Curr Pediatr Rep (2014) 2:26–37
DOI 10.1007/s40124-013-0036-2

HEMATOLOGY/ONCOLOGY (Z FADOO, SECTION EDITOR)

Pediatric Acute Myeloid Leukemia: How to Improve Outcome?

Luca Szalontay · Aziza T. Shad

Published online: 20 December 2013

Abstract Childhood acute myeloid leukemia (AML) represents about 20 % of acute childhood leukemias. Today, the 5-year overall survival rates are close to 70 %. The outcome of childhood AML has significantly improved in the last few decades, secondary to: a better understanding of etiology and risk factors; identification of prognostic factors and their incorporation in treatment protocols; the development of novel therapeutic agents based on cytogenetic and molecular information; implementation of supportive care using evidence-based medicine; and an emphasis on the importance of close follow-up and management of late effects. Further advances in AML management can only occur through continued efforts to understand the disease, and the design of international clinical trials with larger patient groups where novel therapies and treatment protocols can be evaluated.

Keywords Acute myeloid leukemia · Risk stratification · Cytogenetics · Novel chemotherapeutic agent · Neutropenic fever · Late effects

L. Szalontay · A. T. Shad
Department of Pediatrics, Medstar Georgetown University Hospital, Washington, DC 20007, USA

A. T. Shad (✉)
Division of Pediatric Hematology/Oncology, Blood and Marrow Transplantation, Lombardi Comprehensive Cancer Center, Medstar Georgetown University Hospital, 3800 Reservoir Road NW, Washington, DC 20007, USA
e-mail: SHADA@gunet.georgetown.edu

Introduction

The myeloid leukemias of childhood represent a spectrum of hematopoietic malignancies. More than 90 % of myeloid leukemias are acute and the remainder includes chronic and/or subacute myeloproliferative disorders such as chronic myelogenous leukemia (CML) and juvenile myelomonocytic leukemia (JMML). Myelodysplastic syndromes (MDS) represent less than 5 % of myeloid malignancies in children.

Childhood acute myeloid leukemia (AML) is a very heterogeneous disease that represents only 15–20 % of all childhood leukemia, but unfortunately is still responsible for more than half of the deaths from leukemia. The incidence is 7 cases per million children younger than 19 years of age [1]. There is broad overlap between the recommendations for AML management in children and adults, but, early on in the history of treating childhood AML, it was recognized that guidelines and management should be age-specific, and pediatric protocols were essential. Advances in cytogenetics, molecular biology, and now genomics (a number of novel driver mutations in AML have been identified through whole-genome sequencing) are all adding to a better understanding of AML. The aim of this review is to summarize the current knowledge on childhood AML and our strategies to improve the outcome of this leukemia.

Etiology

AML develops through a transformation of hematopoietic progenitor cells that leads to an arrest in differentiation, overgrowth of a malignant clone in the bone marrow, and a decrease in the number of mature, well-functioning blood

cells [2]. Several lines of evidence have led to a model that suggests that AML arises from the cooperation between two classes of genetic alterations that regulate self-renewal and differentiation [2]. Greaves et al. [3] explained the development of childhood AML with a two-step model: leukemia is initiated through chromosomal rearrangements in utero, and the emergence of overt disease is a result of secondary genetic changes.

Risk Factors

Many studies have aimed at determining the risk factors for childhood AML, but evidence is unfortunately still limited, mostly due to small sample sizes, and studies grouping AML with ALL. One way to categorize the possible associations between risk factors and childhood AML is based on the strength of the relationship that was found in different studies and meta-analyses [4•].

Generally Accepted Risk Factors

The most common genetic factor is trisomy 21; children with Down syndrome are at an increased risk of leukemia, and nearly half of these cases are usually a specific subtype of AML, acute megakaryocytic leukemia (M7) [5•]. Other genetic syndromes associated with childhood AML include Fanconi's anemia, Bloom syndrome, Ataxia telangiectasia, Shwachman-Diamond syndrome, and Monosomy 7.

Ionizing radiation in utero is a well-recognized cause of childhood leukemia, including AML [6], and this finding has led to decreased X-ray use in pregnant women.

Suggestive of Increased Risk

Parental age has been in the focus of multiple studies looking at risk factors for childhood AML. Data support an increased risk with older maternal age [7], but are inconclusive for older paternal age. There is some evidence of increased risk with increasing birth order, but this could be secondary to maternal age effect [8]. Some studies also suggest a relationship between prior fetal loss and childhood AML [9]. Birth weight is determined by a combination of genetic and in utero factors. Two independent meta-analyses have suggested that there may be an increased risk with both low and high birth weight [10].

Periconceptional and prenatal exposure may also be associated with an increased risk of childhood AML. There appears to be a positive correlation with alcohol consumption during pregnancy [11], but not with tobacco. Another meta-analysis showed a positive correlation between maternal occupational pesticide exposure and childhood AML; studies for paternal exposure were more heterogeneous [12].

Suggestive of Decreased Risk

Breastfeeding is the only factor that has a protective effect on the development of childhood AML; multiple studies found a decreased risk for AML in children who were breastfed for more than 6 months [13].

Limited Evidence

Most of the data on periconceptional and prenatal exposures indicate non-significant but positive relationships with childhood AML. The most important factors are parental benzene exposure [14], parental smoking [15], antibiotic use during pregnancy [16], and maternal dietary consumption of DNA topoisomerase II inhibitors (e.g., bean, soy, cocoa, coffee, wine, canned vegetables) [17].

Prognostic Factors

In the past, the prognosis for children with AML was only determined by a few limited host and disease factors including morphology, white blood cell count at the time of diagnosis, age, or response to induction therapy. Recent advances in technology have helped to identify molecular and cytogenetic risk factors in AML which provide insight into the molecular heterogeneity of the disease and can explain the previously observed differences in therapeutic response [18].

Classification of AML

Two systems have been used to classify AML into subtypes: the French–American–British (FAB) classification and the newer World Health Organization (WHO) classification.

1. The FAB classification of AML is based on the morphologic and cytochemical features of leukemic blasts in the bone marrow. Subtypes M0 through M5 all start in precursors of white blood cells. M6 AML starts in very early forms of red blood cells, while M7 AML starts in platelet precursors (Fig. 1; Table 1) [19]. Despite the extremely heterogeneous nature of AML, the various subtypes seem to share some common pathways leading to leukemogenesis, and the hierarchical nature of the disease is generally well established.

   About 50–60 % of children with AML can be classified as having M1, M2, M3, M6, or M7 subtypes,

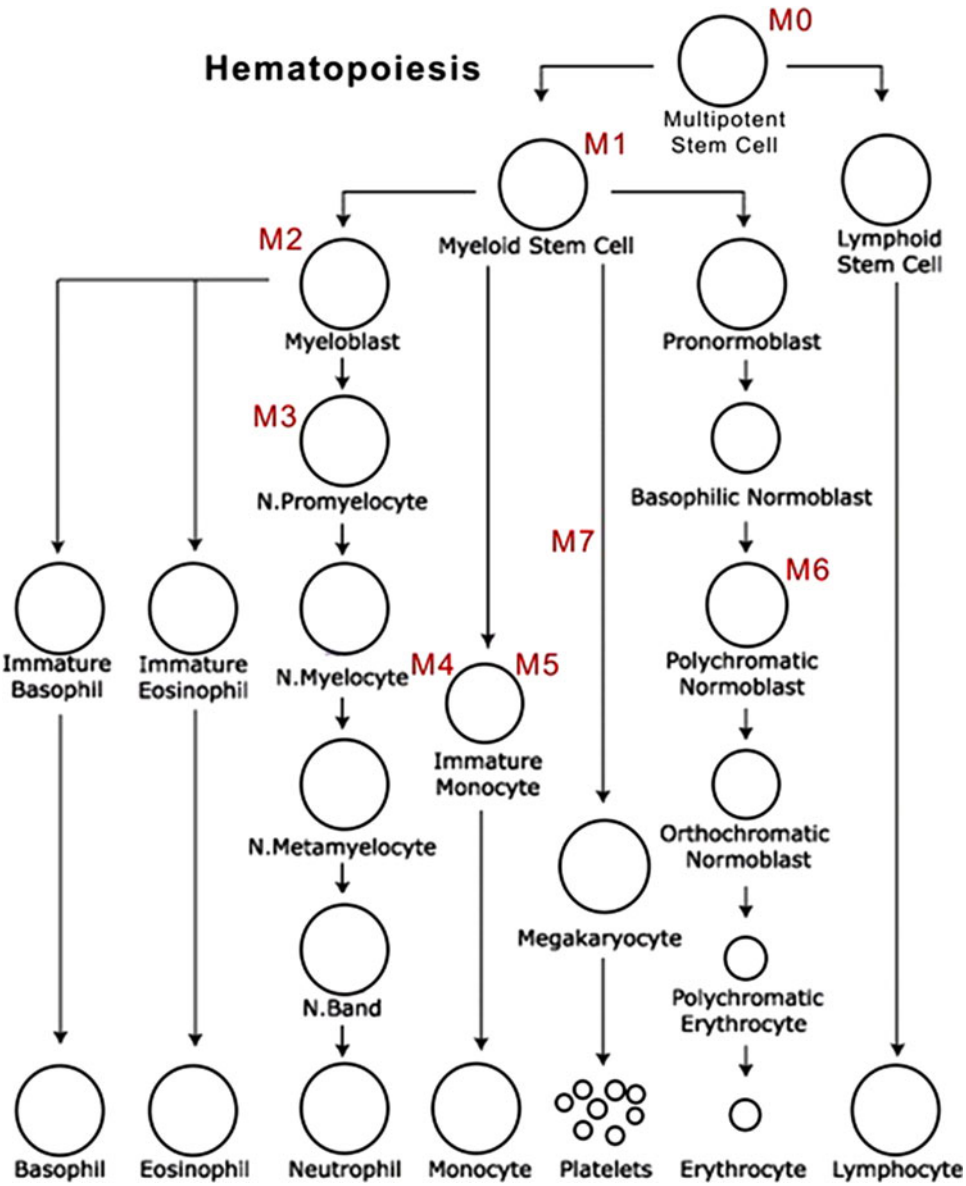

Fig. 1 Hematopoiesis with the French–American–British (FAB) classification

while ~40 % have M4 or M5 subtypes. About 80 % of children younger than 2 years with AML have an M4 or M5 subtype. The response to cytotoxic chemotherapy among children with the different subtypes of AML is relatively similar. One exception is FAB subtype M3, for which all-trans retinoic acid (ATRA) plus chemotherapy achieves remission and cure in approximately 70–80 % of affected children.

2. In 2002, the World Health Organization (WHO) proposed a new classification system that incorporated diagnostic cytogenetic information and more reliably correlated with outcome. In this classification, patients with t(8; 21), inv(16), t(15; 17) and those with MLL translocations, which collectively constituted nearly half of the cases of childhood AML, were classified as "AML with recurrent cytogenetic abnormalities." This classification system also decreased the bone marrow percentage of leukemic blast requirement for the diagnosis of AML from 30 to 20 %; an additional clarification was made that patients with recurrent cytogenetic abnormalities did not need to meet the minimum blast requirement to be considered AML [18, 20, 21]. In 2008, WHO expanded the number of cytogenetic abnormalities linked to AML classification, and for the first time included specific gene mutations (*CEBPA* and *NPM* mutations) in its classification system [21, 22]. Such a genetically based classification system links AML class with outcome and provides significant biologic and prognostic information. With new emerging technologies aimed

Table 1 FAB classification of AML

FAB subtype	Name
M0	Undifferentiated acute myeloblastic leukemia
M1	Acute myeloblastic leukemia with minimal maturation
M2	Acute myeloblastic leukemia with maturation
M3	Acute promyelocytic leukemia (APL)
M4	Acute myelomonocytic leukemia
$M4_{eos}$	Acute myelomonocytic leukemia with eosinophilia
M5	Acute monocytic leukemia
M6	Acute erythroid leukemia
M7	Acute megakaryoblastic leukemia

at genetic, epigenetic, proteomic, and immunophenotypic classification, AML classification will likely evolve further.

Host Factors

The factors having an impact on disease outcome are the following: age, gender, race, BMI, and host polymorphism. Recent studies have demonstrated that young patients with AML have better survival rates because of lower relapse rates [23]. Racial differences have been recently shown to be an important prognostic factor, as African Americans were found to have a significantly worse outcome secondary to a higher rate of relapse [24]. The explanation is thought to be due to polymorphisms in genes involved in drug metabolism and DNA repair (e.g., glutathione S-transferase) [25]. Retrospective analysis of data has found an association between children being overweight (>94th percentile) or underweight (<11th percentile) and early treatment-related mortality, mostly from infection [26].

Response to Therapy

Response to induction therapy has been a major prognostic factor since the beginning of risk stratification. The amount of blasts remaining in the bone marrow after the first course of induction therapy divide patients into three groups: complete remission with blasts less than 5 %, in partial remission patients have blasts between 5 and 15 %, and with resistant disease they have more than 15 % blasts in the bone marrow. The impact of therapy response upon survival has been clearly demonstrated [27]. Patients in partial remission after the first course of induction had better overall survival rates than patients with resistant disease (42 and 22 %, respectively). Patients in partial remission after the first induction course had a high remission rate (89 %) after the second induction course and had an overall survival rate only slightly inferior to the group with complete remission after the first course of treatment. Patients with resistant disease had a poor prognosis even if they entered remission after the second course of induction therapy.

Response to therapy used to be determined by morphologic exam of the bone marrow. More recent methods are based on multiparameter flow cytometry and polymerase chain reaction (PCR). These methods made possible the introduction of minimal residual disease (MRD), which quickly became one of the main prognostic factors in response to therapy. Patients who were MRD-positive after the first course of induction fared significantly worse than patients with no MRD [28]. MRD also has an impact on the success of stem cell transplant (SCT). Patients who were MRD-negative after SCT had a significantly lower relapse rate than patients with MRD [29].

Cytogenetics

Cytogenetics in AML is one of the most important prognostic factors in all age groups. Based on cytogenetics alone, patients can be placed in three major risk groups impacting relapse risk, disease-free survival, and overall survival (Table 2).

Briefly, favorable AML cytogenetics are the following: core binding factor leukemias t(8;21), and inv(16), t(15;17). Core binding factors play a crucial rule in the different stages of hematopoiesis. They are heterodimeric transcription factors containing a DNA-binding alpha subunit and a beta subunit, which increases the affinity and stabilizes the binding of the alpha subunit. Translocation (8;21) disrupts the AML1 gene, which is coding the alpha subunit, whereas inv(16) creates two different fusion genes, which affects the quantity of the beta subunit [30, 31]. Translocation (15;17) fuses the retinoic acid receptor-α gene to the PML gene and it occurs only in acute promyelocytic leukemia (APL). The product of the RARA gene is a nuclear receptor that acts as a transcription enhancer in response to retinoic acid [32].

Unfavorable cytogenetics include complex cytogenetics (three or more distinct cytogenetic abnormalities), monosomy 7, monosomy 5, del(5q), and abnormal chromosome 3. Chromosomes 5q and 7 contain tumor suppressor genes that regulate myeloid growth and differentiation [33, 34]. The 5q-syndrome is characterized by treatment-resistant macrocytic anemia, and MDS that may lead to AML [34].

Intermediate risk cytogenetics refer to all the remaining chromosomal abnormalities, like +8, +21, or 11q23 (MLL)-associated abnormalities. The most common genetic events occurring in children younger than 1 year are the rearrangements of the mixed lineage leukemia (MLL) gene on chromosome 11 [35], and the frequency decreases with age [36]. It plays a key role in hematopoiesis by regulating the

Table 2 Summary of structural chromosomal abnormalities and genetic mutations with their prognosis in childhood AML

Abnormality	Prognosis	Disease type
Cytogenetic		
t(8;21) (q22;q22)	Favorable	AML
inv(16) (p13;q22)	Favorable	AML
t(15;17) (q22;q21)	Favorable	AML M3
t(11;19) (q23;p13.3)	Unfavorable	AML M4 or M5
t(6;11) (q27;q23)	Unfavorable	AML M4 or M5
t(9;11) (p22;q23)	Favorable (with no additional abnormalities or M5)	AML
t(10;11) (p12;q23)	Unfavorable	AML M4 or M5
Monosomy 7	Unfavorable	AML
Monosomy 5	Unfavorable	AML
del 5q	Unfavorable	AML
t(1;22) (q21;p15.5)	Intermediate risk/unfavorable	AML M7
t(6;9) (p23;q34)	Unfavorable	AML
inv3 (q21;q26.2) or t(3;3) (q21;q26.2)	Unfavorable	AML
+8	Intermediate risk	AML
+21	Intermediate risk	AML
t(9;22) (q43;q11)	Unfavorable	AML
t(7;12) (q36;p13)/ t(7;12) (q32;p13)	Unfavorable	AML
t(5;11) (q35;p15.5)	Unfavorable	AML
Genetic mutation		
NPM1	Favorable	AML
CEBPA	Favorable	AML
FLT3-ITD	Context dependent	AML
N-RAS	No prognostic significance	AML
MLL-PTD	Not yet defined	AML
c-KIT	Not yet defined	AML
WT1	Unfavorable combined with FLT3-ITD	AML

homeobox (HOX) genes. It can be involved in several types of rearrangements resulting in different fusion genes encoding chimeric proteins, which localize in the nucleus and show transforming activity [37••]. Young children with Down syndrome have an increased incidence of acute megakaryoblastic leukemia, which suggests that trisomy 21 directly contributes to the malignant transformation of the hematopoietic cells [5•].

Molecular Risk Factors

Genomic alterations of several genes involved in AML development have been recently discovered and linked to the outcome of the leukemia. There are three mutations, which have been already proven to significantly influence the course of the disease. FLT3 is a receptor tyrosine kinase, and its mutation has been associated with higher risk of relapse [38]. Nucleophosmin 1 encodes a nuclear protein, and one of its main tasks is the regulation of centrosome duplication. Patients with NPM1 mutation showed improved survival [39]. CCAAT/enhancer-binding protein alpha (CEBPA) gene is encoding a transcription factor, which plays a crucial role in granulopoiesis, and loss of its activity results in a block of normal differentiation. Patients with CEBPA mutation showed longer event-free survival and decreased incidence of relapse [40]. Researchers examined other well-known mutations associated with different malignancies, such as WT-1 or c-KIT mutations, but they did not demonstrate a significant impact on the prognosis.

Children with Down syndrome represent a special patient group. The first genetic event in leukemogenesis is considered to be trisomy 21, while the second genetic event is a mutation of the X-linked GATA1 gene, which is an important blood-specific transcription factor in the development of the erythroid and megakaryocytic lineages. Molecular studies of newborn blood samples suggest that the GATA1 mutation occurs in utero, while the genetic abnormalities (e.g., mutations in JAK3, p53, FLT3 genes) playing a crucial part in the evolution of acute megakaryoblastic leukemia usually happen in early childhood [5•].

In the last 10–15 years, these prognostic factors have been incorporated into therapeutic decision-making, allowing us to reduce toxicity for those who can be cured with less intensity, to develop target therapy to specific types of AML, and most importantly to improve the overall survival and event free survival rates [41•].

Clinical Features and Diagnosis

The signs and symptoms of AML are mainly due to the replacement of bone marrow with malignant cells. Bone marrow failure presents as pallor, fatigue, exercise intolerance, bruising or epistaxis, and fever caused by different infections. Organ infiltration can cause hepatosplenomegaly, gingival hyperplasia (M4, M5 subtypes), or, especially in children less than 1 year of age, central nervous system involvement and subcutaneous nodules or "blueberry muffin" lesions. Laboratory findings of disseminated intravascular coagulation (DIC) are indicative of APL (M3 subtype). A myeloid sarcoma or chloroma is a solid tumor composed of myeloblasts, typically associated with a t(8;21) translocation in the M2 subtype, and the most

common sites are epidural sites, mediastinum, lungs, and the orbit of the eye.

The basic diagnostic work-up for childhood AML consists of relevant blood tests, bone marrow aspiration and biopsy (flow cytometry, special stains, cytogenetics, FISH, RT-PCR), chest x-ray and lumbar puncture.

Histochemical Evaluation

The treatment for children with AML differs significantly from that for ALL; thus, it is crucial to distinguish AML from ALL. Special histochemical stains performed on bone marrow specimens of children with acute leukemia can be helpful in confirming diagnosis. The stains most commonly used include myeloperoxidase, periodic acid-Schiff (PAS), Sudan Black B, and esterase. In most cases, the staining pattern with these histochemical stains will distinguish AML from AMML and ALL. This approach, which in most developing countries is the only means of making a diagnosis, is slowly being replaced by immunophenotyping using flow cytometry.

Immunophenotyping

The use of monoclonal antibodies to determine cell-surface antigens of AML cells is used to reinforce histologic diagnosis. Various lineage-specific monoclonal antibodies that detect antigens on AML cells should be used at the time of initial diagnostic work-up, along with a number of lineage-specific T-lymphocyte and B-lymphocyte markers to help distinguish AML from ALL and bi-lineal or biphenotypic leukemia [42]. The expression of various CD proteins that are relatively lineage-specific for AML include CD33, CD13, CD14, CDw41 (or platelet antiglycoprotein IIb/IIIa), CD15, CD11B, CD36, and antiglycophorin A.

Treatment

Initially, the general management of childhood AML was adapted from treatment protocols developed to treat adult AML. Over the last 50 years, advances in biological research and the ability to perform large clinical trials in children have made it possible to increase cure rates and improve the quality of life of the long-term childhood AML survivors.

Conventional Chemotherapy

One of the major advances in the last couple of decades has been the introduction of aggressive induction therapy. One or two courses of induction therapy are regularly used, and the standard induction therapy contains 3 days of anthracycline (daunorubicin, idarubicin, or mitoxantrone) and 7–10 days of cytarabine. Several international studies have already proven that the induction regimen comprising of higher doses of anthracyclines has improved long-term survival rates [43]. One of the feared side effects of anthracyclines is acute or late cardiotoxicity, which limits the cumulative dose. To prevent toxicity and further increase the cumulative dose, a liposomal formulation of daunorubicin was developed, which has had promising results according to the AML-BFM 2004 trial [44].

Cytarabine (Ara-C) is one of the most active agents in AML, and the most important in consolidating and maintaining remission. Studies on standard dose versus high dose, and intensively timed cycles versus standard timing of treatment have shown that high dose Ara-C-based intensification regimens can significantly reduce relapse rates [45]. On the other hand, ongoing maintenance therapy after aggressive intensification therapy led to worse survival rates post-relapse, most likely due to increased drug resistance [46].

Stem Cell Transplantation (SCT)

Stem cell transplantation, using myeloablative chemotherapy rather than whole body radiation, can be part of the postremission consolidation therapy. Risk stratification plays an important role in deciding which patient gets the most benefit, including the graft-versus-leukemia effect, with allogeneic SCT. There is consensus that SCT should be offered to patients with high-risk or refractory AML, and to all children with relapsed AML in second complete remission [47]. According to the latest guidelines, MRD is monitored routinely, especially because high levels of MRD prior to SCT have been associated with poorer outcome [48].

New Agents

One of the main reasons behind improvement in survival rates in the last three decades was intensification of the conventional cytotoxic chemotherapies. But they have reached their limits, which has led to the realization that less toxic and more effective therapies are needed. Recent advances in technology have helped us identify molecular and cytogenetic alterations, and novel therapies now specifically target these leukemogenic abnormalities. Several early-phase clinical trials have been already completed with promising results [49•].

The purine nucleoside analog cytarabine has long been the backbone of the conventional AML therapy. Its novel derivative, clofarabine, was designed to have increased efficacy, both via impairing DNA-synthesis and repair and

by inducing apoptosis via mitochondrial pathways [50]. It has been trialed as a single agent, in combination with liposomal daunorubicin, and with targeted therapeutic agents showing encouraging results [51–53].

Internal tandem duplication (ITD) of the fms-like tyrosine kinase 3 (FLT3) gene is a frequent molecular aberration in childhood AML and it increases with age. It results in a constitutive FLT3 signaling, which stimulates proliferation. First-generation FLT3 inhibitors (lestaurtinib and midostaurin) are non-selective compounds, while second-generation inhibitors like quizartinib have selectivity and increased potency for FLT3 [54]. All these agents are already in clinical trials in different stages of development. The best results are being achieved when they are used in combination with conventional chemotherapy. Sorafenib is a multi-kinase inhibitor, and has a strong activity against FLT3. It has been tested in combination with cytarabine, with clofarabine in relapsed/refractory AML [53], and with HSCT after the first remission in children with FTL3-ITD$^+$ AML [38].

Immunotherapy

Immunotherapy in AML is represented by the calicheamicin-conjugated CD33 antibody, gemtuzumab ozogamicin. The drug was used as monotherapy in relapsed/refractory AML, or it was combined with chemotherapy or HSCT, which resulted in the reduction of MRD [55]. Unfortunately, in 2010, the FDA withdrew marketing approval based on lack of benefit in relapsed AML, and increased induction mortality in adults. In spite of the confirmed survival benefit when added to the induction therapy regimen [56], it most likely will be difficult to use in children outside of clinical trials.

There are multiple promising agents, which have been already tested in adult studies, waiting to be included in pediatric trials, including aurora kinase inhibitors, aminopeptidase inhibitors, c-KIT inhibitors, epigenetic therapies, and MEK inhibitors [47].

Special Patient Groups

Acute Promyelocytic Leukemia (APL)

Acute promyelocytic leukemia represents a special patient group. It is characterized by the chromosomal rearrangement t(15;17)(q22;q21), which results in a product containing the retinoic acid receptor-α, which responds to ATRA. APL is a medical emergency because of the risk of hemorrhage secondary to DIC, so treatment needs to be initiated immediately. Standard care consists of an induction therapy with ATRA and anthracycline therapy, followed by an anthracycline-based consolidation therapy. One of the side effects of ATRA, especially with high WBC count, is APL differentiation syndrome with signs and symptoms of fever, weight gain, respiratory distress, and pleural and pericardial effusions. The combined use of ATRA and chemotherapy has helped to decrease the incidence of this feared adverse effect [57]. Maintenance therapy with ATRA using an intermittent dosing schedule has proven to be beneficial in this subtype of AML. Arsenic trioxide (ATO) is a promising agent in the management of relapsed APL [58], and has recently also been used in trials in newly diagnosed patients [59]. A possible synergistic effect was found when ATO and ATRA were combined, demonstrated by the significant shortening in the time to complete remission and decrease in the fusion transcripts detected by RT-PCR [60].

Down Syndrome

Another unique patient population is children with AML in Down syndrome and other genetic disorders. In Down syndrome, the leukemic blast originates from fetal liver hematopoiesis, and 5 % of the children have transient leukemia at birth [61]. In their first 4 years of life, 10–20 % of them will develop myeloid leukemia with megakaryoblastic features. The disease has a good prognosis, and intensity-reduced chemotherapy without SCT results in a survival rate over 85 % [62]. Children with congenital syndromes characterized by impaired DNA-repair or disturbed myelopoiesis are at an increased risk developing AML. The backbone of their therapy is less intensive chemotherapy followed by allo-SCT [63].

Therapy-Related AML/Myelodysplastic Syndromes

The development of AML or MDS following treatment with ionizing radiation or chemotherapy, particularly alkylating agents and topoisomerase inhibitors, is termed therapy-related (t-AML or t-MDS, respectively). The risk of t-AML/t-MDS is regimen-dependent and related to the cumulative doses of chemotherapy agents received, as well as the dose and field of radiation administered [64, 65]. Previously used protocols that employed high cumulative doses of either epipodophyllotoxins (e.g., etoposide or teniposide) or alkylating agents (e.g., mechlorethamine, melphalan, busulfan, and cyclophosphamide) induced excessively high rates of t-AML/t-MDS that in some cases exceeded 10 % [65]. However, most current chemotherapy regimens used to treat childhood cancers have a cumulative incidence of t-AML/t-MDS not greater than 1–2 %. t-AML/t-MDS resulting from epipodophyllotoxins and other topoisomerase II inhibitors (e.g., anthracyclines) usually occur within 2 years of exposure and are

commonly associated with chromosome 11q23 abnormalities [66], although other subtypes of AML (e.g., APL) have been reported [67]. t-AML following exposure to alkylating agents or ionizing radiation often occurs 5–7 years later, and is commonly associated with deletions of chromosomes 5 and 7 or a monosomy [66].

Future improvements in the treatment of childhood AML will come from better risk-group stratification, development of novel therapeutic agents, and the revision of current protocols based on international multi-center trials. It is expected that high-quality cure can be achieved for most of the children with AML [68].

Supportive Care

As aggressive induction, post-remission consolidation, and maintenance therapy started improving the outcome in childhood AML, mortality related to treatment significantly increased. There was an urgent need to develop supportive care guidelines, and, since their institution, there has been a decrease in the number of deaths during the induction phase, when patients are the most susceptible to toxic side effects and infections [69].

1. Hyperleukocytosis is defined as an initial white blood cell count over 100 K/mm^3, and is considered a hematologic emergency. Patients with life-threatening coagulopathy and leukostasis are best treated with leukapheresis or double-volume exchange transfusion. This controlled cell reduction together with induction chemotherapy, enforced diuresis, and administration of rasburicase (recombinant urate oxidase) can prevent severe tumor lysis syndrome [70••, 71].
2. Acute and late cardiotoxicity is one of the main limiting factors of anthracycline use. Development of a liposomal formulation of daunorubicin allows us to administer higher cumulative doses [44]. Cardioprotection with dexrazoxane was a promising option to reduce toxicity, but it was shown to have a possible relationship with a higher rate of secondary malignancies, so the drug is being used with caution [72].
3. Increasing intensity of therapy has resulted in longer periods of severe neutropenia (absolute neutrophil count less than 500 cells/mm^3). During this time, fever may be the only indication of an underlying infection. The Infectious Disease Society of America updated its practice guidelines for the management of neutropenic fever and provided recommendations on risk stratification, and treatment algorithms [73]. Briefly, (1) risk assessment will decide if the patient needs to be hospitalized for IV antibiotic treatment, or can be managed as an outpatient, and will also determine the length of the treatment; (2) laboratory tests should include complete blood cell count with manual differentiation, complete metabolic panel, blood culture, culture specimens from other sites of suspected infection, and a chest x-ray for patients with respiratory symptoms; (3) the appropriate empiric antibiotic treatment is an anti-pseudomonal β-lactam agent, and addition of vancomycin or linezolid needs to be considered if there is a suspected MRSA or VRE infection; (4) antibiotic regimen should be modified based on microbiological data or with unresolved or new signs and symptoms; (5) duration of treatment is determined by the organism and site, or the duration of the neutropenia; and (6) antifungal therapy has to be considered if the fever is persistent or recurs after 4–7 days of antibiotic treatment. Antibiotic prophylaxis with fluoroquinolone might be considered for high-risk patients with prolonged neutropenia [74].
4. The incidence of invasive fungal infection in children with AML is about 20 % [69]. In adults, prophylactic posaconazole has significantly decreased the incidence of invasive aspergillosis, but unfortunately it is not licensed for children younger than 13 years [75]. Cotrimoxazole prophylaxis is routinely used to prevent Pneumocystis jirovecii infection.
5. Neutropenic enterocolitis or typhlitis is another severe complication induced by chemotherapy. It is characterized by fever, right lower quadrant tenderness, diarrhea, nausea, and emesis; symptoms usually improve once the neutropenia is resolved. It usually affects the ileocecal region confirmed by different radiologic imaging modalities. Optimal management is often supportive, while surgical treatment is rarely indicated [76].
6. The earlier-mentioned APL differentiation syndrome presents with fever, weight gain, pleural and pericardial effusion, and respiratory distress. Treatment includes intravenous dexamethasone, temporary discontinuation of ATRA, and supportive measures with diuretics, dialysis, or mechanical ventilation. Severe differentiation syndrome is associated with higher frequency of thrombosis, hepatotoxicity, hemorrhage, or death [77]. Pseudotumor cerebri is another well-known side effect of ATRA, occurring in about 10 % of children, and can be treated with steroids [78].
7. Red blood cell, platelet, and fresh frozen plasma transfusions are routinely used throughout the chemotherapy courses. Washed, leukocyte-reduced, irradiated, and CMV-negative products are preferred to reduce complications.

Better supportive care strategies played a central role in the improving outcome of childhood AML seen in the last

decades. Continuous monitoring and vigilance are crucial to prevent treatment related toxicities and death.

Monitoring Late Effects

Quality of life in long-term survivors of AML is just as important as overall survival rates. The treatment of AML is characterized by higher doses of anthracycline, shorter duration, less frequent use of CNS radiation, and more frequent use of allogeneic SCT. Therapeutic improvements are contributing to a growing number of adolescents and adults, who were successfully treated for childhood AML, but our data are still scarce on the incidence on late sequelae. Frequent follow-up with monitoring for signs and symptoms of relapse and late effects is a vital element in the management of childhood AML (Table 3) [79, 80].

Growth abnormalities are one of the most common late effects, with some requiring growth hormone substitution. CNS radiation often results in short stature and obesity [81], while total body radiation and SCT cause poor overall growth. Endocrinopathies including hypothyroidism, hypogonadism, and even infertility are another burden of aggressive treatment and radiation. There has been no increase in the incidence of birth defects or cancer in babies born to childhood AML survivors [79].

Table 3 End-of-treatment follow-up to monitor late effects in childhood AML

Exam	Frequency
History and physical exam	First year: monthly in the first 6 month, then every other month
	Second year: every 4 months
	Third year: every 6 months
	Annually after the 3rd year
Blood tests (CBC with manual differentiation)	First year: monthly in the first 6 month, then every other month
	Second year: every 4 months
	Third year: every 6 months
	Annually after the 3rd year
Bone marrow aspirate and biopsy	End of treatment and if clinically indicated
Lumbar puncture	End of treatment and if clinically indicated
Cardiac evaluation (EKG, echocardiogram)	End of treatment and 1–5 years depending on anthracycline dose received
	Down syndrome patients will need a cardiac evaluation annually for 5 years, then as needed
Endocrine evaluation	Annually

Cardiac dysfunction following high-dose anthracycline therapy occurs in less than 10 % of the survivors [79]. Serial ECGs and echocardiograms are necessary for early recognition of cardiomyopathy and heart failure. Less than 15 % of long-term survivors developed benign solid tumors, most of them requiring surgery [79]. Other late effects observed amongst these patients were cataracts, radiation-induced dental abnormalities, restrictive lung disease, and chronic GVHD.

During the intensive chemotherapy phases, almost all patients need blood transfusions. The number of patients becoming seropositive for hepatitis B and hepatitis C has been steadily decreasing over the last decade with the more precise screening techniques used for blood products.

Beside physical late effects, neurocognitive and psychosocial issues also deserve attention in follow-up care. Post-SCT, children may have academic difficulties at school with problems in learning, adjustment, and lower self-esteem.

However, the majority of AML survivors do well and appear to attain levels of education, marriage, and employment comparable to those reported in the general population [80].

Conclusion

The outcome of childhood AML has significantly improved since the very first treatment protocols were instituted in the early 1950s; however, we still have a long way to go. While overall survival is almost close to 70 %, the prognosis for certain subtypes such as M7 still remains dismal. Every decade has added something new to diagnosis and treatment, resulting in better survival rates. In the 1970s and 1980s, the introduction of anthracyclines and cytarabine was the first step towards meaningful survival, which was followed by the incorporation of allogeneic SCT in the 1990s. Advances in cytogenetics and molecular genetics in the early twenty-first century have resulted in better risk stratification and development of treatment protocols based on these risk factors. Meanwhile, supportive care and long-term follow-up continues to improve.

It is clear that the direction in which we are heading is individualized treatment. The extensive use of genetic mapping, the development of novel therapeutic agents based on the genomic alterations, and international clinical trials providing evidence-based medicine are key factors in the improvement of AML survival rates in children.

Disclosure Luca Szalontay and Aziza T Shad declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. National Program of Cancer Registries: 1999–2010 Incidence, WONDER On-line Database. United States Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2013.
2. Pui CH, Carroll WL, Meshinchi S, Arceci RJ. Biology, risk stratification, and therapy of pediatric acute leukemias: an update. J Clin Oncol. 2011;29:551–65.
3. Greaves M. Infection, immune responses and the aetiology of childhood leukemia. Nat Rev Cancer. 2006;6:193–203.
4. • Puumala SE, Ross JA, Aplenc R, Spector LG. Epidemiology of childhood acute myeloid leukemia. Pediatr Blood Cancer. 2013;60:728–33. *This paper identifies definitive and possible risk factors in developing childhood AML.*
5. • Khan I, Malinge S, Crispino JD. Myeloid leukemia in Down syndrome. Crit Rev Oncog. 2011;16:25–36. *A great review on myeloid leukemia in Down syndrome including the role of the genes on chromosome 21.*
6. Doll R, Wakeford R. Risk of childhood cancer from fetal irradiation. Br J Radiol. 1997;70:130–9.
7. Johnson KJ, Carozza SE, Chow EJ, Fox EE, Horel S, McLaughlin CC, Mueller BA, Puumala SE, Reynolds P, Von Behren J, Spector LG. Parental age and risk of childhood cancer: a pooled analysis. Epidemiology. 2009;20:475–83.
8. Reynolds P, Von Behren J, Elkin EP. Birth characteristics and leukemia in young children. Am J Epidemiol. 2002;155:603–13.
9. Perrillat F, Clavel J, Jaussent I, Baruchel A, Leverger G, Nelken B, Philippe N, Schaison G, Sommelet D, Vilmer E, Hémon D. Breast-feeding, fetal loss and childhood acute leukemia. Eur J Pediatr. 2002;161:235–7.
10. Caughey RW, Michels KB. Birth weight and childhood leukemia: a meta-analysis and review of the current evidence. Int J Cancer. 2009;124:2658–70.
11. Latino-Martel P, Chan DS, Druesne-Pecollo N, Barrandon E, Hercberg S, Norat T. Maternal alcohol consumption during pregnancy and risk of childhood leukemia: systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2010;19:1238–60.
12. Wigle DT, Turner MC, Krewski D. A systematic review and meta-analysis of childhood leukemia and parental occupational pesticide exposure. Environ Health Perspect. 2009;117:1505–13.
13. Kwan M, Buffler P, Abrams B, Kiley VA. Breastfeeding and the risk of childhood leukemia: a meta-analysis. Public Health Rep. 2004;119:521–35.
14. Magnani C, Pastore G, Luzzatto L, Terracini B. Parental occupation and other environmental factors in the etiology of leukemias and non-Hodgkin's lymphomas in childhood: a case–control study. Tumori. 1990;76:413–9.
15. Rudant J, Menegaux F, Leverger G, Baruchel A, Lambilliotte A, Bertrand Y, Patte C, Pacquement H, Vérité C, Robert A, Michel G, Margueritte G, Gandemer V, Hémon D, Clavel J. Childhood hematopoietic malignancies and parental use of tobacco and alcohol: the ESCALE study (SFCE). Cancer Causes Control. 2008;19:1277–90.
16. Kaatch P, Scheidemann-Wesp U, Schuz J. Maternal use of antibiotics and cancer in the offspring: results of a case–control study in Germany. Cancer Causes Control. 2010;21:1335–45.
17. Spector LG, Xie Y, Robison LL, Heerema NA, Hilden JM, Lange B, Felix CA, Davies SM, Slavin J, Potter JD, Blair CK, Reaman GH, Ross JA. Maternal diet and infant leukemia: the DNA topoisomerase II inhibitor hypothesis: a report from the Children's Oncology Group. Cancer Epidemiol Biomarkers Prev. 2005;14:651–5.
18. Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. Blood. 2002;100:02–2292.
19. Hoffman R, Benz EJ, Silberstein LE, Heslop HE, Weitz JI, Anastazi J. Hematology: Basic principles and practice. 6th ed. Philadelphia: Churchill Livingstone/Elsevier; 2012.
20. Hasle H, Niemeyer CM, Chessells JM, et al. A pediatric approach to the WHO classification of myelodysplastic and myeloproliferative diseases. Leukemia. 2003;17(2):277–82.
21. Swerdlow SH, Campo E, Harris NL, et al., editors. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon: International Agency for Research on Cancer; 2008.
22. Jaffe ES, Harris NL, Stein H, et al. Pathology and genetics of tumours of haematopoietic and lymphoid tissues. Lyon: IARC Press; 2001 World Health Organization Classification of Tumours, 3.
23. Chessells JM, Harrison CJ, Kempski H, Webb DK, Wheatley K, Hann IM, Stevens RF, Harrison G, Gibson BE. Clinical features, cytogenetics and outcome in acute lymphoblastic and myeloid leukaemia of infancy: report from the MRC Childhood Leukaemia working party. Leukemia. 2002;16:776–84.
24. Rubnitz JE, Lensing S, Razzouk BI, Pounds S, Pui CH, Ribeiro RC. Effect of race on outcome of white and black children with acute myeloid leukemia: the St. Jude experience. Pediatr Blood Cancer. 2007;48:10–5.
25. Davies SM, Robison LL, Buckley JD, Tjoa T, Woods WG, Radloff GA, Ross JA, Perentesis JP. Glutathione S-transferase polymorphisms and outcome of chemotherapy in childhood acute myeloid leukemia. J Clin Oncol. 2001;19:1279–87.
26. Lange BJ, Gerbing RB, Feusner J, Skolnik J, Sacks N, Smith FO, Alonzo TA. Mortality in overweight and underweight children with acute myeloid leukemia. JAMA. 2005;293:203–11.
27. Wheatley K, Burnett AK, Goldstone AH, Gray RG, Hann IM, Harrison CJ, Rees JK, Stevens RF, Walker H. A simple, robust, validated and highly predictive index for the determination of risk-directed therapy in acute myeloid leukaemia derived from the MRC AML 10 trial. United Kingdom Medical Research Council's Adult and Childhood Leukaemia Working Parties. Br J Haematol. 1999;107:69–79.
28. Langebrake C, Creutzig U, Dworzak M, Hrusak O, Mejstrikova E, Griesinger F, Zimmermann M, Reinhardt D. Residual disease monitoring in childhood acute myeloid leukemia by multiparameter flow cytometry: the MRD-AML-BFM Study Group. J Clin Oncol. 2006;24:3686–92.
29. Maurillo L, Buccisano F, Del Principe MI, Del Poeta G, Spagnoli A, Panetta P, Ammatuna E, Neri B, Ottaviani L, Sarlo C, Venditti D, Quaresima M, Cerretti R, Rizzo M, de Fabritiis P, Lo Coco F, Arcese W, Amadori S, Venditti A. Toward optimization of postremission therapy for residual disease-positive patients with acute myeloid leukemia. J Clin Oncol. 2008;26:4944–51.
30. de Bruijn MF, Speck NA. Core-binding factors in hematopoiesis and immune function. Oncogene. 2004;23:4238–48.
31. Strout MP, Marcucci G, Caligiuri MA, Bloomfield CD. Core-binding factor (CBF) and MLL-associated primary acute myeloid

leukemia: biology and clinical implications. Ann Hematol. 1999;78:251–64.
32. de Thé H, Chomienne C, Lanotte M, Degos L, Dejean A. The t(15;17) translocation of acute promyelocytic leukaemia fuses the retinoic acid receptor alpha gene to a novel transcribed locus. Nature. 1990;347:558–61.
33. Luna-Fineman S, Shannon KM, Lange BJ. Childhood monosomy 7: epidemiology, biology, and mechanistic implications. Blood. 1995;85:1985–99.
34. Giagounidis AA, Germing U, Aul C. Biological and prognostic significance of chromosome 5q deletions in myeloid malignancies. Clin Cancer Res. 2006;12:5–10.
35. Emerenciano M, Koifman S, Pombo-de-Oliveira MS. Acute leukemia in early childhood. Braz J Med Biol Res. 2007;40:749–60.
36. Mrozek K, Heerema NA, Bloomfield CD. Cytogenetics in acute leukemia. Blood Rev. 2004;18:115–36.
37. •• Braoudaki M, Tzortzatou-Stathopoulou. Clinical cytogenetics in pediatric acute leukemia: an update. Clin Lymphoma Myeloma Leuk. 2012;12:230–7. *Summarizes the significant risk-stratifying chromosomal aberrations and genetic mutations.*
38. Meshinchi S, Alonzo TA, Stirewalt DL, Zwaan M, Zimmerman M, Reinhardt D, Kaspers GJ, Heerema NA, Gerbing R, Lange BJ, Radich JP. Clinical implications of FLT3 mutations in pediatric AML. Blood. 2006;108:3654–61.
39. Hollink IH, Zwaan CM, Zimmermann M, Arentsen-Peters TC, Pieters R, Cloos J, Kaspers GJ, de Graaf SS, Harbott J, Creutzig U, Reinhardt D, van den Heuvel-Eibrink MM, Thiede C. Favorable prognostic impact of NPM1 gene mutations in childhood acute myeloid leukemia, with emphasis on cytogenetically normal AML. Leukemia. 2009;23:262–70.
40. Fröhling S, Schlenk RF, Stolze I, Bihlmayr J, Benner A, Kreitmeier S, Tobis K, Döhner H, Döhner K. CEBPA mutations in younger adults with acute myeloid leukemia and normal cytogenetics: prognostic relevance and analysis of cooperating mutations. J Clin Oncol. 2004;22:624–33.
41. • Radhi M, Meshinchi S, Gamis A. Prognostic factors in pediatric acute myeloid leukemia. Curr Hematol Malig Rep. 2010;5:200–6. *Provides a detailed analysis of most relevant factors associated with outcome in childhood AML.*
42. Kuerbitz SJ, Civin CI, Krischer JP, et al. Expression of myeloid-associated and lymphoid-associated cell-surface antigens in acute myeloid leukemia of childhood: a Pediatric Oncology Group study. J Clin Oncol. 1992;10(9):1419–29.
43. Woods WG, Kobrinsky N, Buckley JD, Lee JW, Sanders J, Neudorf S, Gold S, Barnard DR, DeSwarte J, Dusenbery K, Kalousek D, Arthur DC, Lange BJ. Timed-sequential induction therapy improves postremission outcome in acute myeloid leukemia: a report from the Children's Cancer Group. Blood. 1996;87:4979–89.
44. Creutzig U, Zimmermann M, Bourquin JP, Dworzak MN, Fleischhack G, Graf N, Klingebiel T, Kremens B, Lehrnbecher T, von Neuhoff C, Ritter J, Sander A, Schrauder A, von Stackelberg A, Starý J, Reinhardt D. Randomized trial comparing liposomal daunorubicin with idarubicin as induction for pediatric acute myeloid leukemia: results from Study AML-BFM 2004. Blood. 2013;122:37–43.
45. Bloomfield CD, Lawrence D, Byrd JC, Carroll A, Pettenati MJ, Tantravahi R, Patil SR, Davey FR, Berg DT, Schiffer CA, Arthur DC, Mayer RJ. Frequency of prolonged remission duration after high-dose cytarabine intensification in acute myeloid leukemia varies by cytogenetic subtype. Cancer Res. 1998;58:4173–9.
46. Wells RJ, Woods WG, Buckley JD, Odom LF, Benjamin D, Bernstein I, Betcher D, Feig S, Kim T, Ruymann F, et al. Treatment of newly diagnosed children and adolescents with acute myeloid leukemia: a Children's Cancer Group study. J Clin Oncol. 1994;12:2367–77.
47. Bonanomi S, Connor P, Webb D, Ancliff P, Amrolia P, Rao K, McCloskey D, Hemmatpour S, Goulden N, Veys P. Successful outcome of allo-SCT in high-risk pediatric AML using chemotherapy-only conditioning and post transplant immunotherapy. Bone Marrow Transplant. 2008;42:253–7.
48. Walter RB, Gooley TA, Wood BL, Milano F, Fang M, Sorror ML, Estey EH, Salter AI, Lansverk E, Chien JW, Gopal AK, Appelbaum FR, Pagel JM. Impact of pretransplantation minimal residual disease, as detected by multiparametric flow cytometry, on outcome of myeloablative hematopoietic cell transplantation for acute myeloid leukemia. J Clin Oncol. 2011;29:1190–7.
49. • Moore AS, Kearns PR, Knapper S, Pearson ADJ, Zwaan CM. Novel therapies for children with acute myeloid leukemia. Leukemia. 2013;27:1451–60. *This paper goes over the novel agents and protocols developed in the last decade and playing a significant role in the improved outcome of childhood AML.*
50. Bonate PL, Arthaud L, Cantrell WR Jr, Stephenson K, Secrist JA 3rd, Weitman S. Discovery and development of clofarabine: a nucleoside analogue for treating cancer. Nat Rev Drug Discov. 2006;5:855–63.
51. Jeha S, Razzouk B, Rytting M, Rheingold S, Albano E, Kadota R, Luchtman-Jones L, Bomgaars L, Gaynon P, Goldman S, Ritchey K, Arceci R, Altman A, Stine K, Steinherz L, Steinherz P. Phase II study of clofarabine in pediatric patients with refractory or relapsed acute myeloid leukemia. J Clin Oncol. 2009;27:4392–7.
52. Kearns P, Graham NJ, Cummins M, Gibson B, Graingr JD, Keenan R, et al. Phase I study of clofarabine and liposomal daunorubicin in childhood acute myeloid leukemia. J Clin Oncol. 2011;29(suppl):abstr 9521.
53. Inaba H, Rubnitz JE, Coustan-Smith E, Li L, Furmanski BD, Mascara GP, Heym KM, Christensen R, Onciu M, Shurtleff SA, Pounds SB, Pui CH, Ribeiro RC, Campana D, Baker SD. Phase I pharmacokinetic and pharmacodynamic study of the multikinase inhibitor sorafenib in combination with clofarabine and cytarabine in pediatric relapsed/refractory leukemia. J Clin Oncol. 2011;29:3293–300.
54. Knapper S. The clinical development of FLT3 inhibitors in acute myeloid leukemia. Expert Opin Investig Drugs. 2011;20:1377–95.
55. Aplenc R, Alonzo TA, Gerbing RB, Lange BJ, Hurwitz CA, Wells RJ, Bernstein I, Buckley P, Krimmel K, Smith FO, Sievers EL, Arceci RJ. Safety and efficacy of gemtuzumab ozogamicin in combination with chemotherapy for pediatric acute myeloid leukemia: a report from the Children's Oncology Group. J Clin Oncol. 2008;26:2390–5.
56. Reinhardt D, Diekamp S, Fleischhack G, Corbacioglu C, Jürgens H, Dworzak M, Kaspers G, Creutzig U, Zwaan CM. Gemtuzumab ozogamicin (Mylotarg) in children with refractory or relapsed acute myeloid leukemia. Onkologie. 2004;27:269–72.
57. Sanz MA, Grimwade D, Tallman MS, Lowenberg B, Fenaux P, Estey EH, Naoe T, Lengfelder E, Büchner T, Döhner H, Burnett AK, Lo-Coco F. Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. Blood. 2009;113:1875–91.
58. Niu C, Yan H, Yu T, et al. Studies on treatment of acute promyelocytic leukemia with arsenic trioxide: remission induction, follow-up, and molecular monitoring in 11 newly diagnosed and 47 relapsed acute promyelocytic leukemia patients. Blood. 1999;94:3315–24.
59. Mathews V, George B, Lakshmi KM, Viswabandya A, Bajel A, Balasubramanian P, Shaji RV, Srivastava VM, Srivastava A, Chandy M. Single-agent arsenic trioxide in the treatment of newly diagnosed acute promyelocytic leukemia: durable remissions with minimal toxicity. Blood. 2006;107:2627–32.
60. Shen ZX, Shi ZZ, Fang J, et al. All-trans retinoic acid/As_2O_3 combination yields a high quality remission and survival in newly

diagnosed acute promyelocytic leukemia. Proc Natl Acad Sci USA. 2004;101:5328–35.
61. Gamis AS, Alonzo TA, Gerbing RB, Hilden JM, Sorrell AD, Sharma M, Loew TW, Arceci RJ, Barnard D, Doyle J, Massey G, Perentesis J, Ravindranath Y, Taub J, Smith FO. Natural history of transient myeloproliferative disorder clinically diagnosed in Down syndrome neonates: a report from the Children's Oncology Group Study A2971. Blood. 2011;118:6752–9.
62. Klusmann JH, Creutzig U, Zimmermann M, Dworzak M, Jorch N, Langebrake C, Pekrun A, Macakova-Reinhardt K, Reinhardt D. Treatment and prognostic impact of transient leukemia in neonates with Down syndrome. Blood. 2008;111:2991–8.
63. Mehta PA, Ileri T, Harris RE, Williams DA, Mo J, Smolarek T, Auerbach AD, Kelly P, Davies SM. Chemotherapy for myeloid malignancy in children with Fanconi anemia. Pediatr Blood Cancer. 2007;115:138–45.
64. Leone G, Mele L, Pulsoni A, et al. The incidence of secondary leukemias. Haematologica. 1999;84(10):937–45.
65. Pui CH, Ribeiro RC, Hancock ML, et al. Acute myeloid leukemia in children treated with epipodophyllotoxins for acute lymphoblastic leukemia. N Engl J Med. 1991;325(24):1682–7.
66. Andersen MK, Johansson B, Larsen SO, et al. Chromosomal abnormalities in secondary MDS and AML. Relationship to drugs and radiation with specific emphasis on the balanced rearrangements. Haematologica. 1998;83(6):483–8.
67. Ogami A, Morimoto A, Hibi S, et al. Secondary acute promyelocytic leukemia following chemotherapy for non-Hodgkin's lymphoma in a child. J Pediatr Hematol Oncol. 2004;26(7):427–30.
68. Kaspers GJL, Zwaan CM. Pediatric acute myeloid leukemia: towards high-quality cure of all patients. Haematologica. 2007;92:1519–32.
69. Woods WG. Curing childhood acute myeloid leukemia (AML) at the half-way point: promises to keep and miles to go before we sleep. Pediatr Blood Cancer. 2006;46:565–9.
70. •• Creutzig U, van den Heuvel-Eibrink MM, Gibson B, Dworzak MN, Adachi S, de Bont E, Harbott J, Hasle H, Johnston D, Kinoshita A, Lehrnbecher T, Leverger G, Mejstrikova E, Meshinchi S, Pession A, Raimondi SC, Sung L, Stary J, Zwaan CM, Kaspers GJ, Reinhardt D. Diagnosis and management of acute myeloid leukemia in children and adolescents: recommendations from an international expert panel. Blood. 2012;120:3187–205. *This paper contains our knowledge on the latest diagnostic and therapeutic innovations on childhood acute leukemia while setting standards for diagnosis, response assessment, and treatment.*
71. Inaba H, Fan Y, Pounds S, Geiger TL, Rubnitz JE, Ribeiro RC, Pui CH, Razzouk BI. Clinical and biologic features and treatment outcome of children with newly diagnosed acute myeloid leukemia and hyperleukocytosis. Cancer. 2008;113:522–9.
72. US Food and Drug Administration. FDA statement on dexrazoxane. July 2011.
73. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2011;52:427–31.
74. Gafter-Gvili A, Fraser A, Paul M, et al. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. Cochrane Database Syst Rev. 2012;1:CD004386.
75. Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ, Helfgott D, Holowiecki J, Stockelberg D, Goh YT, Petrini M, Hardalo C, Suresh R, Angulo-Gonzalez D. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med. 2007;356:348–59.
76. Altinel E, Yarali N, Isik P, Bay A, Kara A, Tunc B. Typhlitis in acute childhood leukemia. Med Princ Pract. 2012;21:36–9.
77. Montesinos P, Bergua JM, Vellenga E, Rayón C, Parody R, de la Serna J, León A, Esteve J, Milone G, Debén G, Rivas C, González M, Tormo M, Díaz-Mediavilla J, González JD, Negri S, Amutio E, Brunet S, Lowenberg B, Sanz MA. Differentiation syndrome in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and anthracycline chemotherapy: characteristics, outcome, and prognostic factors. Blood. 2009;113:775–83.
78. Gregory J, Feusner J. Acute promyelocytic leukemia in childhood. Curr Oncol Rep. 2009;11:439–45.
79. Leung W, Hudson MM, Strickland DK, Phipps S, Srivastava DK, Ribeiro RC, Rubnitz JE, Sandlund JT, Kun LE, Bowman LC, Razzouk BI, Mathew P, Shearer P, Evans WE, Pui CH. Late effects of treatment in survivors of childhood acute myeloid leukemia. J Clin Oncol. 2000;18:3273–9.
80. Mulrooney DA, Dover DC, Li S, Yasui Y, Ness KK, Mertens AC, Neglia JP, Sklar CA, Robison LL, Davies SM. Twenty years of follow-up among survivors of childhood and young adult acute myeloid leukemia: a report from the Childhood Cancer Survivor Study. Cancer. 2008;112:2071–9.
81. Schell MJ, Ochs JJ, Schriock EA, Carter M. A method of predicting adult height and obesity in long-term survivors of childhood acute lymphoblastic leukemia. J Clin Oncol. 1992;10:128–33.