Chapter 2

Acute Lymphoblastic Leukemia in Children

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Additional information is available at the end of the chapter

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1. Introduction

Extraordinary advances in the treatment outcome of childhood acute lymphoblastic leukemia (ALL) rank as one of the most successful stories in the history of oncology, with the current rate of approximately 80% of children being cured [1-5]. The improvements made have been mainly due to the development of intensive multiagent chemotherapy, identification of clinical and biologic variables predictive for outcome and their use in stratifying treatment, significant advances in supportive care, and development of large-scale, highly disciplined multi-institutional national and international clinical trials [6,7]. In spite of this success, there remains place for improvement, including the development of better treatment for the minority of patients who relapse, the development of less toxic therapy, and focusing attention on screening and management of late effects that may potentially arise as a result of antileukemic treatment [8,9].

2. Epidemiology

ALL is the most common childhood malignancy, accounting for close to 25% of all cancers in children and 72% of all cases of pediatric leukemia [10,11]. ALL occurs at an annual rate of 3 to 4 cases per 100.000 children less than 15 years of age [12]. Approximately 3,000 children in the United States and 5,000 children in Europe are diagnosed with ALL each year [13]. A sharp peak in incidence is observed among children aged 2 to 5 years. Males are affected more often than females except in infants, the difference being greater among pubertal children. There is a geographic variation in the frequency of ALL. The incidence is lowest in North Africa and the Middle East, and highest in the industrialized Western countries, suggesting that this may reflect more exposure to environmental leukemogens [6]. Numerous investigators have reported the occurrence of leukemic clusters in different geographic areas, thus pointing

towards infectious and/or environmental causes of at least some cases of ALL [14-17]. Several studies have suggested a link between maternal reproductive history and the risk of ALL. Fetal loss is associated with a higher risk for ALL in subsequent children [18]. There is evidence that increased in utero growth rates and Insulin Growth Factor (IGF) pathways play a role in the development of ALL [19,20].

3. Pathogenesis

ALL represents the malignant proliferation of lymphoid cells blocked at early stages of differentiation. Although a variety of hypotheses regarding potential pathogenic mechanisms in the development of pediatric ALL have been described, the etiology for the overwhelming majority of children with ALL remains unclear. The favored concept is that leukemogenesis reflects a complex interaction between multiple genetic and environmental factors [21].

Genetic factors play a significant role in the etiology of ALL. Molecular techniques have documented the presence of the same leukemia-specific genetic abnormalities in neonatal blood Guthrie spots and stored cord blood as in diagnostic samples from children with ALL [22]. This is evidence that important initiating events that contribute to leukemogenesis may begin *in utero* [23,24]. Consistent with Knudson's two-hit hypothesis [25], postnatal oncogenic mutations may subsequently lead to clinically detectable leukemia [26]. Recent genome-wide association studies have identified germline single nucleotide polymorphisms that predispose subjects to development of ALL. The affected genes include *ARID5B* and *IKZF*, which are involved in B-cell transcriptional regulation and differentiation [27,28].

The occurrence of familial leukemia has been reported, including aggregates within the same generation or in several generations. Siblings of children with ALL have two- to four-fold greater risk of developing the disease than unrelated children [29]. There is a higher risk for ALL in identical twins. The overall concordance rate of ALL in monozygotic twins is estimated to be as high as 25%, and is thought to be the result of shared *in utero* circulation [30]. Leukemias with the (4,11) translocation and the *MLL-AF4* fusion gene have a very high concordance rate and a brief latency, while others may present with disease after a long latency period [31]. The risk for ALL among both mono- and dizygotic twins is highest in infancy, diminishes with age, and after the age of 7 years the risk to the unaffected twin approaches that for general population [30].

Several constitutional chromosomal abnormalities and specific inherited syndromes have been linked to childhood ALL. Children with Down syndrome (DS) are 10 to 20 times more likely to develop ALL and acute myeloid leukemia (AML) than non-DS children [32]. ALL predominates in all but the neonatal age group, but the high incidence of AML (megakaryocytic) in patients with DS under age 5 causes the overall ratio of ALL: AML to be close to 1:1 [33,34]. Higher risk of ALL is documented in children with Beckwith-Wiedeman syndrome, neurofibromatosis and Schwachman's syndrome. Other underlying disorders may be chromosomal-breakage syndromes such as ataxia-teleangiectasia, Bloom's syndrome, Fanconi anemia, and Nijmegen breakage syndrome [21].

In addition to genetic influences, environmental factors including irradiation and certain chemicals, viral infection and immunodeficiency may also play a role.

Exposure to ionizing radiation is linked to leukemia. The high incidence of leukemia is documented in survivors of the atomic bomb explosions in Japan during World War II, ALL being more frequent in children and AML in adults [35]. There is an increased risk of leukemia in children exposed to diagnostic irradiation *in utero*, particularly during the first trimester [36]. The risk for developing leukemia from postnatal exposure to diagnostic radiography is difficult to determine [37]. One study suggested 0.8% increased risk of leukemia in pediatric orthopedic patients who required repeated diagnostic radiographs [38]. Therapeutic irradiation has been implicated as well. An increased ALL incidence is observed in neonates administered irradiation to treat thymic enlargement and children who received scalp irradiation for treatment of tinea capitis [6]. Conflicting results exist about the risk from exposure to electromagnetic fields [39,40] and routine emissions from nuclear power plants [41,42].

With the exception of chronic postnatal exposure to household paints and paint solvents [43], the role of other toxic chemicals in the development of childhood ALL is controversial. There is strong evidence that chemotherapy, including alkylating agents and epipodophyllotoxins, has leukemogenic potential, mostly causing secondary AML [44]. Other factors that may potentially be involved in the development of childhood ALL include parental chemical exposure. Maternal exposures to DNA-damaging agent dipyrone and baygon, indoor insecticides, and pesticides in the garden have been linked to ALL [45]. The risk appears to be enhanced by the presence of *CYP-1A1m1* and *CYP-1A1m2* polymorphisms [46]. Paternal exposures to pesticides and fungicides, alcohol consumption, and smoking history have been associated with ALL in offspring [47,48].

The role of viral infection in the pathogenesis of childhood leukemia has been studied extensively. The interest has been due mainly to the overlapping age patterns of childhood infection and peak incident ALL, documented viral etiology for some animal and human cancers, and the seasonal variation in ALL incidence rates. Various associations have been described between ALL and influenza, chicken pox, measles and mumps, happening either to the mother during the pregnancy or to the index child [6]. The only common feature of these studies is the lack of consistency. A possible inverse association with hepatitis A virus, as a measure of general hygiene, has been shown [49]. Epstein-Barr virus (EBV) has been associated with B-cell leukemia and endemic Burkitt lymphoma [50,51]. Since both EBV-positive and EBV-negative B-cell leukemia/lymphoma have comparable gene rearrangements and postulated oncogenic mechanisms, it is doubtful that EBV is causative.

Children with various primary immunodeficiencies, including severe combined immunodeficiency, X-linked agammaglobulinemia, and Wiskott-Aldrich syndrome, as well as those receiving chronic treatment with immunosuppressive drugs, have an increased risk of developing lymphoid malignancies predominantly lymphomas. ALL may occur but is uncommon [6]. The development of malignancy in immunocompromised patients frequently correlates with infection, whether it is de novo, reactivated, or chronic.

4. Classification

It has long been recognized that ALL is a biologically heterogeneous disease. The classification depends on characterizing leukemic lymphoblasts to determine the morphology, immunophenotype, and cytogenetic and molecular genetic features. Morphology alone usually is adequate to establish a diagnosis but the other studies have a major influence on the choice of optimal therapy and the prognosis.

4.1. Morphologic classification

A number of classification systems have been proposed to classify lymphoblasts morphologically. Generally accepted is the system proposed by the European French-American-British (FAB) Cooperative Working Group in 1976 [52]. The FAB system defines three categories of lymphoblasts (Figure 1). L1 blasts are typically smaller with scant cytoplasm and inconspicuous nucleoli. L2 blasts are pleomorphic larger cells with more abundant cytoplasm and prominent nucleoli. Lymphoblasts of L3 type, notable for deeply basophilic cytoplasm and cytoplasmic vacuolization, are morphologically identical to Burkitt's lymphoma cells containing *myc* translocations [53]. Approximately 85% of children with ALL have predominant L1 morphology, 14% have L2, and 1% has L3.

With the exception of L3 subtype, these distinctions hold little practical value [54]. The recent World Health Organization (WHO) International panel on ALL recommended that the FAB classification be abandoned and advocated the use of the immunophenotypic classification mentioned below [55]. The 2001 WHO scheme subdivided cases into precursor B-cell, precursor T-cell, and mature B-cell ALL (Table 1). The WHO classification was updated in 2008, and has become worldwide accepted as based on the recognition of distinct diseases using a multidisciplinary approach. It incorporates morphologic, biologic, and genetic information into a working nomenclature that has clinical relevance [56].

4.2. Immunological classification

The development of monoclonal antibodies targeted to specific cell surface and cytoplasmatic antigens has revolutionized biological classification of ALL. It has been recognized that ALL subtypes correspond to distinct stage of lymphocyte maturation, but leukemia cells often demonstrate aberrant antigen expression. Hence, a panel of antibodies is needed to establish the diagnosis and to distinguish among the different immunologic subclasses of blasts [57]. Typical patterns are: CD19/CD22/CD79a (B-lineage), CD7/cytoplasmatic CD3 (T-lineage), and CD13/CD33/CD65/MPO (myeloid) [58]. B-lineage ALL accounts for 80% of childhood ALL. CD10 is commonly expressed on the cell surface, and this leukemic subset is referred to as *CALLA*$^+$ or common ALL. B-cell leukemias can be further subclassified as early pre-B, pre-B, transitional pre-B and mature B. Mature B-cell ALL, which accounts for only 1-3% of pediatric ALL is regarded as being synonymous with L3 morphological FAB type, and should be differentiated from other B-lineage ALL. T-lineage ALL cases can be classified according to the stages of normal thymocyte development that they resemble (early, mid-, or late thymocyte), or in some studies as pro-T, pre-T, cortical T or mature T [59,60]. The only distinctions

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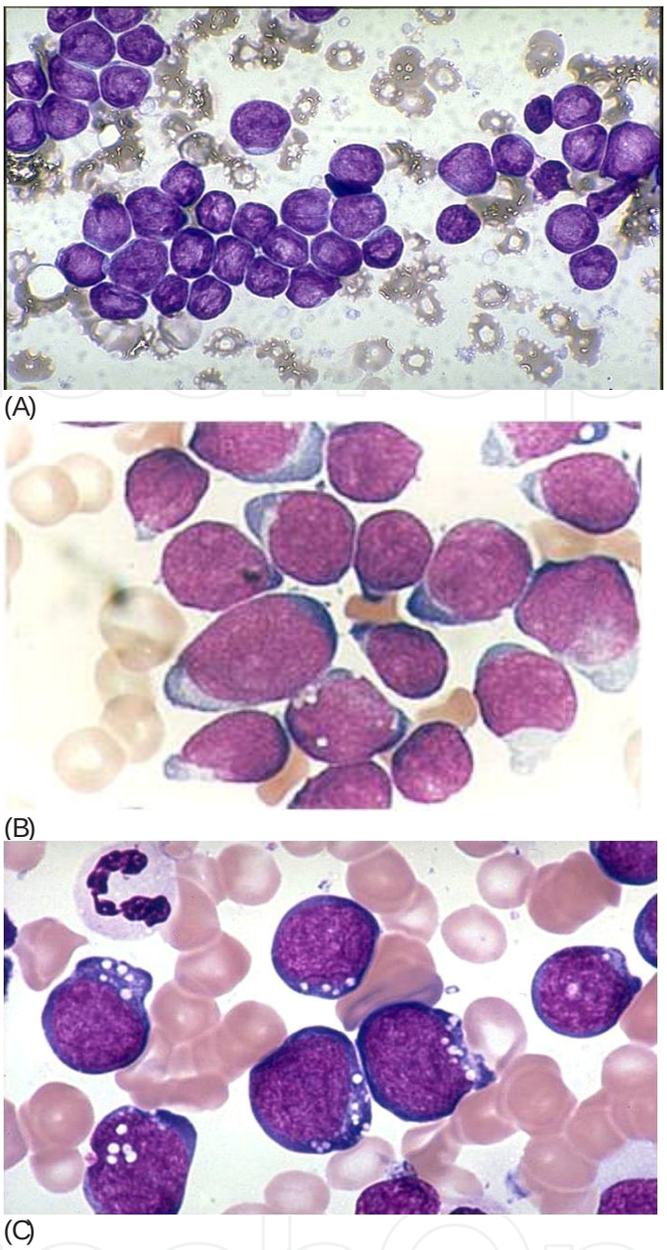

Figure 1. FAB (French American and British) morphological classification of lymphoblasts. (A) L1 lymphoblasts. (B) L2 lymphoblasts. (C) L3 lymphoblasts.

of therapeutic importance are those between T-cell, mature B, and other B-lineage (B-cell precursor) immunophenotypes [21]. The co-expression of myeloid antigens may occur on otherwise typical lymphoblasts in 5% to 30% of childhood ALL (My+ ALL). Although once thought to have an adverse prognosis, the presence of some myeloid-associated antigens in cells that predominantly mark as lymphoblasts has no prognostic significance [61,62]. By contrast, mixed-lineage leukemias represent a heterogeneous category of poorly differentiated acute leukemias that possess characteristics of both lymphoid and myeloid precursor cells. In biphenotypic leukemia a single dominant populations of blasts simultaneously coexpress both lymphoid and myeloid antigens [63]. Bilineal or biclonal leukemia is acute leukemia with two

WHO classification
Precursor B-cell ALL/LBL
Cytogenetic subgroups
t(9;22)(q34,q11),BCR/ABL
t(v;11q23);MLL rearranged
t(1;19)(q23;p13),PBX1/E2A
t(12;21)(p13;q22);TEL/AML1
Hypodiploid
Hyperdiploid, >50
Precursor T-cell ALL/LBL
Mature B-cell leukemia/lymphoma
ALL= acute lymphoblastic leukemia;
LBL= lymphoblastic lymphoma;
MLL= mixed lineage leukemia

Table 1. World Health Organization classification of acute lymphoblastic leukemia

distinct population of blasts in a single patient [64]. „Lineage switch" is the term used to describe a conversion from one phenotype at diagnosis to a different phenotype during therapy or at relapse. Mixed-lineage leukemias (biphenotypic, bilineal, and lineage switch) represent only 3% to 5% of acute leukemias occurring in patients of all ages [6,65].

4.3. Genetic classification

The role of cytogenetics in determining the biologic basis of ALL has been widely recognized. With the refinement of classic cytogenetic techniques, development of additional approaches including polymerase chain reaction (PCR) and fluorescence in situ hybridization (FISH), and merging with the molecular genetic techniques of spectral karyotyping (SKY) and comparative genomic hybridization (CGH), alterations are detected in the leukemic cells of virtually all pediatric ALL cases [66]. Cytogenetic abnormalities are important aspects of diagnosis, risk assessment, treatment and prognosis in childhood ALL. Approximately 70 percent of pediatric patients can be readily classified into therapeutically relevant subgroups based on cytogenetic and molecular genetic changes [21]. Children with hyperdiploidy (> 50 chromosomes) and the concurrent trisomies of chromosomes 4, 10, and 17 ("triple trisomies") have a favorable prognosis with a 5-year event-free survival (EFS) rate of 90% [67,68]. The presence of translocation t(12;21) is also associated with a superior EFS rate. It results in *RUNX1-ETO* fusion, formerly known as *TEL/AML1* based on the older names of the same genes fused by the breakpoint [69,70]. Hyperdiploidy accounts for one-third of newly diagnosed B-precursor ALL cases, and *TEL-AML1* for additional 25%. By contrast, hypodiploidy (< 45 chromosomes) and Philadelphia chromosome-positive (Ph+) ALL are associated with poor prognosis, with overall EFS rates generally < 50%. Hypodiploid karyotype occurs in 6% to 9% cases of pediatric ALL. The worst outcome is observed in children with near-haploid ALL (23 – 29 chromosomes), with reported EFS rates of 25% [6,21,71]. Philadelphia chromosome is a small marker chro-

mosome present in 3% to 5% of pediatric ALL. Initially described as truncated chromosome 22, it was discovered as the result of a reciprocal translocation between c-ABL oncogene sequences on chromosome 9 and "breakpoint cluster region" (BCR) gene on chromosome 22, t(9;22)(q34;q11), resulting in the oncogenic *BCR-ABL* gene fusion [72]. Children with Ph+ ALL tend to be older, have higher initial leukocyte counts, higher frequency of central nervous system (CNS) leukemia, and respond poorly to conventional (non-tyrosine kinase inhibitor inclusive) therapy [6]. Abnormalities of the *MLL* (mixed lineage leukemia) gene at 11q23, which are seen in 5% to 10% of pediatric ALL and in up to 70% of infant leukemia, are another unfavorable cytogenetic subgroup. *MLL* rearrangements involve more than 30 different reciprocal translocations, with t(4;11)(q21;q23)(*MLL-AF4*) being the most frequent [73].

In the last decade, the application of new genome-wide screening techniques have led to the discovery of many new genetic abnormalities in childhood ALL. The exact role of these abnormalities in leukemogenesis, association with chemotherapy sensitivity or resistance and with clinical response to therapy, as well as their role as potential therapeutic targets is yet to be elucidated, but holds the promise of improving personalized therapy for every child with ALL.

5. Clinical presentation

Children with ALL often present with signs and symptoms that reflect bone marrow infiltration with leukemic blasts and the extent of extramedullary disease spread. The duration of symptoms may vary from days to months, frequently accumulating in a matter of days or weeks, and culminating in some event that brings the child to medical attention. Most of children have 3- to 4- week history of presenting symptoms. The initial presentation includes manifestations of the underlying anemia – pallor, fatigue, exercise intolerance, tachycardia, dyspnea, and sometimes congestive heart failure; thrombocytopenia – petechiae, purpura, easy bruising, bleeding from mucous membranes; neutropenia – fever whether low- or high-grade, infection, ulcerations of buccal mucosa. Anorexia is common, but significant weight loss is infrequent. Bone pain is present in one-third of patients, particularly affects long bones, and may lead to a limp or refusal to walk in young children. Bone pain reflects leukemic involvement of the periosteum, bone infarction, or expansion of marrow cavity by lymphoblasts. Joint pain and joint swelling are rarely seen [74].

Physical examination may show enlarged lymph nodes, liver and spleen. It is a common misperception that a significant lymphadenopathy and hepatosplenomegaly are hallmarks of childhood ALL. In rare cases, predominantly in patients with T-cell ALL, respiratory distress or signs of superior vena cava syndrome due to enlargement of mediastinal lymph nodes may be presenting symptoms. CNS involvement occurs in less than 5% of children with ALL at initial diagnosis. It usually presents with signs and symptoms of raised intracranial pressure (headache, vomiting, papilledema) and parenchimal involvement (seizures, cranial nerve palsies). Other rare sites of extramedullary invasion include heart, lungs, kidneys, testicles, ovaries, skin, eye or gastrointestinal tract [6,21]. Such involvement usually occurs in refractory or relapsed patients.

6. Laboratory findings

The first clue to a diagnosis of ALL is typically an abnormal result on a complete blood count. An elevated white blood cell (WBC) count (> 10.000/mm^3) occurs in approximately half of the children, with 20% showing the initial WBC greater than 50.000/mm^3. In other half of children with ALL number of WBC can be normal or low. Peripheral blood smears show blasts in most cases. In children with leukopenia, very few to none blasts are detected. Neutropenia is a common finding and is associated with an increased risk of infection. Approximately 80% of children present with anemia (hemoglobin < 10g/dL), which is usually normochromic and normocytic with low number of reticulocytes. Thrombocytopenia (platelet count < 100.000/mm^3) occurs in 75% of children at diagnosis. Spontaneous bleeding appears in patients with less than 20.000-30.000 platelets/mm^3, but severe hemorrhage is rare, provided that fever and infection are absent [6]. Rarely, transient pancytopenia may be the prodrome to childhood ALL.

To definitively establish the diagnosis of ALL, a bone marrow aspirate is generally necessary. Leukemia should be suspected in children whose marrows contain more than 5% blasts, but a minimum of 25% blast cells is required by the standard criteria before the diagnosis is confirmed [6]. More recently proposed classification systems have lowered the blast cell percentage to 20% for many leukemia types, and do not require any minimum blast cells when certain morphologic and cytogenetic features are present [53]. Usually the marrow is hypercellular and characterized by a homogeneous population of leukemic cells. A bone marrow aspirate may be difficult to obtain at the time of diagnosis. This is caused by the density of blasts in the marrow, but may be due to marrow fibrosis, infarction or necrosis. In such cases, bone marrow biopsy is required. Touch-preparation cytologic examination of the biopsy specimen can be helpful when aspiration is not successful [21].

A variety of other abnormal laboratory findings are frequently seen in children with ALL at diagnosis. Elevated serum uric acid levels reflect a high leukemic cells burden and the resultant increased breakdown of nucleic acids. Most patients have an elevated lactic dehydrogenase (LDH) level due to rapid cell turnover. The serum potassium level may be high in children with massive cell lysis, often together with hyperuricemia. Hypercalcemia may result from marked bone leukemic infiltration or from the production of an abnormal parathormone-like substance. Serum hypocalcemia may be secondary to hyperphosphatemia, and calcium binding phosphate released by lymphoblasts. Abnormal renal function from uric acid nephropathy and renal leukemic infiltration may be present. Liver dysfunction due to leukemic infiltration is usually mild regardless to the degree of hepatomegaly. Coagulation abnormalities may be seen but are usually not a feature of the disease, apart from a minority of patients presenting with disseminated intravascular coagulation [6].

Initial CNS involvement is found in fewer than 5% of children with ALL. CNS leukemia is most often detected in an asymptomatic child with cytologic examination of cerebrospinal fluid (CSF) after cytocentrifugation, revealing pleocytosis and the presence of blasts. Based on CSF findings, CNS involvement in ALL is defined as follows: CNS-1 status describes a patient with <5 WBC/mm^3 and without detectable blasts in the diagnostic CSF, CNS-2 status is defined as <5 WBC/mm^3 and the presence of blasts, and CNS-3 status includes patients with ≥5 WBC/

mm^3 and blasts on CSF or cranial nerve involvement or presence of cerebral mass [6,75]. Traumatic lumbar puncture (TLP) is defined as CSF with >10 red blood cells (RBC)/mm^3, with or without blasts (TLP+ or TLP-) [76]. In case of TLP+, the following formula can be helpful in defining the presence of CNS leukemia:

$$\frac{\text{CSF WBC}}{\text{CSF RBC}} > \frac{\text{Blood WBC}}{\text{Blood RBC}}$$

In symptomatic children, intracranial pressure is usually increased, and proteinorrhachia and hypoglycorrhachia are common [6,77].

7. Prognostic factors and risk classification

The identification of clinical and biologic features with prognostic value has become essential in the design of modern clinical trials. It is common practice to assign patients into different risk groups on the basis of prognostic factors, and to tailor treatment accordingly to the predicted likelihood of relapse. However, there is disagreement between large cooperative groups over the risk criteria and the terminology of defining prognostic subgroups.

Usually, childhood ALL cases are divided into standard-, intermediate- and high-risk group. Factors most often included into risk stratification are: age at diagnosis, initial WBC count, sex, race, the presence of extramedulary disease, blast immunophenotype and cytogenetics, early response to induction therapy, and minimal residual disease (MRD) [78,79].

Age at diagnosis and initial WBC count are the two features universally accepted as prognostic factors [12]. Children under 1 year and greater than 10 years of age (6 years in BFM study) have a inferior prognosis compared with children in the intermediate age group. Infants with ALL who are younger than 1 year at diagnosis have the worst prognosis [6]. There is a linear relation between initial WBC count and outcome in children with ALL; those with WBC greater than 50.000/mm^3 are recognized as having poorer prognosis [62]. Certain biologic features, e.g. T-cell ALL and infants with t(4;11), are associated with higher initial WBC counts. In most studies, girls have better prognosis than boys. This is partly due to the risk of testicular relapse, the higher incidence of T-immunophenotype and unfavourable DNA index in boys, but other genetic and endocrine effects may be present [80]. The effect of race on prognosis has been controversial, but some recent studies still report that American black children have slightly poorer outcomes when compared with white children. Asian children with ALL fare slightly better than white children [81]. The prognostic significance of cytogenetic factors and immunophenotype is discussed previously in the "Classification" section. Although early pre-B-cell ALL has better prognosis and mature T-cell ALL has a worse survival, immunophenotype is not an independent prognostic factor in the analyses of current trials [6]. Clinical features indicating the extent of extramedullary disease, i.e. the degree of hepatosplenomegaly and lymphadenopathy, presence of a mediastinal mass, and CNS disease at diagnosis, once emerged as useful prognostic indicators, disappeared as the treatment improved.

The rapidity of response to initial therapy is one of the most important prognostic indicators. BFM protocol uses the response in the peripheral blood to one week of systemic prednisone

[78,82]. Others use the response in the bone marrow after one or two weeks of induction therapy. Rapid early responders have the best EFS. Residual leukemia demonstrable in bone marrow on day 14 of induction is an independent predictor of inferior outcome. Children who do not achieve a complete remission (defined as <5% blasts in the bone marrow of normal cellularity and the absence of other evidence of leukemia) within the usual 4- to 6- week induction period have highest rate of relapse and shortened survival [6]. In recent years, measurement of MRD is incorporated in many trials. Numerous techniques have been developed to detect and quantify small amount of residual leukemic cells, with flow cytometry being the most accessible (Fluorescence activated cell sorter „FACS" analysis) [83]. The definition of remission status is also being re-examined in ongoing clinical trials. MRD levels that are undetectable or less than 10^{-4} at the end of induction therapy (or preferably earlier) are associated with the best prognosis. Conversely, day 29 induction MRD values of greater than 0.01% have a higher risk of relapse [84-86]. In the near future, gene expression profile analysis could better define distinctive genetic subclasses in childhood ALL and identify genes which may be responsible for leukemogenesis, thus leading to new targeted therapy strategies [87,88].

8. Differential diagnosis

The child with ALL typically presents with nonspecific symptoms. Thus, ALL may mimic a variety of nonmalignant and other malignant conditions. The acute onset of bleeding tendency may suggest immune thrombocytopenia. The latter disorder typically presents in an otherwise well child with a history of a preceding viral infection, and normal hemoglobin value, WBC count, and differential. Failure of other single cell lines, as seen in transient erythroblastopenia of childhood and congenital or acquired neutropenia, may lead to a suspicion of leukemia. ALL and congenital or acquired aplastic anemia may present with pancytopenia. The results of bone marrow aspiration and/or biopsy usually distinguish these two diseases. Pediatricians must also consider ALL in the differential diagnosis of patients presenting with hypereosinophilia which, in rare cases, has preceded the diagnosis of ALL or may be a presenting feature of leukemia [89]. ALL presenting with hypereosinophilia must be differentiated from eosinophilic myeloid leukemia (AML M4Eo), which is strongly associated with alterations of chromosome 16. Infectious mononucleosis and some other viral infections can be confused with ALL. Detection of atypical lymphocytes in peripheral blood smear and serologic evidence of Epstein-Barr or cytomegalovirus infection helps make a diagnosis. Children with pertussis and parapertussis may present with marked leukocytosis and lymphocytosis, but the affected cells are mature lymphocytes. Bone and joint pain in ALL may mimic juvenile rheumatoid arthritis, rheumatic fever, or osteomyelitis. These presentations also can require bone marrow aspirate if a treatment with steroids for suspected rheumatoid diseases is planned. Lastly, ALL must be distinguished from acute myelogenous leukemia and small round cell tumors that invade bone marrow including neuroblastoma, rhabdomyosarcoma, Ewing sarcoma, and retinoblastoma, but these neoplasms usually have distinct other findings [6]. By contrast, in the case of non-Hodgkin lymphoma (NHL) there may be marked overlap in clinical presentation. When staging NHL, by convention, more than 25% blast cells in the marrow establish

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the diagnosis of ALL, whereas a child with 5% to 25% blasts is classified as having stage IV NHL [3].

9. Treatment

Pediatric ALL is a clonal heterogeneous disease with many distinct subtypes, and a uniform approach to antileukemic treatment is no longer appropriate. Although the specific approaches to various risk groups and the terminology describing the phases of therapy may vary between clinical trials, the backbone of modern ALL treatment protocols consists of four or five main treatment elements: remission-induction phase, early intensification, consolidation/CNS preventive therapy, delayed intensification (sometimes divided into re-induction and re-consolidation phases), and maintenance or continuation therapy targeted at eliminating residual disease [21,90].

Induction Therapy. The first goal of antileukemic therapy is to induce a complete remission and restore normal hematopoiesis. Intensive induction therapy improved the remission rate to approximately 98%. Almost all protocols use glucocorticoid (prednisone/ dexamethasone), vincristine and L-asparaginase as so-called three-drug backbone plus intrathecal therapy. It is a matter of debate whether the addition of antracycline has an impact on the remission induction rate and on the duration of remission [6,91,92]. A recent meta-analysis showed that anthracyclines significantly reduced bone marrow relapse when added to standard therapy but did not increase EFS due to the concomitant increased incidence of treatment related deaths [91]. BFM protocols use prednisone as a single systemic agent in the first week of treatment and this was shown to reduce tumor load in a controlled way to avoid metabolic complications [93]. Most controversial in induction regimens is the choice of glucocorticoid, prednisone being used more frequently. It appears that the use of dexamethasone results in a lower rate of bone marrow and CNS relapse, which is probably due to higher free plasma levels and better CNS penetration of the drug [94]. There are data, however, that dexamethasone leads to more acute and long-term complications [95,96]. Three forms of L-asparaginase are available, each with different pharmacologic and pharmacokinetic profile. The specific preparation, dose, route and schedule of administration vary [97]. Pegylated form with relatively long half-life is less immunogenic and less likely to develop neutralizing antibodies, and many study groups incorporate PEG-asparaginase in current treatment protocols [98]. Failure of induction therapy occurs in about 2% of children with ALL. This may be due to early death (most often caused by infection or bleeding) or to chemoresistant leukemic cells. With institution of more intensive therapy, the overall EFS for this minor non-responsive patient population is 30% to 40% [99,100].

Early Intensification. With restoration of normal hematopoiesis, children in remission become candidates for intensification therapy. The aim of early intensification therapy, administered immediately after remission induction, is to eradicate residual leukemic cells [101,102]. There is no consensus on the best regimens and their duration. BFM protocol uses a post-induction course consisting of 6-mercaptopurine, cyclophosphamide, low-dose cytarabin plus intrathe-

cal methotrexate. Other cooperative groups use different combinations of drugs which also lower the amount of any remaining MRD in the bone marrow [21,93].

Consolidation/ Central Nervous System Preventive Therapy. The goal of the consolidation phase is to continue to strengthen the remission in the bone marrow and to provide CNS prophylaxis. The concept of CNS prophylaxis is based on postulates that CNS is a sanctuary site for leukemic cells, which are undetected at diagnosis and are protected by the blood brain barrier from systemic chemotherapy. CNS prophylaxis can be achieved by radiation (cranial or craniospinal), intrathecal chemotherapy, high dose systemic chemotherapy, or combinations of these [103,104]. The occurrence of long-term neurologic and neuroendocrine sequelae, as well as the risk of secondary CNS neoplasms, has limited the use of cranial irradiation to a selected group of patients with an increased risk of CNS relapse [75]. Many current protocols use high-dose systemic methotrexate (four doses are given biweekly) in parallel with intrathecal chemotherapy (either intrathecal methotrexate or triple IT: methotrexate with cytarabine and hydrocortisone). The doses of intrathecally administered drugs are based on age. Effective CNS prophylactic regimens have reduced the incidence of isolated CNS relapse to less than 5% [6].

Delayed Intensification. Addition of a delayed intensification (DI) phase after standard induction/consolidation therapy has improved outcome for children with ALL [4]. The intensity of chemotherapy varies considerably depending on risk group assignment. DI mainly consists of a late repetition of the initial remission induction and early intensification phases. A 7-week DI was introduced with BFM studies in the 1980s, beginning at week 16 [105]. To minimize the development of drug resistance, cytotoxic agents were altered: prednisone was replaced with dexamethasone, doxorubicin was substituted for daunorubicin, and mercaptopurine was replaced with thioguanine [21]. Together with other drugs used in this phase, the minimal residual leukaemia cells may be further cleared up. American Children's Cancer Group included BFM backbone and also demonstrated that DI, consising of reinduction and reconsolidation, improved treatment success [106,107]. Subsequent trials have focused on augmenting DI for less favorable patient groups [108]. On most trials, children with very high-risk features, treated with multiple cycles of intensive chemotherapy during the consolidation phase, have been considered candidates for allogeneic stem cell transplantation in first remission.

Maintenance Therapy. After the completion of 6 to 12 months of more aggressive treatment, lower doses of cytotoxic drugs are used to prevent relapse. Maintenance or Continuation Therapy is unique among therapies for malignancies. The aim of the maintenance phase is to further reduce minimal residual cells that are not detectable with current techniques at this stage of treatment. Maintenance chemotherapy generally continues up to the time point of two or three years after the diagnosis or after achievement of morphological remission. On some studies, boys are treated longer than girls, while on others, there is no difference in the duration of treatment based on gender. Reduction of the duration of maintenance to less than 2 years led to an increased relapsed risk. However, patients with more aggressive leukemias who had received significantly more intensive treatment, have less benefit of maintenance therapy [21].

The usual maintenance regimen for children with ALL is a combination of mercaptopurine (6-MP) administered daily and methotrexate (MTX) administered weekly. Doses are usually

adapted according to leukocyte count, using a target of 2.000 to 3.000/mm^3 [93]. There are large individual differences in the doses that are tolerated or needed to achieve the target leukocyte count. It has been shown that maintaining the highest tolerable dose of 6-MP and MTX leads to a better outcome [21]. The effect of 6-MP is better when the drug is given in the evening and without milk products [93,109]. The frequency of drug administration also may be associated with the outcome. Children who receive maintenance therapy on a continuous rather than an interrupted schedule have longer remissions. Compliance problems may diminish the efficacy of maintenance therapy. Intensification of the maintenance by the administration of vincristine/dexamethasone pulses was shown to provide no extra benefit [110].

10. Relapsed ALL

Despite current intensive front-line therapies, approximately 20% of children with ALL experience relapse, accounting for a large proportion of pediatric cancer patients [111]. Relapse is defined as the reappearance of leukemic cells at any site in the body. It may be isolated event at one site (medullary or extramedullary) or may be combined (medullary and extramedullary). Most relapsed leukemias retain their original immunophenotype and genotype, but rarely another cell lineage ("lineage switch") is observed. Molecular studies are helpful in distinguishing lineage switch from secondary leukemia, which usually occurs years later [44, 112]. In general, relapsed leukemia is less responsive and requires much more intensive treatments. Isolated extramedullary relapse is more favorable than bone marrow relapse [113]. Combined relapses have a better outcome compared to isolated medullary relapses; combined relapses in fact tend to be later and to display better response to chemotherapy [3,74].

Medullary relapse. Bone marrow remains the most common site of relapse in pediatric ALL and generally implies a poor prognosis for most patients. Later relapse is more favorable than earlier relapse [114,115]. The definition of early versus late marrow relapse varies; many groups define "early" as a marrow recurrence within 36 months from initial diagnosis, or as less than 6 months after completing the initial treatment protocol [111]. The two approaches to the treatment of medullary relapse are chemotherapy and hematopoietic stem cell transplantation (HSCT). For patients who receive only chemotherapy, a second course of CNS-directed therapy should be administered to prevent subsequent CNS relapse [21]. With aggressive multidrug reinduction therapy, second remission is achieved in 66% to 82% for early B-lineage marrow relapse, and 90% to 95% for late B-lineage marrow relapse. Second remission may be more elusive for relapsed T-cell disease. However, intensive relapse regimens generally have not resulted in improvement in salvage rates and have reached the limit of tolerability. Longer-term overall EFS rates for early relapse are 10% to 20%, compared to 40% to 50% for late marrow relapse. Outcomes for second and greater relapse are even worse. Although third remission can be achieved in approximately 40% of patients, responses are not sustained and most patients will ultimately die from their disease [74,116]. These results have given HSCT a significant role in the treatment of relapsed ALL [117]. Allogeneic HSCT is the treatment of choice in children who develop early medullary relapse [118]. Autologous transplantation offers no advantage over chemotherapy. For patients without histocompatible

related donors, the options are HSCT from matched unrelated donors, umbilical cord blood transplant, and T-cell-depleted haploidentical HSCT [119,120]. In most studies, patients transplanted in earlier remissions fare significantly better than patients transplanted after multiple relapses [21].

Extramedullary relapse. Although extramedullary relapse frequently presents as an isolated finding, most occurrences are associated with MRD in the bone marrow, and it likely represents a local manifestation of systemic failure. Accordingly, these patients require intensive systemic treatment to prevent subsequent bone marrow relapse. The distinction between early and late extramedullary relapse is generally 18 months from initial diagnosis (compared with 36 months for medullary relapse) [74].

Central nervous system relapse is observed in less than 5% of children with ALL. It occurs more frequently in children with T-ALL or mature B-ALL. Intrathecal chemotherapy alone fails to cure CNS leukemia. Most regimens include intrathecal chemotherapy until CSF remission, in parallel with a systemic induction therapy, followed by consolidation chemotherapy, cranio-spinal irradiation (2.400 to 3.000 cGy cranial, and 1.200 to 1.500 cGy spinal) and maintenance intrathecal chemotherapy [6]. Factors influencing outcome include whether CNS relapse is early or late (EFS 83% and 46%, respectively), and whether the child received prior CNS irradiation [121]. For patients with earlier prophylactic irradiation, long-term secondary remission does not exceed 30%, and these patients are candidates for HSCT [6,21].

Testicular relapse occurs in less than 2% of children with ALL. Optimal therapy includes the use of systemic chemotherapy and local radiotherapy (2.400 cGy to both testes). Bilateral testicular irradiation is indicated for all patients; unilateral radiotherapy may be followed by relapse in the contralateral testis [6]. The impact of a testicular relapse on the prognosis depends whether it was early or late, and whether the recurrence is an isolated or combined event. Prolonged disease-free survival can be obtained for more than two thirds of patients with an isolated late relapse [6,122].

Leukemic relapse occasionally occurs at other extramedullary sites, including the eye, ear, ovary, uterus, kidney, bone, muscle, tonsil, mediastinum, pleura, and paranasal sinus. Optimal treatment is unclear, and may include local control measures and intensification of systemic chemotherapy.

11. Outcome

See also “Prognostic factors and risk classification”

The outcome of newly diagnosed pediatric ALL has increased significantly over the past decades. More than 95% of children achieve remission, and approximately 80% are expected to be long-term event-free survivors. The 5-year EFS varies considerably depending on risk category, from 95% (low risk) to 30% (very high risk), with infant leukemia having the worst outcomes (20% for patients younger than 90 days) [123]. An analysis of long-term survival

among 21,626 people who were treated for childhood ALL in Children's Oncology Group (COG) trials from 1990-2005 found a 10-year survival of almost 84% [124].

Pediatric ALL is potentially highly curable in low-income countries, mostly due to improved supportive care with intensive chemotherapy protocols. Recent studies report overall survival rates over 60% in India [125,126], and 5-year EFS over 78% in Lebanon [127].

Similarly to frontline ALL therapy, treatment outcome for relapsed patients depends on clinical and biological characteristics of the disease. Factors indicating a poor prognosis in previously treated patients include: relapse on therapy or after a short initial remission, bone marrow involvement, T-cell immunophenotype, unfavorable cytogenetics (i.e., the presence of t(9;22) and t(4;11), and persistent levels of MRD after the first course of chemotherapy for relapse. Roughly, conventional intensive chemotherapy and radiotherapy can cure only one third of all children with relapsed ALL, with percentages ranging from 0 to 70% depending on the pattern of prognostic factors present at relapse [74,128,129].

12. Hematopoietic stem cell transplantation

HSCT has been an important treatment modality in the management of a portion of high-risk or relapsed childhood ALL. There is a need to reassess periodically the indications for HSCT, owing to the continuos improvement in chemotherapy approaches, development of novel therapeutics, precise assessment of the risk of relapse, and transplantation procedures [130].

HSCT in first remission. There is no consensus on the indications for transplantation in childhood ALL in first complete remission (CR1) among major international study groups. Historically, children with Ph+ ALL and matched sibling donor have been transplanted in CR1 [131-134]. In a recent COG study, intensive chemotherapy plus continuos imatinib exposure after remission induction therapy yielded a 3-year EFS of 80%, more than twice that of historical controls, and comparable to those of matched-related or matched-unrelated transplant [135]. Infants with *MLL*-rearranged ALL were identified early on as having a particularly poor prognosis, and universally have been considered candidates for transplantation in CR1. However, most recent COG study failed to show an advantage of HSCT over chemotherapy [136], while Interfant-99 study showed that the benefit was restricted to a very high-risk subgroup with 2 additional unfavorable prognostic features: age <6 months and either poor response to steroids or leukocyte count ≥ 300 x 10^9/L [137]. Similarly, somewhat ambiguous results have been reported from studies that attempt to compare EFS after transplant or chemotherapy for children with hypodiploid ALL [138], poor early responders [99,139], persistent MRD, and high-risk T-cell ALL [140,141]. Overall, there is no absolute indication for HSCT in children with ALL in CR1. In view of the dismal outcome of *MLL*-rearranged infant ALL, poor early responders with Ph+ ALL, and early T-cell precursor ALL, these patients are reasonable candidates for evaluation of HSCT in first remission [130].

HSCT in second or subsequent remission. The indications for relapsed or multiple relapsed ALL are less controversial among study groups. Although in the recent past HSCT would have been

recommended for every child with matched-sibling donor, newer risk-based strategies suggest indications based upon the site of relapse and its timing in relation to completion of frontline therapy. Children with isolated marrow relapse on treatment or within 6 months of completion of treatment (or 36 months from diagnosis by COG definition), and those with combined marrow and extramedullary relapse within 18 months from diagnosis should be considered for HSCT [130]. The best approach for children with a late relapse is less clear-cut, as a significant proportion of them can be cured with further chemotherapy [142]. HSCT is indicated for patients with second or greater relapse, whether marrow, isolated extramedullary, or combined [130].

Donor selection and stem-cell source. Understanding how transplantation outcomes are influenced by donor source is a critical component of the therapeutic decision-making process. Matched-sibling donor is considered the gold standard for all indications [143]. Since only 20% to 25% of children with an indication for allogeneic HSCT have a MSD, for the remaining patients, a matched unrelated donor (MUD) is an alternative [130,144]. Over the past several decades, international registries have enlisted more than 18 million volunteers worldwide as potential unrelated stem cell donors. The chance of finding a suitable donor mainly depends on race/ethnicity (Caucasians being more likely to find a match), and the frequency of the HLA phenotype of the patient [145]. As a proportion of patients may not be able to rapidly identify a suitable MUD, other alternative graft sources, umbilical cord blood, haploidentical (haplo)-related donor and mismatched unrelated donor are available [146]. The outcomes of unrelated donor transplants have improved markedly in the last years, mainly due to advances in HLA typing and supportive care [147,148].

13. Novel therapies

Novel therapies in pediatric ALL are needed to improve treatment outcomes in newly-diagnosed patients with a poor prognosis and for patients with relapsed/refractory disease that have limited treatment options. New agents use a variety of approaches to selectively target leukemic cells, by altering intracellular signaling pathways, regulating gene expression, or targeting unique cell surface receptors. Use of these agents in frontline therapy provide the possibility of minimizing toxicity to normal cells [149,150].

Clofarabine is a second-generation purine nucleoside analogue approved for the treatment of pediatric patients with relapsed/refractory ALL treated with at least 2 prior regimens [151,152]. New trials are exploring the use of clofarabine in combination with cyclophosphamide and etoposide, and clofarabine in combination with cytarabine [153,154].

Imatinib mesylate (a selective inhibitor of the BCR-ABL protein kinase) has been combined with conventional chemotherapy in children with newly diagnosed and relapsed Ph+ ALL. Dramatic improvement of early EFS was achieved, with no additional toxicities [135,155]. Dasatinib, a second-generation tyrosine kinase inhibitor with potent activity against imatinib-resistant leukemic cells, is currently being tested in several phase I-III studies of pediatric Ph + ALL [156,157].

Infant ALL presents another challenge, with poor outcome particularly in children with *MLL* rearrangements. Overexpression of wild-type Fms-like tyrosine kinase (FLT3) in *MLL*-rearranged ALL is a target that is being investigated in infant ALL [158]. Lestaurtinib (CEP-701), a highly selective small molecule FLT3 tyrosine kinase inhibitor, is being combined with chemotherapy in infants with newly diagnosed ALL and *MLL* rearrangements [159].

Nelarabine (2-amino-9β-D-arabinosyl-6-methoxy-9H-guanine) is specifically cytotoxic to T-cell lineage blasts and is being studied incorporated into a frontline treatment study for children with newly diagnosed high-risk T-cell ALL [160].

Other groups of agents that have shown promising activity in the pediatric preclinical testing for ALL include a BCL-2 protein inhibitor (ABT-263), a mammalian target of rapamycin (mTOR) inhibitors (sirolimus) [161], and an aurora A kinase inhibitor (MLN8237) [162]. Monoclonal antibodies directed against a variety of specific targets such as cells expressing CD 19 (SAR3419, XMAb5574), CD 20 (rituximab) [163,164], CD22 (epratuzumab) [165], CD33 (gemtuzumab) [166] and CD52 (alemtuzumab) [167] are being developed or already in clinical trials. The major advantage of monoclonal antibody therapy is that the toxicities are limited and nonoverlapping compared with cytotoxic drugs, making them attractive candidates for combined therapy [168].

14. Late consequences

With the increasing number of children and adolescents treated of ALL, a large spectrum of adverse long-term sequelae is observed in survivors of ALL. The late effects of therapy associated with significant morbidity may include second neoplasms, neurotoxicity, cardiotoxicity, endocrine abnormalities, bone toxicity, and adverse psychosocial effects. The greatest risk for second neoplasms as well as other late consequences occurs in children who received cranial or craniospinal irradiation.

Second neoplasms. Second and subsequent neoplasms in survivors of childhood ALL are predominantly brain tumors (gliomas of varying histologic grades) and hematopoietic neoplasms (AML and myelodysplastic syndrome) [6]. The median latency period for high-grade brain tumor is 9 years but almost 20 years for low-grade tumors. Secondary AML has been linked to intensive treatment with epipodophyllotoxins and other topoisomerase II inhibitors, and has very low long-term survival rate [169]. Increasing number of solid tumors, consisting of skin, breast, bone, soft tissue, and thyroid neoplasms, have been reported. The 10-year cumulative incidence of second neoplasms is estimated at 14.6% [170,171].

Neurotoxicity. Understanding the risks of CNS toxicity is critically important in long-term follow-up of childhood ALL survivors. Although intrathecal and systemic chemotherapy or radiotherapy alone can be sufficient to induce CNS changes, the combination may be more neurotoxic. Four pathologically distinct findings of delayed CNS toxicity have been identified: cortical atrophy, necrotizing leukoencephalopathy, subacute leukoencephalopathy, and mineralizing microangiopathy [172]. Numerous studies have demonstrated abnormal CT and MRI scans in asymptomatic ALL patients who received CNS preventive therapy, as well as a significant association between these radioimaging abnormalities and neuropsychologic

dysfunction [173,174]. Survivors of pediatric ALL have an increased risk for adverse psychosocial outcomes including lower cognitive functioning, executive function, depression, and decreased educational attainment [6,175].

Cardiotoxicity. Anthracyclines are the most common class of chemotherapeutic agents associated with adverse effects on the heart. Anthracycline-induced cardiomyocyte death results in hypertrophy of existing myocytes and interstitial fibrosis. The incidence of cardiomyopathy is related to the cumulative dose of anthracyclines [176]. Female and younger patients are at a higher risk. The anthracycline-induced cardiomyopathy is a progressive disorder that manifests with signs of congestive heart failure. Rapid progression of symptoms may occur with pregnancy, anesthesia, or exercise [177,178]. Dexrazoxane, a potent iron-chelating agent, provides long-term cardioprotection without compromising oncological efficacy in doxorubicin-treated children with high-risk ALL [179-181].

Endocrine abnormalities. Neuroendocrine morbidities, primarily involving the hypothalamus, have been documented in children who were treated with cranial radiotherapy. Essentially all of the hypothalamic-pituitary axes are at risk, but the principal findings are impaired growth hormone responses to provocative stimuli [6]. Growth delay is notified in some children with ALL [6,182]. Precocious puberty has been reported in some children receiving cranial irradiation, mostly in girls who receive cranial radiation in doses of 24 Gy or higher [183]. There appears to be a higher prevalence of obesity and metabolic syndrome among children who have successfully completed therapy for ALL [184,185]. Primary gonadal damage has been documented in patients of both sexes treated on cyclophosphamide-containing intensive treatment regimens. In most cases, girls with ALL retain intact reproductive function [6]. Studies of male survivors who received chemotherapy for childhood ALL showed evidence of subsequent gonadal dysfunction [186,187].

Bone toxicity. The most common chemotherapy-induced skeletal late effects are glucocorticoid-induced osteonecrosis and reduced bone mineral density. Risk factors for osteonecrosis have included adolescent age, females, white race, higher body mass index, lower albumin, and elevated cholesterol [74,188]. Limited data suggest that statins modulate cholesterol metabolism and may protect against osteonecrosis [189]. Multiple candidate gene studies have indicated several polymorphisms in genes putatively related to the development of osteonecrosis, getting conflicting results [190,191]. Reduced bone mineral density and increased fracture risk have been reported in children off chemotherapy for ALL. Routine recommendations include adequate dietary intake of calcium and vitamin D, and weight-bearing exercise. The use of bisphosphonates and other absorption-reducing agents in childhood ALL survivors remain investigational [192,193].

15. Conclusions

Pediatric ALL is a heterogeneous disease, which at present can be cured in approximately 80% of children. Improvements in long-term survival rates may have reached a plateau as further intensification of therapy may lead to a higher rate of treatment-related deaths. Therefore hope for future progress lies in the better understanding of the biology of pediatric ALL which will

allow for the more individualized therapy. The ultimate goals are to provide curative therapy to every child with ALL and help develop preventive measures.

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