. They are clonal events, which may concern pluripotent hematopoietic stem cells or progenitors at higher levels of differentiation. Primary genetic changes are usually chromosomal translocations. It is believed that some of the disruptions appear during fetal development, especially when it concerns infant leukemia with rearrangements of the *MLL* gene, ALL with translocation *ETV6-RUNX1* and AML with translocations affecting chromosomes 8 and 21. Specific, recurring rearrangements define particular subtypes of childhood leukemia [9,19,20,26].

ALL

Distinctive chromosomal translocations characterize separate ALL subtypes. Unfortunately, correlation between them and particular groups singled out in the FAB classification is scarce, except for L3 often being associated with t (8;14). Usually, translocations lead to activation of genes participating in the pathological process [4,10,12,14,18].

An illustrative example concerns aberrations in the T-cell receptor locus (TCR) in T-cell ALL and less common aberrations in the immunoglobulin receptor locus (BCR – B-cell receptor) in B-cell ALL. These alterations are formed during rearrangement of antigen receptor genes, which occurs during lymphocyte maturation as part of the diversification mechanism, when adjacent genes undergo ineligible recombination with TCR or BCR loci. The problem of expression deregulation concerning so-called partner genes participating in translocations, predominantly oncogenes, lies in placing them in the area of strong antigen promoter and enhancer control or eliminating negative regulators of expression [8,11,29]. Moreover, chromosomal aberrations may produce chimeric proteins formed by fusion of coding regions of two genes; at least one of them is a known transcription factor or signaling molecule. Another essential point is delineated by molecular abnormalities, which affect gene properties. In consequence, the undesirable changes in the cell's genetic material impact expression of multiple genes responsible for proper maturation of lymphoid B and T progenitors [2,20]. The problem also concerns factors engaged in the early stages of hematopoietic development such as *TAL1* generating TALL, *RUNX1*, *MLL* and *ETV6* corresponding to B-ALL. For later phases, *TCF3* and *PAX5* mutations initiating B-ALL and *NOTCH1* and *MYB* resulting in T-ALL should be mentioned. Mutual relations of individual components concerning protein-protein and protein-DNA interactions contribute to the defective course of the whole cascade of fundamentally integrated processes [2,11].

T-ALL

Structural rearrangements of chromosomes typical for T-ALL contribute to activation of oncogenes mainly by translocation in *TCR* loci. Regions especially vulnerable to aberration are 14q11 in the locus *TCRA/D* and 7q34 in *TCRB*. Regular thymopoiesis is supervised by a number of transcription factors, but their presence at fragile sites of chromosomes poses a serious threat of mechanism failure [5,10,29]. Among the most significant factors, NOTCH1 should be listed, responsible for self-renewal of hematopoietic stem cells and development of T cells. Its mutation alters at least five substantial pathways involving: *TAL1*, *LYL1*, *LMO1*, *LMO2*, *TLX1*, *TLX3*, *MYC*. The pathology is reflected in increased expression of oncogenes (e.g. *MYC*) and decreased expression of suppressor genes *p16/INK4A*, *p14/ARF* (*CDKN2A*), *TP53*, *RB*. Deregulation caused by rearrangement may also impact E proteins from class A of the bHLH (basic helix-loop-helix) family (TCF3, TCF12) and from class B (LYL1, TAL1, TAL2, bHLHB1), both DNA-binding. *TCF3* gene products take part in TCR recombination and accompany *TCF12* in negative control of proliferation and differentiation. Proteins from class B of the bHLH family are characterized by tissue-specific expression, which physiologically does not involve the thymus, but is identified as ectopic in T-ALL. In view of the ability to heterodimerize with class A proteins, they may disrupt their proper action during hematopoiesis. Changes in *TAL1* and *LYL1* are often connected with deregulation of LMO1/2 proteins. Rearrangements also involve homeobox genes class I (*HOXA-D*) and II (*TLX1*, *TLX3*). All the evidence suggests that *HOXA-D* loci 7p15, 17q21, 12q13, 2q31 are engaged in regular hematopoiesis as regulators of stem cell maintenance and line determination. Both lack of these factors and their overexpression have far-reaching consequences for T cell development. Homeobox genes class

II code for HOX protein cofactors and also may become a target for aberrations [2,5,8]. Recurring in T-ALL translocations, *PICALM-MLLT10* and *MLL* rearrangements are responsible for excessive activation of *HOX*. Region 11q23 of the *MLL* gene, which functions as a transcription regulator maintaining a constant expression profile, often succumbs to rearrangements and forms fusion genes. Besides the known translocation t(11;19) where the partner for *MLL* is the *MLLT1* gene, there are also other fusions with *MLLT10*, *MLLT4*, *AFF1*, and *FOXO4* [8].

Table 2. Chromosomal rearrangements in T-ALL

Abnormality	Gene
del(1)(p32)	SIL-TAL1
t(1;14)(p32;q11)	TAL1-TCRA/D
t(11;14)(p13;q11)	LMO2-TCRA/D
t(8;14)(q24;q11)	MYC-TCRA/D
inv(7)(p15q34)/ t(7;7)(p15;q34)	HOXA-TCRB
t(11;14)(p15;q11)	LMO1-TCRA/D
t(14;21)(q11;q22)	bHLH-TCRA
t(7;9)(q34;q32)	TAL2-TCRB
t(7;19)(q34;p13)	LYL1-TCRB
t(7;10)(q34;q24)	TCRB-TLX1
t(10;14)(q24;q11)	TLX1-TCRA/D
t(11;19)(q23;p13.3)	MLL-MLLT1 (ENL)
t(5;14)(q35;q32)	TLX3-BCL11B
t(5;7)(q35;q21)	TLX3-CDK6
t(5;14)(q35;q11)	TLX3-TCRA/D
t(10;11)(p12;q14)	PICALM-MLLT10
t(9;22)(q34;q11)	BCR-ABL1
episomal amplification of locus 9p34	NUP214-ABL1
t(9;12)(p24;p13)	ETV6-JAK2
t(1;7)(p34;q34)	LCK-TCRB
t(7;11)(q34;q24)	*TCRB*- unidentified gene
del(6)(q)	*6q16* unidentified gene
t(7;9)(q34;q34.3)	NOTCH1-TCRB

A substantial proportion of tests carried out on patients do not reveal karyotype defects. However, detailed analyses of these cases uncover cryptic abnormalities such as microdeletions resulting in loss of suppressor genes, e.g. 9p21, oncogene activation in the absence of chromosomal aberrations in the corresponding locus or translocations due to breakpoints in the *INK4/ARF* area and terminal fragments of chromosomes, e.g. t(5;14)(q35;q32). Overexpression of *TAL1*, *LYL1*, *LMO1/2*, *HOX*, and *TLX1* is also observed when none of the mentioned alterations is found. Mutations in components of the TCR pathway signaling cascade seem to be crucial for T-ALL pathogenesis – most frequently they include the *RAS* oncogene and *ABL1*. Their activation promotes survival and proliferation of the cells [5,8].

B-ALL

The most common pediatric B-lineage leukemia is B-cell precursor ALL (BCP-ALL). Prevailing chromosomal abnormalities affecting 50% of patients in this particular type of malignancy are: t(12;21)(p13;q22) representing *ETV6-RUNX1* fusion and high hyperdiploidy characterized by gains of whole chromosomes. The fact that truly deserves attention is that 20% of cases of hyperdiploid leukemia, predominantly with 4, 10, 17, 18 trisomies, are identified with FLT3 tyrosine kinase receptor gene mutation, and other mutations in *NRAS*, *KRAS*, and *PTPN11* [2,10,20]. Relatively seldom but well-known aberrations seem to be t(9;22)(q34;q11.1) *BCR-ABL1* and rearrangements of *MLL*, especially t(4;11)(q21;q23) *MLL-AFF1*. High incidence of mutations is detected in genes modulating proper lymphoid development, in particular development and maturation of B cells such as transcription factors PAX5, TCF3, EBF1, LEF1, the family of transcription factors IKAROS (*IKZF1*, *IKZF2*, *IKZF3*), the pre-B cell receptor gene (*VPREB1*), genes activating recombinase (*RAG1/2*), and B-cell linker (*BLNK*). They are altered by point mutations, deletions, amplifications and structural rearrangements, often at a submicroscopic level. Cases concerning deletions of genes listed above are assigned as *BCR-ABL1*-like leukemia due to convergence in expression profiles with classic t(9;22) despite its absence. Features that delineate this type of BCP-ALL are activating mutations in the JAK-STAT pathway connected with *CRLF2* overexpression, mediating signal transduction from cytokine receptors. *CRLF2* also translocates to the 14q32 locus of immunoglobulin heavy chain (*IGHα*), in a similar manner as genes from the *CEBP* or *ID* family and the cytokine receptor for erythropoietin (*EPOR*). Another noticed defect is intrachromosomal amplification of chromosome 21 (iAMP21), often related to *RUNX1* overexpression and coexistence of other vast rearrangements. Disruptions frequently concern genes controlling cell cycle progression headed by *CDKN2A*, although the mutation is more common for T-ALL [10,12,20,26].

Table 3. Chromosomal rearrangements in BCP-ALL

Aberration	Fusion gene
t(12;21)(p13;q22)	ETV6-RUNX1
t(9;22)(q34;q11)	BCR-ABL1
t(1;19)(q23;p13.3)	TCF3-PBX1
t(17;19)(q22;p13)	HLF-TCF3
t(4;11)(q21;q23)	MLL-AFF1
translocations of IGHα(14q32)	
t(X;14)(p22;q32)/ t(Y;14)(p11;q32)	P2RY8-CRLF2
t(14;19)(q32;q13)	IGHα-CEBPA
t(8;14)(q11;q32)	CEBPD-IGHα
t(14;14)(q11;q32)/ inv(14)(q11;q32)	CEBPE-IGHα
t(14;20)(q32;p13)	IGHα-CEBPB
t(14;19)(q32;q13)	IGHα-CEBPG
t(6;14)(p22;q32)	ID4-IGHα
t(14;19)(q32;q13)	IGHα-EPOR

AML

The majority of patients suffering from AML, especially in the pediatric group, are burdened by recurring chromosomal translocations resulting in protein fusion formation involving loci of transcription factors and coactivators. This collection includes core-binding factor (*CBF*), α-retinoic acid receptor (*RARA*), transcription factors from the HOX family and coactivators: CREB-binding protein (*CBP*), *p300*, *MOZ*, *TIF2*, and *MLL*. They ensure an appropriate course of hematopoiesis, yet lose their function by ineligible rearrangements and drive differentiation impairment [15]. Among them a crucial role is played by a group of *CBF* rearrangements – a gene coding for a heterodimeric transcription factor consisting of the subunits CBFB and RUNX1. They are prone to aberrations, the most common being t(8;21), inv(16) and t(12;21). Chimeric proteins may also be formed as a result of fusion between a transcription factor, which retains the ability to bind DNA, and a protein capable of interaction with the corepressor complex, thereupon ensuing transcription block, as in the case of *PML-RARA* fusion. In leukemogenesis the fusions are supported by mutations triggering excessive proliferation and hematopoietic progenitor survival, which concern surface receptors, receptor tyrosine kinases KIT and FLT3, and RAS [14,15,16,18,21].

Abnormal karyotype is a hallmark of an overwhelming proportion of childhood AML cases. Patients are usually burdened by more than a single alteration. It is observed that some recurring abnormalities correlate with age. AML which develops among children up to three years old is often related to 11q23 rearrangements, the frequency decreasing in older patients. Moreover, in this age group the following aberrations are seldom detected: +8, t(8;21), t(15;17), inv(16). Some of the abnormalities predominate in young children and infants, e.g. t(1;22)(p13;q13), t(7;12)(q36;p13). Among adolescents more common are t(8;21)(q22;q22) and inv(16) rearrangements. Several alterations generally do not affect pediatric patients, yet are common in adults, e.g. -5/del(5q). The highlighted changes in the genome also correlate with the age distribution of FAB categories: in early childhood M4, M5 and M7 appear to be frequent, while later M0-M3 are more common [7,18,19]. On the other hand, there is also leukemia diagnosed as normal at the cytogenetic level. Some of these cases are believed to harbor molecular alterations and cryptic chromosomal rearrangements in *FLT3*, *NPM1*, *CEBPA*, *MLL* (commonly as a partial tandem duplication), *NRAS*, *WT1*, and *RUNX1* [7,14,21,27].

CML

CML, which in the WHO classification is categorized as a subtype of myeloproliferative neoplasm (MPN), encompasses only 2% of childhood leukemia cases and occurs predominantly among patients over 15 years old. It is assumed that the disease has the same features and course as in adults. The cytogenetic basis of CML is chromosomal translocation t(9;22)(q34;q11). It forms during reciprocal shift of long arm fragments between chromosomes 9 and 22 [1,23]. The shortened chromosome 22 is named Philadelphia chromosome (Ph) and carries oncogenic tyrosine kinase BCR-ABL1, involved in a broad range of cellular interactions, mostly pertaining to primary tasks performed by normal proteins of translocated genes. Constitutive activation of kinase drives

Table 4. Chromosomal rearrangements in childhood AML

Abnormality	Gene	AML FAB
t(1;22)(p13;q13)	RBM15-MKL1	M7
t(15;17)(q22;q21)	PML-RARA	M3
inv(16)(p13q22)/ t(16;16)(p13;q22)	CBFB-MYH11	M4, 0, 1, 2, 5
t(16;21)(p11;q22)	FUS- ERG	all except M3
t(6;9)(p23;q34)	DEK-NUP214	M2, 4
t(6;17)(q23;q11.2)		M1, 5
t(7;12)(q36;p13)	ETV6- HLXB9	M0, 1
inv(8)(p11q13)	MOZ-TIF2	M4
t(8;16)(p11;p13)	MOZ-CBP	M4, 5
t(8;21)(q22;q22)	RUNX1-RUNX1T1	M2
abnormalities of 3q		
inv(3)(q21q26)/t(3;3)(q21;q26)	EVI1-RPN1	M7
t(3;21)		M7
***MLL* rearrangements(11q23)**		M4, 5
t(9;11)(p21;q23)	MLL-MLLT3	
t(10;11)(p13;q23)		
t(11;19)(q23;p13)	MLL-ELL	
t(9;11)(p22;q23)	MLLT3-MLL	M5
t(6;11)(q27;q23)	MLLT4-MLL	M4, 5
t(10;11)(p12;q23)	MLLT10-MLL	M4, 5
t(11;19)(q23;p13.3)	MLL-ENL	M4, 5
***NUP98* rearrangements (11p15)**		
t(2;11)(q35;p15)	PMX1-NUP98	
t(5;11)(q35;p15)	ANKRD28-NUP98	
t(5;11)(q35;p15.5)	NSD1-NUP98	M2, 4
t(6;11)(q24.1;p15.5)	NUP98-C6orf80	M7
t(7;11)(p15;p15)	HOXA11-NUP98	
inv(11)(p15q22)	NUP98-DDX10	
(11;17)(p15;p21)	NUP98-?	
t(11;12)(p15;q13)	NUP98-HOXC13	

unrestrained and excessive proliferation in comparison with original cells. Disrupted functioning also affects other processes – differentiation, survival, apoptosis, cell cycle, DNA repair, adhesion. It is caused by activation of multiple cellular signaling pathways by kinase such as RAS/MAPK, PI3K, and STAT. Clones display genetic instability resulting in acquisition of additional changes in the genome [1,23].

MDS

Another group of hematopoietic disorders is MDS, which are rare in children and correspond to less than 3% of hematologic malignancies in this age group. The majority of pediatric patients with diagnosed MDS are assigned to aggressive and poor prognosis FAB subtypes such as RAEB and RAEB-t [17]. The most common is JMML belonging to the MDS/MPN group according to the WHO classification. It is characterized by very similar features as CMML, which refers to adult patients in the FAB classification. In recent decades many mutations connected with JMML have been discovered in genes coding for the RAS protein family, protein tyrosine phosphatase (PTPN11) and neurofibromin 1 (NF1) – components of the RAS/MAPK pathway. Activation of signal transduction and hypersensitivity of myeloid precursor cells to granulocyte and monocyte colony stimulating factor (GM-CSF) lead to excessive proliferation. Cytogenetic analysis is a crucial component for diagnosis and disease differentiation, e.g. between MDS and AML with low blast count. Reported in MDS, chromosome 7 and 5 abnormalities and phenotypic effects caused by genes localized on their long arms prove that in MDS pathogenesis an essential role is played by hematopoietic growth factors and their receptors. Karyotype disruption may have a complex nature and involve more than one chromosome. A significant diagnostic point is to exclude *BCR-ABL1* fusion. The proliferative advantage of altered cells and genetic instability determine the ability of syndromes to progress to AML [17,19].

Conclusions

Research conducted for years on hematological malignancies has shown that the genetic background of leukemia is an essential factor determining initiation, promotion and progression of the disease. Analysis of genomic lesions provides better understanding of pathobiological processes leading to malignancy. For many leukemia categories well-known genetic alterations have become widely approved prognostic factors [16]. However, current regimens still appear unsatisfactory, as the effectiveness of medical care defined by 5-year event-free survival (EFS) ranges between 76 and 86% in ALL and 49 and 63% in AML [6,21]. There are still leukemia subtypes which do not succumb to standard treatment procedures. The comprehensive collection of data obtained in current testing procedures requires appropriate and reasonable interpretation. Investigation of broad correlations between genetic disruptions and their mutual cooperation at different stages in the course of disease is needed. It seems crucial to introduce acquired knowledge into clinical practice. Versatile analyses enable attempts to designate specific markers for separate subtypes of leukemia, which unambiguously state the prognosis. Aforementioned recurrent mutations and rearrangements may serve as a basis for classification revision, separation of distinctive disease units from main subtypes of leukemia and further patients' stratification. Novel criteria can improve treatment management and provide individually adjusted medication, optimized and reoriented for specific subgroups. Efforts focus on personalization and development of targeted therapy directed at the molecular level of the disease. This approach is expected to yield minimization of overall threats related to radical treatment, negative influence on normal cells and tissue, precise elimination of the disease source and selection of patients who will benefit from the particular scheme.

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