Diagnosis and management of childhood myelodysplastic syndrome and juvenile myelomonocytic leukemia

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ABSTRACT
Myelodysplastic and myeloproliferative disorders are rare in children. Contemporary classification includes three main groups: myelodysplastic syndrome (MDS), juvenile myelomonocytic leukemia (JMML), and the myeloid leukaemias of Down syndrome (ML-DS).

Separating MDS from AML may be a challenge and biological features rather than an arbitrary cut-off in blast count may be more important in distinguishing MDS from AML. The presence of genetic aberrations in the Ras signal transduction pathway in most patients with JMML has contributed major insight into the pathogenesis of JMML and facilitates the diagnosis. Hematopoietic stem cell transplantation is the treatment of choice for MDS and JMML. Reduced AML therapy is very successful in ML-DS. JMML in infants with Noonan syndrome often regresses spontaneously.

Introduction
Myelodysplastic and myeloproliferative disorders are rare in children and in many aspects different from the diseases in adults, requiring a pediatric approach to their diagnosis and management. Contemporary classification includes three main groups: myelodysplastic syndrome (MDS), juvenile myelomonocytic leukaemia (JMML), and the myeloid leukaemias of Down syndrome (ML-DS).

MDS is the only one of the main subgroups in children that has a partial overlap with the spectrum of disease in adults. However, there are significant differences between MDS in children and adults (Table 1). There is no sharp age distinction between adult and childhood MDS, and young adults with MDS share many of the features of childhood MDS and may benefit from similar management aiming at curing the patient with MDS, which is often not realistic in adults.

There are very few protocol-based studies on pediatric MDS. Most studies on MDS and JMML have been performed by the European Working Group of MDS in childhood (EWOG-MDS) (www.ewog-mds.org).

Classification
The WHO classification from 2001 recognized JMML, previously termed juvenile chronic myeloid leukaemia (JCML) or chronic myelomonocytic leukaemia (CMMML), as a separate entity, but the classification of MDS did not acknowledge the special features of MDS in children. A pediatric approach to the WHO classification separated myelodysplastic and myeloproliferative disorders in children into three main groups: JMML, MDS, and ML-DS (Table 2).

MDS is subdivided into refractory cytopenia of childhood (RCC), RAEB and RAEB-T. The change in nomenclature from RA to RCC reflects that anemia is not a prerequisite for the diagnosis. The revised WHO classification from 2008 keeps JMML separate and recognizes ML-DS and RCC as unique groups. Children with more than 2% blasts in the peripheral blood (PB) or 5% in the bone marrow (BM) are classified as RAEB using the same criteria as in adults. RAEB-T is kept for selected patients but it is emphasized that the diagnosis cannot rely on a single blast count but must be a comprehensive evaluation of clinical features, natural course, morphology, immunophenotype, and cytogenetics.

Epidemiology
Combined population-based data from Denmark and British Columbia (BC) in Canada showed an annual incidence of MDS of 1.8 and of JMML of 1.2 per million children, corresponding to a total of 6% of all hematological malignancies in children (Table 3). Data from the UK suggest a lower incidence of MDS of 0.8/million (Table 3).

The male/female distribution in pediatric MDS is equal, with a median age at presentation of 6.8 years. This is in contrast to the male predominance in JMML and a median age at presentation of 1.8 years. Down syndrome has been reported in 25% of those with a morphologic diagnosis of MDS but is no longer included in the
MDS occurs with increased frequency in inherited BM failure disorders. The risk is highest in Fanconi anemia, dyskeratosis congenita, and severe congenital neutropenia (SCN). Myeloid leukemia develops in a large fraction of patients with Fanconi anemia during childhood or early adult life. The risk varies according to genetic subgroup and associated abnormalities. The traits of Fanconi anemia may be subtle and the diagnosis should always be considered, even in adults. The cumulative incidence of MDS/AML in dyskeratosis congenita may be as high as reported in Fanconi anemia. Screening of telomere length and telomerase mutations in sibling donors is advised to prevent potentially fatal graft failure. The 15-year cumulative risk of MDS in SCN is 15%. The risk of MDS is highest in patients with a poor response to G-CSF.

### Myelodysplastic syndromes

#### Pathophysiology

MDS is a clonal disease arising in a progenitor cell restricted to myelopoiesis, erythropoiesis and megakaryopoiesis, but the initiating events have remained obscure, in children as in adults. Mutation in the tumor-suppressor gene TET2 was recently identified in 20% of adult patients with various myeloid disorders including MDS. However, TET2 mutations are not seen in JMML and have not yet been studied in pediatric MDS. Inherited disorders with DNA repair defects like Fanconi anemia or acquired mutations in genes maintaining genetic stability may result in a mutator phenotype predisposing to MDS. Subsequent events, e.g., mutations in proto-oncogenes like RAS, TP53, or WT1, and karyotypic changes like monosomy 7, may be part of a final common pathway of disease progression.

#### Clinical and laboratory features

The presenting features in almost all cases of MDS are those of pancytopenia. Single lineage cytopenia may occasionally be the presenting characteristic. In a few cases the cytopenia is an incidental finding during a routine work-up. Not all children with RCC have anemia, but macrocytosis (elevated MCV) is a characteristic finding. Fetal hemoglobin (HbF) is frequently moderately elevated. WBC is low to normal. Leukocytosis is generally not a feature of MDS, and in the case of increased WBC the diagnosis should be reconsidered. Some patients present with moderate hepatosplenomegaly but most have no organomegaly.

The BM cellularity varies but hypocellular RCC is more common in children than in adults. Both PB and BM display characteristic dysplastic features with megaloblastic erythropoiesis, bizarre small or unusual large megakaryocytes, and dysgranulopoiesis. The characteristic dysplastic features are suggestive of MDS but not diagnostic. Interobserver variation in the evaluation of dysplasia exists and centralized review is recommended.

#### Cytogenetics

An abnormal karyotype is found in 55% of children with advanced primary MDS and in 76% with secondary advanced MDS. Monosomy 7 is the most common...
mon cytogenetic abnormality in childhood MDS, seen in 25% of all patients. Trisomy 8 and trisomy 21 are the most common numerical abnormalities after monosomy 7. Constitutional trisomy 21 is clinically obvious when present, whereas constitutional trisomy 8 mosaicism may be clinically silent and should be tested for when trisomy 8 is found in the BM.

Monosomy 7, as the only cytogenetic aberration, is not an unfavorable feature in childhood MDS, whereas structural complex abnormalities are associated with a very poor outcome. Monosomy 7 is associated with a shorter time to progression in children with RCC. Favorable cytogenetic aberrations, identified in adults as -Y, 20q- and 5q-, are so infrequent in children that they are of no practical importance.

AFL specific translocations, e.g., t(8;21)(q22;q22), t(15;17)(q22;q12), or inv(16)(p13q22), should be considered as AML regardless of the blast count.

Immunophenotype

Flow cytometry immunophenotyping does not have the same diagnostic yield in MDS as in acute leukemia. Few data on immunophenotype characteristics of MDS in children have been reported. No consensus is available on standard protocols and techniques of flow cytometry in childhood MDS.

Refractory cytopenia versus aplastic anemia

A trephine biopsy is fundamental for the evaluation of a child with suspected aplastic anemia or MDS. Careful sequential morphologic studies are necessary to establish the correct diagnosis. The typical biopsy in MDS shows hypoplasia, scarcely scattered granulopoiesis, patchy islands of immature erythropoiesis, and micromegakaryocytes. Immunohistochemical studies may be helpful in demonstrating a high expression of p53 and a low expression of survivin in MDS, compared with patients with non-clonal BM failures.

Separating MDS from AML

AML is the major differential diagnosis of advanced MDS. There are significant differences in clinical features, cytogenetics and response to therapy between MDS and AML, reflecting fundamental biologic differences, thus making the morphologically based classification a surrogate marker for the distinction between biological entities. Blast count in a single specimen is insufficient to differentiate MDS from AML. Biological features rather than any arbitrary cut-off in blast count may be more important in distinguishing MDS from (chemosensitive) AML.

Prognosis and natural course

Children with RCC and RAEB or even RAEB-T may show a long and stable clinical course without treatment. Blood transfusions may only be required infrequently and severe infections are rarely seen. The condition may smolder with unchanged cytopenia for months or even years. In a series of 67 children with primary RCC, four died from complications of pancytopenia prior to therapy or progression and 20 progressed to more advanced MDS at a median of 1.7 years from presentation. RCC with monosomy 7 is associated with a higher risk of progression, and once progression has occurred, the outcome is inferior even after HSCT.

The International Prognostic Scoring System (IPSS) for MDS weighed data on BM blast count, cytopenia and cytogenetics and separated patients into four prognostic groups. Children show more poor risk features than adults, but only thrombocytopenia and BM blasts >5% correlate with poor survival in children. Overall the IPSS provides little diagnostic information in children but identifies a very small group (7%) of the patients with low-risk disease and a very favorable outcome.

Adolescence and complex cytogenetics are associated with a poorer outcome.

Treatment

Myeloablative therapy is the only treatment option with a realistic curative potential. Immunosuppressive therapy with antithymocyte globulin and cyclosporine in children with hypoplastic RCC results in complete or partial response in 70%, with overall and failure-free survival rates at 3 years of 90% and 60%, respectively. The long-term outcome of immunosuppressive therapy in MDS is not known.

AML type chemotherapy

Conventional intensive chemotherapy without HSCT is unlikely to eradicate the primitive pluripotent cells involved in MDS and associated with a complete remission rate of less than 60%, treatment-related mortality rate between 10 and 30%, many relapses, and an overall survival rate of less than 30%. However, a few studies have reported outcomes in MDS patients not significantly different from those in AML, especially in patients with RAEB-T or AML following MDS. Children with monosomy 7 diagnosed as AML have a poor response to induction chemotherapy, as in MDS patients, but in contrast to MDS those who responded well to chemotherapy had an outcome similar to other AML patients.

Hematopoietic allogeneic stem cell transplantation

HSCT is the therapy of choice for virtually all forms of MDS in childhood. Myeloablative therapy with busulfan, cyclophosphamide, and melphalan has cured more than half of children with MDS both after matched family donor (MFD) and matched unrelated donor (MUD) HSCT. Stage of disease has a significant effect on relapse and outcome following HSCT, with a very low relapse rate in RCC. In children with RCC and absence of profound cytopenia, postponement of HSCT with a watch-and-wait strategy may be justified, especially in patients with a normal karyotype. A fludarabine based reduced-intensity conditioning regimen in 19 children with RCC and normal karyotype resulted in an overall survival and DFS at 3 years of 64% and 74%, respectively, comparable to those of patients treated with myeloablative HSCT. It remains unknown whether AML-type induction chemotherapy prior to HSCT for advanced MDS can reduce relapse and thus improve DFS. Data from EWOG-MDS on children with primary advanced MDS showed no benefit of intensive AML-type therapy preceding HSCT. Small series of patients transplanted as
first line therapy have shown survival of 65-70%.\textsuperscript{35,45} Considering the significant morbidity and mortality of induction chemotherapy and the high rate of TRM following HSCT, highest in adolescents,\textsuperscript{36} most children with MDS may benefit from HSCT as first line therapy, sparing the toxicity related to induction chemotherapy. Children without a matched donor and progressive disease should be considered for haploidentical HSCT.\textsuperscript{46}

Relapse following HSCT is associated with a very grave outcome. Successful withdrawal of immunosuppressive therapy and donor leukocyte infusions in early relapse have occasionally been reported.\textsuperscript{46-49}

**Myeloid leukemia and Down syndrome**

Individuals with Down syndrome (DS) have a more than 150-fold increased risk of myeloid leukemia during the first five years of life.\textsuperscript{44} The recognition of the unique biological features of the GATA1 mutated myeloid malignancy has resulted in consensus about the term myeloid leukemia of Down syndrome (ML-DS),\textsuperscript{1,10} and it is no longer relevant to talk about MDS or AML in young children with DS. The rare occurrence of myeloid leukemia in older DS children (4 years or older) may be different from ML-DS being GATA1 negative and a higher risk of relapse.\textsuperscript{49,51}

**Transient abnormal myelopoiesis**

Increased WBC with circulating megakaryoblasts, often accompanied by anemia and thrombocytopenia, may be seen in up to 10% of newborns with DS.\textsuperscript{4} The percentage of blasts is often higher in blood than in BM. The condition is referred to as transient abnormal myelopoiesis (TAM), transient leukemic reaction, or transient myeloproliferative disorder. The presentation is indistinguishable from leukemia and some have therefore favored the name transient leukemia.\textsuperscript{52-53}

Generally no chemotherapy is indicated in TAM; however, in those with progressive hepatic or pulmonary problems or a very high WBC, a short course of low-dose cytarabine may be very effective.\textsuperscript{4} ML-DS develops 1-3 years later in about 20% of those who have recovered from TAM. The risk is higher in those with acquired clonal cytogenetic abnormalities\textsuperscript{50} or persistently elevated WT1 expression.\textsuperscript{51}

**Pathobiology**

Leukemia in children with trisomy 21 mosaicism selectively involves the trisomic cells, indicating that the additional chromosome 21 is the first hit in the multistep process leading to leukemia. Patients with TAM and ML-DS have an acquired mutation in the GATA1 gene.\textsuperscript{52} The GATA1 gene encodes a transcription factor essential for the normal erythroid and megakaryocytic differentiation, in accordance with the selective involvement of these two lineages in ML-DS.\textsuperscript{49}

**Clinical and laboratory features**

Isolated thrombocytopenia is often the presenting feature of ML-DS. Platelet count and WBC are lower at diagnosis than in non-DS patients, in contrast to the very high WBC seen in TAM. In most cases the blast cells have morphologic and antigen features of megakaryoblasts, although other morphological variations may occur. Many patients have a relatively indolent course, characterized by a period of thrombocytopenia and dysplasia, with relatively few blasts in the BM.

**Cytogenetics**

Numerical aberrations, mainly trisomy 8 and an extra chromosome 21 (tetrasomy 21), are the most common acquired cytogenetic abnormalities.\textsuperscript{60} The recurrent structural aberrations seen in AML are not found in ML-DS.

**Treatment**

In contrast to TAM, ML-DS is fatal if untreated but responds well to AML treatment, with a very favorable outcome. ML-DS cells with GATA1 mutation are very responsive to cytarabine and anthracyclines.\textsuperscript{61-62} Several groups have reported long-term survival in DS patients well above 80%.\textsuperscript{63-65} DS children are at a low risk for relapse and due to the high risk for treatment related toxicity, they benefit from less time-intensive therapy, allowing recovery prior to initiation of the next chemotherapeutic course.\textsuperscript{66,67}

**Juvenile myelomonocytic leukemia**

JMML is a unique pediatric disorder, the pediatric equivalent of what the FAB group termed CML. JMML was previously named juvenile chronic myeloid leukaemia (JCML), recognizing the distinction from CML occurring in older children and adults.

**Clinical and laboratory features**

Patients present with pallor, fever, infection, bleeding or symptoms from the organomegaly.\textsuperscript{15} Elevated WBC with absolute monocytes, anemia, and thrombocytopenia are almost universal. WBC at presentation exceeds 50 x 10^9/L in 30% and is above 100 x 10^9/L in 7%.\textsuperscript{68} Increased fetal hemoglobin (HbF) is a main characteristic of JMML, with the notable exception of those with monosomy 7, who almost all have normal HbF for their age.\textsuperscript{69}

**Cytogenetics**

Monosomy 7 (mostly as the sole abnormality) is present in 25-50% of JMML, 10% have other aberrations, and 60% show a normal karyotype.\textsuperscript{15} Data from the EWOG-MDS did not show any major clinical differences between JMML in patients with and without -7.\textsuperscript{15}

**Differential diagnoses**

JMML may mimic infections and immunodeficiency, delaying the diagnosis. On the other hand infections,
inborn errors of metabolism and immunodeficiency may cause monocytosis and organomegaly and represent diagnostic pitfalls. A diagnosis of JMML, especially in infants, should therefore be made with caution. A period of observation is recommended in cases without clear-cut features. Several viral infections mimicking JMML have been reported.

The international consensus on current diagnostic criteria of JMML includes molecular genetics as a mandatory part of the work-up, as incorporated in the EWOG-MDS 2006 protocol (www.ewog-mds.org). Blood film appearance is characteristic and often more helpful in diagnostics than BM morphology, where monocytosis often is much more discrete.

Pathophysiology

In vitro studies indicating that a defect in the GM-CSF signal transduction pathway plays a major role in the pathogenesis of JMML led to studies of the Ras signal transduction pathway. Members of the Ras family of signalling proteins regulate cellular proliferation by cycling between an active guanosin triphosphate (GTP)-bound state (Ras-GTP) and an inactive guanosine diphosphate (Ras-GDP)-bound state. Ras point mutations causing high constitutive Ras-GTP levels are noted in 25% of JMML patients. Children with neurofibromatosis type 1 (NF1) have an increased risk of malignant myeloid disorders, especially JMML. About 15% of children with JMML carry the clinical diagnosis of NF1. The NF1 gene functions as a tumor-suppressor gene, and loss of the normal NF1 allele has been noted in leukemic cells of NF-1 patients, with loss of heterogeneity (LOH) as the second event. NF1 and RAS mutations are mutually exclusive in JMML patients, indicating that one abnormality is sufficient to activate Ras.

Recent studies of CBL in the subset of JMML patients without mutations in RAS or PTPN11 identified mutations in 40% corresponding to 10-15% of JMML patients overall and no CBL mutations in the JMML samples with known mutations in RAS or PTPN11. The identification of homozygous CBL mutations in JMML suggests that CBL is a new tumor suppressor gene and indicates that CBL may have a role in deregulating the Ras pathway in JMML. CBL mutations in JMML have so far all been germline mutations associated with developmental delay. With somatic PTPN11 mutations in 35%, RAS gene mutations in 25%, germline NF1 gene mutation in 10-15% and CBL mutation in another 10-15%, mutually exclusive abnormalities of the Ras signalling pathway are identified in 85% of the JMML patients.

Natural course and prognostic factors

JMML is in most cases a rapidly fatal disorder if left untreated. Low platelet count, age above 2 years, high hemoglobin F, and high BM blast count at diagnosis are the main factors predicting a short survival. Multivariate analysis demonstrates a presenting low platelet count as the strongest factor predicting a poor survival. Non-transplanted children presenting with a platelet count < 35 x 10^9/L have an almost 100% mortality within the first year from diagnosis. Blastic transformation is infrequent with JMML and most untreated patients die from organ failure due to infiltration of the leukemic cells.

The prognostic value of genetic subtype is not yet established. Gene expression may separate JMML into subgroups with distinct prognosis. A high-methylation phenotype characterizes an aggressive biologic variant and is an independent strong molecular predictor of relapse.

Infants with Noonan syndrome (NS) may show a JMML-like myeloproliferative disorder (NS/MPD) with spontaneous regression. NS/MPD is diagnosed during the first few months of life, often during the first weeks. In the majority the hematological abnormalities gradually resolve but normalization may take several months or even years, especially the monocytosis and splenomegaly, which may persist for several years.

NS/MPD has striking parallels with the transient leukemia/TAM of newborns with Down syndrome. Unlike the GATA1 mutation in TAM, the NS/MPD has no somatic molecular marker and there is no documented effective therapy in those NS patients with an aggressive course.

Following the identification of PTPN11 germline mutation in 50% of patients with NS, studies in non-NS JMML showed somatic PTPN11 mutations in 35%.

The PTPN11 mutations found in JMML have a stronger SHP-2 activation than the mutations in NS, whereas the mutations in NS/MPD have an intermediate gain of function effect. It is presumed that the strong activation resulting from the PTPN11 mutation in JMML is incompatible with life when occurring as a germline mutation.

Treatment

Intensive chemotherapy is mostly unsuccessful in JMML because of an increased risk of treatment-related death, a low rate of true remissions and long-term survival less than 10%. The evaluation of the efficacy of JMML therapy is hampered by the lack of uniform criteria of response and divergent responses in hepatosplenomegaly, white cell, and platelet count as well as the fact that about 20% of patients observed without therapy show response. Purine analogs, etoposide, and cytarabine as single agents are associated with the best response rates for white cell count and spleen size.

Busulfan-based myeloablative allogeneic SCT results in overall survival in more than half the patients after both family and unrelated donor HSCT or cord blood. Younger age at HSCT and male sex predict for improved survival. Disease recurrence remains the major cause of treatment failure. Reduced intensity and duration of GvHD prophylaxis may significantly contribute to successful leukemia control and both acute and chronic GvHD are associated with a lower risk of relapse.

Older age, female sex, increased percentage of HbF, and blast percentage in the BM above 20% predicted the occurrence of relapse in univariate analysis. Monosomy 7 is associated with an outcome comparable to or even better than that of patients with normal karyotype. Relapse occurs early, at a median of 2-4 months from
transplantation, and generally within the first year. Early detection of donor cells by increasing mixed chimerism may be successfully eradicated by reducing ongoing immunosuppressive therapy. Donor lymphocyte infusion (DLI) in JMML relapse is largely unsuccessful. A second or even a third transplantation gives a relatively high chance of survival.

References


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