REVIEW Libri Oncol., Vol. 33 (2005), N^{o} 1-3, 79 – 83

SUCCESSFUL TREATMENT OF LEUKEMIAS IN CHILDREN

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Summary

Malignant diseases are the second leading cause of mortality in children, secondary only to traffic and other accidents. Leukemias are the most common malignancy in children. In the last decade, great advances have been made in the diagnosis and management of malignant diseases of childhood, with the highest achievements in the treatment of leukemia in children. Thus, the majority of children with leukemia can now be successfully treated. The principles of diagnosis and treatment of leukemias in children are presented.

KEY WORDS: *leukemia, children, treatment*

USPJEŠNO LIJEČENJE DJEČJIH LEUKEMIJA

Sažetak

Nakon nesretnih slučajeva i prometnih nesreća maligne bolesti su na drugom mjestu među uzrocima smrtnosti u djece. Od malignih bolesti u djece najčešće su leukemije.

Posljednjih desetak godina su dijagnostika i liječenje malignih bolesti u djece znatno napredovali. Najveći napredak postignut je u liječenju dječjih leukemija, tako da se većina djece s leukemijom danas može izliječiti. U radu se iznose načela dijagnostike i liječenja dječjih leukemija.

KLJUČNE RIJEČI: *leukemije, djeca, liječenje*

Leukemias are the most common malignancies of childhood, accounting for 25%-30% of all malignant diseases in children. According to the degree of cell differentiation, leukemias are classified into acute (AL) and chronic (CL) leukemias. In Europe and USA, acute lymphatic leukemia (ALL) accounts for more than 75%, acute myeloid leukemia (AML) for 20%, acute undifferentiated leukemia (AUL), acute mixed-lineage leukemia and acute biphenotypic leukemia for <0.5%, and chronic leukemias, primarily chronic myeloid leukemia (CML) of adult type and juvenile myelomonocytic leukemia (JMML) for some 3% of cases. Leukemia may occasionally occur at birth or soon thereafter; it is congenital leukemia which can be acute lymphatic or acute myeloid leukemia. Three to four new cases of acute leukemia *per* 100,000 children are detected *per* year. In the USA, 2500-3000 new cases of ALL and 500 cases of AML are diagnosed *per* year. The highest incidence of the disease onset is between age 2 and 5 years (1).

Acute leukemia is a syndrome of clonal malignant diseases of hematopoietic stem cells. If

left untreated, the disease has lethal outcome within a few months due to inadequate function of normal hematopoiesis. Leukemia is caused by genome disorder within a single hematopoietic stem cell. New cells with biological characteristics identical to the initial one are formed by this cell division. This clonal cell population predominates in growth, suppressing the normal one. When thus formed clonal cell population grows large enough, it causes clinically recognizable disease. A number of diagnostic procedures are currently available, first of all molecular biology tests, to detect and monitor the markers that characterize and confirm clonal expansion of malignant tumors of the hematopoietic system (2).

Ionizing radiation, chemicals (benzene in AML), drugs (use of alkylating agents alone or in combination with radiotherapy increases the risk of AML), and genetic predispositions listed below play a significant role in the development of leukemias:

(a) monozygotic twins – if leukemia develops in one of the twins during the first 5 years of life, the other is at a 20% risk to develop leukemia;
(b) in the siblings of leukemia patients, the prevalence of leukemia is fourfold that in the general population;
(c) chromosome aberrations (Table 1); and
(d) congenital agammaglobulinemia, Poland's syndrome, Schwaman-Diamond syndrome, ataxia-telangiectasia, Li-Fraumeni syndrome, neurofibromatosis, Diamond-Blackfan anemia, and Kostmann's disease are associated with an increased prevalence of leukemia.

As ALL and AML are very heterogeneous diseases, the grade of tumor cell malignancy should be determined as precisely as possible before therapy initiation in order to achieve the highest rate of favorable therapeutic outcome at highest efficacy and minimal side effects (early and late, frequently even life-threatening). Cyto-

Table 1.

RISK OF LEUKEMIA IN PATIENTS WITH CHROMOSOME ABERRATIONS

Group	Risk	Time interval (yrs)
Trisomy 21 (Down syndrome)	1 *per* 95	<10
Bloom syndrome	1 *per* 8	<30
Fanconi's anemia	1 *per* 12	<16

Table 2.

IMMUNOLOGIC CLASSIFICATION OF ACUTE LYMPHATIC LEUKEMIAS (ALL)

B-ALL (80%)	pro-B ALL
	common ALL
	pre-B ALL
	B-ALL
T-ALL (15%-20%)	undifferentiated T-ALL
	cortical T-ALL
	differentiated T-ALL

morphology, cytochemistry, immunophenotyping, cytogenetic and molecular genetic analyses of bone marrow biopsy are crucial in the diagnostic work-up, allowing for (along with some other assays such as cerebrospinal fluid analysis, etc.) patient categorization according to the risk level into the groups of standard, moderate and high risk. Each of these groups requires different, more or less invasive therapeutic protocol.

Acute leukemias are classified according to their morphological, cytochemical, immunologic, cytogenetic and molecular genetic characteristics. Morphological classification of ALL (FAB; French-American-British classification) divides ALL into three morphological types: L1 (85%), L2 (14%), and L3 (1%). AML are morphologically divided into eight types: M0 – M7. Cytochemistry is helpful in the subclassification of acute leukemias, e.g., PAS and Sudan black as nonenzymatic assays, and peroxidase, alkaline phosphatase, esterases, and acid phosphatase as enzymatic ones. ALL are generally PAS positive and less frequently acid phosphatase positive (usually immunologic T-ALL), and very rarely undifferentiated. Immunologic classification is presented in Table 2, and correlation of immunophenotyping, cytogenetic and molecular genetic findings in Table 3.

Most authors now agree that the major prognostic factors include: (a) age; (b) leukocyte count; (c) immunophenotype; (d) cytogenetic finding (Table 4); (e) DNA index; (f) organomegaly; (g) presence or absence of central nervous system (CNS) disease; (h) response to initial steroid therapy; and (i) blast percent in bone marrow on day 15 and 33 of therapy (3).

Current therapeutic protocols for acute leukemias consist of: (a) induction (remission induction; vincristine, pronisone or dexamethasone, L-asparaginase with or without anthracycline);

Table 3.

CORRELATION BETWEEN IMMUNOPHENOTYPE AND CYTOGENETIC FINDING IN ACUTE LYMPHATIC LEUKEMIA (ALL)

Immunophenotype	Rate	Cytogenetic finding	Molecular genetic finding
Pro-B-ALL	2%	t(4;11)	MLL-AF4
		t(11;19)	
Common ALL	3%-5%	t(9;22)	BCR-ABL
		t(12;21)	
		Hyperdiploidy	
Pre-B-ALL	5%-6%	t(1;19)	E2A-PBX1
B-ALL	1%-2%	t(8;14)	MYC-IGH
		t(8;22)	
		t(2;8)	
Undifferentiated T-ALL	1%	t(11;14)	TTG2-TCRD
		t(10;14)	
		t(8;14)	
		t(1;14)	
Cortical T-ALL		t(8;21)	
Differentiated T-ALL		t(15:17)	

Table 4.

PROGNOSTIC VALUE OF CYTOGENETIC ABNORMALITIES IN ACUTE LYMPHATIC LEUKEMIA (ALL)

Chromosome aberration	5-year relapse free survival (EFS)
Hyperdiploidy	
>50 chromosomes	80% (65%-90%)
47-50 chromosomes	90% (50%-98%)
triploidy, 66-73 chromosomes	unknown, probably good
tetraploidy, 82-94 chromosomes	unknown, probably <60%
(mostly T-ALL; L2 morphology; expression of one or more myeloid antigens)	
Normal diploidy, 46 chromosomes	80% (65%-90%)
Hypodiploidy, <46 chromosomes	71% (55%-85%)
Pseudodiploidy	73% (55%-85%)
t(1;19)	53%
t(4;11)	45%
t(9;22)	14%

(b) prophylaxis for CNS leukemia; intrathecal administration of methotrexate with or without cytosine arabinoside, and hydrocortisone with medium (2 g/m^2) or high (5 g/m^2) doses of methotrexate; along with prophylactic CNS radiotherapy (1200 Gy) in T-ALL, high-risk ALL (HR-ALL) and AML; (c) second induction for additional remission reinforcement (attempting to destroy residual leukemia cells); and (d) remission maintenance therapy (for continuous suppression of leukemia cell growth, further leukemia volume reduction, while trying to prevent the resistant clone of leukemia cells to form). The treatment takes 24 to 36 months, depending on the treatment protocol (in male children usually 36 months because of the higher risk of the disease relapse) (4).

In HR-ALL patients: t(9;22) (BCR/ABL), t(4;11) (MLL/AF4), if remission is not achieved on day 33 of therapy; poor response to pronisone); after one month of induction therapy, blocks of high-dose cytostatics (dexamethasone 20 mg/m^2/day, vincristine 1.5 mg/m^2 or vindesine 3 mg/m^2, daunorubicin 30 mg/m^2, cytosine arabinoside 2 g/m^2, methotrexate 5 g/m^2, cyclophosphamide 200 mg/m^2 or ifosfamide 800 mg/m^2, L-asparaginase 25,000 IU/m^2, intrathecally methotrexate, cytosine arabinoside, hydrocortisone) are administered. This therapy is followed by allogeneic transplantation of peripheral stem cells; however, in the lack of compatible donor another induction with prophylactic CNS radiotherapy is administered, with remission maintenance therapy (Purinethol, methotrexate) for another year.

In HR-AML, remission induction and stabilization are followed by allogeneic transplantation of peripheral stem cells; if there is no compatible donor, intensive cytostatic therapy is continued with prophylactic CNS radiotherapy and remission maintenance therapy for another year (thioguanine with periodical, monthly reinduction with cytosine arabinoside) (5).

Nowadays, first remission is achieved in 99% of ALL and 95% of AML cases. Cure is recorded in 85%, 75% and 55% of ALL patients, and 55%, 65% and 40% of AML patients at standard, moderate and high risk, respectively (6).

B-ACUTE LYMPHATIC LEUKEMIA

Mature B type ALL is extremely rare (1%-2% of all ALL cases). Morphologically, it is usually L3 form, while cytogenetically the following translocations are detected: t(8;14), t(8;22), t(2;8). Until recently, the prognosis was extremely poor; however, it has improved over the past few years to approach the prognosis in other high-risk ALL

types. The treatment is identical to that for Burkitt's lymphoma.

T-ACUTE LYMPHATIC LEUKEMIA

T-type ALL accounts for 15%-20% of acute leukemias in children. The history is generally rather short-term, with initial symptoms occurring 10-15 days prior to diagnosis. The disease usually occurs in older children (8-16 years), with a male predominance, and is associated with pronounced hepatosplenomegaly, frequently presence of a tumor mass in the anterior mediastinum, an increased risk of CNS diseases (at the time of diagnosis or in relapse), and testicular diseases. Leukocyte count is significantly elevated; hemoglobin frequently exceeds 10 g/dL. Morphologically, it is usually of L2 type, positive for acid phosphatase, immunologically T type (undifferentiated, cortical or differentiated), translocations t(11;14), t(10;14), t(8;14), t(1;14), t(8;21), t(15;17); molecular genetic alterations: MYC-IGH, TTG2-TCRD. These patients can achieve first remission, however, with a high rate of systemic and extramedullary relapses. The prognosis is poor, yet therapeutic results have considerably improved over the past few years with the use of aggressive chemotherapy and radiotherapy (7).

INFANT LEUKEMIA

Infant ALL (2%-3% of ALL in children) is a biologically specific entity that differs significantly from ALL in older children. The blasts show fetal characteristics; myeloid antigens are frequently present, and there is a relatively high resistance to cytostatics. Immunophenotypically, early pre-B CALLA (CD10) negative type is most common; a prognostically unfavorable translocation t(4;11)(q21;q23) is usually detected, with MLL-AF4 genetic alteration. The prognosis is poor in children younger than 12 months, and extremely poor in those younger than 6 months. These patients show a high incidence of unfavorable prognostic factors such as increased leukocyte count, massive organomegaly, CNS leukemia, failure of complete remission at 14 days of therapy (slow remission induction); almost all patients exhibit remission induction, however, there is a high incidence of systemic and extramedullary relapses. Infants with ALL require very intensive therapy. Most centers consider that the achievement of remission should be followed by allogeneic transplantation of peripheral stem cells. Long-term survival free from signs of disease (EFS) is about 40% (8).

CONGENITAL LEUKEMIA

Leukemia diagnosed between the birth and sixth week of life is termed congenital leukemia. It is a very rare disease of as yet unknown etiology. Congenital leukemia is usually associated with trisomy 21, Turner syndrome, mosaic trisomy 9, and mosaic monosomy 7. Several examples of congenital juvenile myelomonocytic leukemia have been reported. The main characteristics of its clinical picture include subcutaneous leukemic nodules (leukemia cutis), hepatosplenomegaly, lethargy, pallor, purpura (petechiae), and respiratory distress. It usually occurs as a monocytic subtype of AML, and occasionally as ALL (pre-B immunophenotype). In case of congenital leukemia in Down syndrome or congenital leukemia with normal karyotype, therapy should be delayed as long as possible because spontaneous remission may occasionally occur. If exacerbation of the disease has been observed, chemotherapy should be administered. Chemotherapy should also be used in case of congenital leukemia with chromosome aberrations in tumor cells because this type shows rapid progression and is associated with extremely poor prognosis.

CHRONIC MYELOID LEUKEMIA

CML is a rare disease of childhood. Less than 3% of 100 children with leukemia develop chronic leukemia, which is nearly always of myeloid type. In children, CML occurs in two types: juvenile type or adult type, which is more common and similar to CML in adults. The adult type of CML has 3 stages: chronic stage, acceleration stage, and blast crisis. In adult type CML, best therapeutic results are achieved by peripheral stem cell transplantation. Initially, hydroxyurea is administered in an attempt to achieve

hematologic remission; if a compatible donor is not found within 6 months, interferon is introduced in therapy, with somewhat better results. In chronic stage of CML, imatinib mesylate (Glivec, ST1571; ABL tyrosine kinase inhibitor) is currently used for cytoreduction, producing best results; however, when stable remission has been achieved, peripheral stem cell transplantation is required. Protocols for AML in combination with peripheral stem cell transplantation are used in children with juvenile type CML, however, with rather modest results (9).

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