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REVIEW ARTICLE

Childhood acute myeloid leukaemia

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Abstract:
Over past decades, remarkable progress has been made in the treatment and in the understanding of the molecular pathogenesis of acute myeloid leukaemia (AML). At present, up to 65% of paediatric AML patients experience long term survival, owing to more effective use of antileukaemic therapy, improvements in supportive care and better risk stratification. However significant challenges remain including better methods to predict which patients can be cured and which one need more intensive therapy. This brief review describes well established biologic features and clinical parameters, risk stratifications, prognostic factors and current approach in treatment strategies.

***Keywords*:** acute myeloid leukaemia, children, diagnosis, therapy
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Inroduction

Acute myelogenous leukaemia (AML) is a clonal malignant disease of the bone marrow in which haematopoietic progenitor cells are arrested at an early stage of development due to acquired genetic alterations that lead to failure of differentiation and to overproliferation. Over past decades, remarkable progress has been made in the treatment and in the understanding of the molecular pathogenesis of acute myeloid leukaemia. At present, up to 65% of paediatric AML patients experience long term survival, owing to more effective use of antileukaemic therapy, improvements in supportive care and better risk stratification [1]. Further improvement in the outcome of childhood leukaemia will probably depend on the development of new therapeutic strategies [2].

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Epidemiology

Acute leukaemia represents 35% of all childhood cancer and AML constitutes 15% to 20% of acute leukaemias. The incidence of paediatric AML is estimated to be between five and seven cases per million persons per year [3]. AML rates are highest in the first two years of life and then decrease with a nadir at approximately 9 years of age, to slowly increase again during adolescence.

Etiology

Most children with *de novo* AML have no identifiable predisposing factor [3]. Epidemiological studies of acute leukaemias have examined a number of possible risk factors in order to determine the aetiology of leukaemia [4]. The exact aetiology of childhood leukaemia remains uncertain, but several risk factors have been associated with the development of AML [5]. Known risk factors include several congenital and genetic disorders such as Down syndrome, Fanconi anaemia, Bloom syndrome, Kostmann syndrome, Diamond–Blackfan syndrome, neurofibromatosis and others. These inherited diseases are characterized by defective DNA repair, chromosome aneuploidy or chromosomal abnormalities such as translocations. Ionizing radiation, some drugs, exposure to toxins such as alkylating agents, topoisomerase inhibitors and benzene, as well as conditions such as myelodisplastic syndromes and paroxysmal nocturnal hemoglobinuria are all implicated in a causal relationship with childhood leukaemia[3,6]. Secondary AML from epipodophyllotoxin

therapy (etoposide or teniposide) appears to be cumulative-dose-dependent and is usually associated with chromosomal translocations involving band 11q23 (*MLL* gene rearrangement), while alkylating agent-induced AML generally presents the loss of chromosome 5q or 7q [7].

Pathophysiology

The occurrence of AML involves a leukemogenic event that arises in the stem cell at different stages of differentiation, preserving the capacity for self-renewal while severely disrupting the normal haematopoietic cell lineage development [8-10]. Chromosomal abnormalities are detected in the majority of children with AML and shown to be involved in leukemogenesis but no single mutation is sufficient to cause AML [8,11]. A multiple-step mechanism of pathogenesis encompasses the synergistic action of class I mutations (that confer a proliferative advantage) and class II mutations (that prevent differentiation) within the same haematopoietic stem cell, leading to the transformation into acute leukaemia [8]. Mutations in a number of genes that regulate proliferation or survival in haematopoietic progenitors have been identified and include activating mutations in RAS family members, in receptor tyrosine kinases FLT3 and KIT, as well as BCR/ABL and TEL/PDGFβR gene fusions. Mutations in genes that impair differentiation and/or apoptosis include AML/ETO and PML/RARα fusions, mutations in CEBPA, CBF, HOX family members, as well as CBP/P300, co-activators of TIF, MLL rearrangements [3].

Classification, diagnosis and clinical presentation

The diagnosis of AML is established based on a combination of morphologic, immunophenotypic and cytogenetic findings. The FAB cooperative group proposed a classification system based primarily on morphologic and cytochemical features of the leukaemic cells. Subsequent revisions included immunophenotypic or electron-microscopic confirmation for the M0 and M7 subclasses. The FAB group recognizes eight subgroups of AML and also requires a minimum of 30% leukaemic cells in the bone marrow for the diagnosis of AML [12,13]. Modern advances in immunophenotyping, cytogenetic analyses and molecular genetic complement the FAB system and allow clinicians to distinguish between AML and ALL in more than 90% of cases. The World Health Organisation (WHO) has created a new classification on the basis of both morphologic and cytogenetic characteristics. The WHO system classifies AML into four groups: AML with recurrent cytogenetic translocations, AML with myelodysplasia-related features, therapy-related AML and myelodysplastic syndromes, and AML not otherwise specified. The threshold for the diagnosis of AML in the WHO classification has been reduced from 30% to 20% of blasts in the blood or bone marrow [14]. In addition, patients with clonal recurring cytogenetic abnormalities t(8;21)(q22;q22), inv(16)(p13;q22) or t(16;16)(p13;q22), and t(15;17)(p22;q12) are classified as having AML regardless of blast percentage.

Novel methods for molecular and biological characterisation of leukaemias such as gene expression profiling or intracellular phosphoprotein phosphorylation measured by multiplex flow cytometry will significantly improve the current classification [15,16].

Classically, children with acute leukaemia present with symptoms and signs related to infiltration of the bone marrow by leukaemic cells, such as fever, pallor and fatigue, cutaneus and mucosal bleeding, bone pain, anorexia and weight loss. Massive lymphadenopathy and hepatosplenomegaly are less common, except in infants with AML. Gingival hyperplasia is occasionally observed, while chloromas, solid tumours consisting of blasts, often occur in the cranium (figure 1). Central nervous system is involved at diagnosis in approximately 15% of cases, while testicular infiltration is rare. Disseminated intravascular coagulation (DIC) can be observed in all AML subtypes but is much more common in APL. Hyperleukocytosis is often seen in monocytic leukaemia and may present with signs of leukostasis, most often affecting the lungs and brain [3,17].

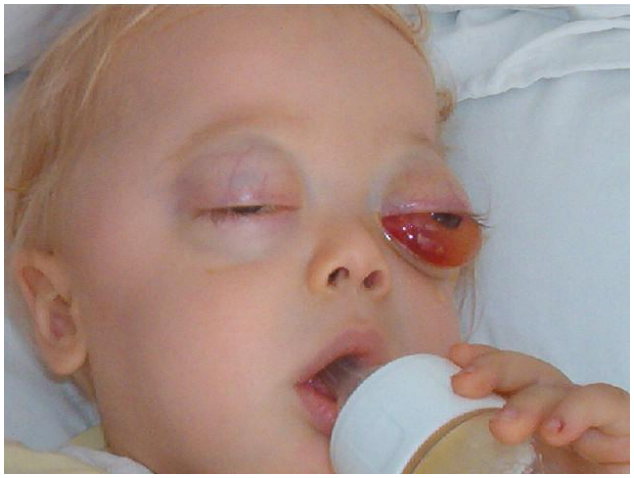

Figure 1. Photograph of the patient showing marked bilateral bulbar protrusion with chemosis of the left conjunctiva.

Prognostic factors and minimal residual disease

Prognostic factors in childhood AML include host factors, response to therapy and disease characteristics [18]. Host factors, such as gender, age, race and constitutional abnormalities, have been shown to be associated with

outcome in childhood AML. Age above 10 years is associated with poor outcome [3,18,19]. Female patients have a slightly better outcome than male patients. Black children have less favourable outcome than white children. Underweight and overweight patients have a greater risk of treatment-related death [18,20,21].

Response to therapy has been an important predictor of clinical outcome. Response to therapy can be measured by morphologic or cytogenetic bone marrow examination. Induction failure, morphologically apparent presence of disease (more than 15% blasts in blood or marrow), suggests a dismal outcome. Persistence of disease below the morphologically visible level, detection of minimal residual disease (MRD), has been evaluated as a prognostic factor in AML. The only AML subtype where MRD currently is of clinical use is APL. Detection of persistent t(15;17) fusion product by RT-PCR is significantly associated with high risk of relapse [22,23]. Presence of AML/ETO and CBFβ-MYH11 fusion transcripts is a negative predictor of outcome, but necessity for therapeutic intervention in order to improve the prognosis has yet to be determined [24,25]. Flow cytometric detection of MRD is correlated with shorter disease-free survival, but there is, as yet, no answer whether therapeutic intervention in MRD-positive patients would alter the overall clinical outcome [18,26,27].

Clinical characteristics, such as WBC at diagnosis, FAB classification, and cytogenetics have also been related to prognosis. WBC count greater than 100000/μL has been linked to unfavourable outcome. Megakaryoblastic leukaemia in non-Down syndrome patients has a significantly poorer outcome [3,28-30].

Among cytogenetic findings, t(8;21), inv(16) and t(15;17) are considered favourable, whereas a complex kariotype, -5, del(5q), -7 and abnormality of 3q are associated with poor outcome [18,31,32].

Among molecular abnormalities, a number of mutations are under investigation. Most studies of children with AML showed that FLT3/ITD mutations are associated with induction failure and poor outcome and FLT3/ITD mutations are found to be the strongest independent predictor of outcome [33-37]. Prognostic significance of c-kit mutations has yet to be established, although some reports suggest an association with poor outcome [38,39].

Other, novel molecular alterations that might have potential prognostic implications, such as mutation in the CCAT/enhancer binding protein (CEBPA-α), nucleophosmin (NPM), expression level of Wilms tumor (WT1) and BAALC (brain and acute leukemia, cytoplasmic) gene, expression of ERG and AF1 gene, VEGF (vascular endothelial growth factor) ligand expression, partial tandem duplication of MLL gene, gene expression profile and proteomic signature remain to be established in pediatric AML [3,18].

Treatment

The prognosis of children with AML has improved over past decades owing to aggressive induction therapy and aggressive post-remission therapy with an emphasis on high dose ARA/C-based chemotherapy, blood and marrow transplantation and supportive care [1,40]. Despite various treatment strategies of international cooperative groups, the results of induction, remission and overall survival are similar [3,41]. Therapy consists of a few intensive therapy blocks such as one or two induction blocks and consolidation blocks according to risk group classification. Risk stratification is not unique among various cooperative groups and is mainly based on cytogenetics and early response to treatment [1]. In the German BFM studies, two risk groups were identified [42]. The BFM favourable risk group includes children with FAB M1 or M2 with Auer rods, M3 and M4eo, with 5% or less leukaemic cells in the bone marrow on day 15 after induction chemotherapy, Down syndrome, and patients with t(8;21) and inv(16). The United Kingdom Medical Research Council trials have separated good, standard and poor risk groups based on karyotype and response to the first round of induction [43]. The good risk patients are children with karyotypes t(8;21), inv(16), t(15;17) or FAB M3 morphology irrespective of response to induction course 1. The poor risk patients have karyotypes -5, -7, del(5q), abn(3q) and complex karyotype or more than 15% bone marrow blasts after course 1 but without favourable genetics. The standard risk patients include those with neither favourable nor unfavourable cytogenetics and less than 15% bone marrow blasts after course 1.

All induction regimens are designed to provide fast clearance of blasts, which is crucial for successful remission induction. Traditionally, the combination of cytarabine and daunomycine forms the backbone of AML induction therapy. A third and/or fourth drug etoposide or 6-thioguanine is usually added to this combination [3,41]. Newer anthracycline therapy, such as idarubicine, has as yet not been demonstrated to be superior [3,43,44]. Further induction intensification is likely to be of no benefit in terms of overall survival due to prolonged pancytopoenia and therapy delay, although some CCG studies demonstrated higher complete remission rates with intensely timed induction therapy [45]. Patients with APL are treated with molecularly targeted therapy, *i.e.* induction regimens containing ATRA in combination with chemotherapy. ATRA has significantly reduced morbidity and mortality due to DIC resulting from cell lysis [46,47]. Children with Down syndrome are treated with less

intensive therapy because of a significant risk of early mortality and good response to induction therapy [48-50]. Consolidation therapy, as post-remission therapy, includes multiple intensive cytarabine blocks in combination with other cytostatic agents. The optimal number of consolidation chemotherapy cycles and optimal cumulative cytarabine dose have not been determined. However, three or four cycles are usually administered [1,3,17,48].

Many cooperative groups use intrathecal chemotherapy for CNS prophylaxis but not all of them do so, as CNS relapse is rare and high dose cytarabine does penetrate into the CNS. So far there is no clear association between prophylactic intrathecal therapy and CNS relapse [3,51,52,53]' Cranial irradiation is generally not used or is used only in patients with CNS leukaemia. Only the BFM group performs cranial irradiation as CNS prophylactic therapy [53].

Allogeneic haematopoietic stem cell transplantation (HSCT) has been extensively used in the treatment of paediatric AML in the first complete remission. Several studies have shown better survival in children with allogeneic HSCT using an HLA-matched related donor, compared to chemotherapy alone [1,48,54]. As only a limited number of patients has a suitable donor, and bearing in mind acute and late effects of HSCT, as well as the risk of treatment-related mortality and the improved outcome with chemotherapy, many paediatric oncologists now recommend chemotherapy alone, especially for children with favourable prognosis, such as APL, AML in Down syndrome or AML with t(8;21) or inv(16) [1,3,55,56]. Patients with factors of high risk are candidates for matched HSCT, although high risk patients are not well defined across different oncology groups. High risk features in most paediatric groups include monosomy 7, FLT3 internal tandem duplication and refractory disease after two induction courses.

Novel therapies

Novel therapeutic approaches based on improved understanding of cellular and molecular biology of leukaemia include the use of monoclonal antibodies (e.g. anti-CD33 immunotoxin, gemtuzumab ozogamycin, GO), inhibitors of kinases and other signalling molecules (e.g. FLT3 inhibitors such as lestauritinib, farnesyltransferase inhibitor, under investigation as a potential RAS targeted therapy, mTOR inhibitors), agents that target epigenetic regulation of gene expression (inhibitors of histone deacetylase, HDAC, such as valproic acid and methyltransferases such as azacitidine and decitabine) and proteasome inhibitors (e.g. bortezomib the molecular target of which is nuclear factor- B, NF-κB) [2]. Clofarabine, a second generation purine nucleoside, has shown efficacy in selected paediatric leukemias [57].

The development of new therapy modalities is likely to improve the outcome of patients with AML, but extensive prospective multi-centric trials are to be conducted in order to prove the efficacy of some or all of these emerging anti-leukaemic agents.

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