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Myelodysplastic Syndromes in Children: Where Are We Today?

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ABSTRACT

Myelodysplastic syndromes (MDSs) and other myeloproliferative disorders (MPDs) are rare entities, particularly in children. The latest classification of MPDs separates them into 3 major groups: MDS, juvenile myelomonocytic leukemia, and Down syndrome–associated myeloid leukemia.

Although the blast count plays a central role in differentiating leukemias from MDSs, it is by no means sacrosanct; biological features as well as disease characteristics are also important considerations for diagnosis. Genetic alterations in MDSs have increasingly been noted in a majority of patients and when detected make diagnosis easy. Hematopoietic stem cell transplant is the treatment of choice, while newer agents have shown promise in adults and are presently in the advanced stages of clinical trials.

INTRODUCTION

Myelodysplastic syndromes (MDSs) are a heterogenous group of hemopoietic clonal disorders characterized by ineffective hemopoiesis and frequent evolution to leukemia. These disorders were earlier variously described as preleukemia or pre–acute lymphoblastic leukemia. They are largely diseases of the elderly and exhibit a dramatic increase in incidence with age.[1] However, in children, MDS is often seen in association with genetic disorders and inherited bone marrow failure syndromes.[2] Of concern is the fact that until recently, owing to a lack of consensus on criteria for diagnosing the disease in children, many patients with refractory anemia were not diagnosed earlier in the disease. As a result, some patients succumb to complications without a diagnosis. Alternatively, a few children with chronic unresponsive anemia die of frank leukemia subsequent to progression of the disease.

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EPIDEMIOLOGY

The estimated incidence of pediatric MDS in Europe and Canada varies from 1 to 4 cases per million per year[3,4] and is equal in males and females. The median age at presentation in children is 6.8 years.[5] MDS is strongly associated with congenital disorders and genetic syndromes that are evident in about 50% of pediatric patients. These include Down syndrome, trisomy 8 syndrome, Fanconi anemia, congenital neutropenia (Kostmann syndrome), Diamond Blackfan anemia, dyskeratosis congenita, neurofibromatosis type 1, and acquired aplastic anemia with previous myelosuppressive therapy.[2]

CLASSIFICATION

The classification and diagnostic criteria for MDS in children have been progressively simplified over the years. The initial 1982 French-American-British classification of MDS[6] (Table 1) in adults neither addressed the specific disease characteristics seen in children nor did it consider the frequent association of congenital anomalies in these patients. However, the classification did have some prognostic significance.

The 2001 World Health Organization (WHO) classification[7] incorporated both cell morphology and cytogenetics and reduced the bone marrow blast threshold for distinguishing acute myelogenous leukemia (AML) from MDS from 30% to 20%. However, the classification was based on reviews of adult patients and gave importance to the refractory anemia with ring sideroblasts (RARS) subtype and the unique 5q- syndrome. Both are extremely uncommon in children. In addition, the classification did not adequately consider the unique features of Down syndrome associated with myeloid leukemia (ML-DS).

The WHO pediatric modification (2003)[8] separated the myeloproliferative disorders (MPDs) into 3 groups: MDS, juvenile myelomonocytic leukemia

Table 1. French-American-British Classification of Myelodysplastic Syndromes (1982)

1.	Refractory anemia
2.	Refractory anemia with ring sideroblasts
3.	Refractory anemia with excess blasts
4.	Refractory anemia with excess blasts in transformation
5.	Myelomonocytic leukemia

(JMML), and Down syndrome diseases. The MDSs were further subdivided into refractory cytopenia, refractory anemia with excess blasts (RAEB), and refractory anemia with excess blasts in transformation (RAEB-T). The RARS subgroup, primarily noted in adults, is extremely uncommon in children with MDS and was excluded in this classification. This classification applies to both primary (de novo) and secondary MDS, reflects that anemia is not essential for diagnosis, and applies to more than 95% of all childhood MDS patients.

The revised WHO (2008) classification [9] (Table 2) has a separate section on childhood MDS, further separates JMML, and recognizes ML-DS as a distinct group of disorders. The 2008 update also defines precisely the criteria for accurately defining refractory cytopenia of childhood (RCC). Children with $<2\%$ blasts in the blood, $<5\%$ blasts in the marrow, and persistent cytopenias associated with dysplasia in at least 2 cell lineages are included in this group. The bone marrow of these children is often hypocellular with no MDS-related cytogenetic abnormalities present. Children with 2%-4% blasts in the blood—even if the blast percentage in the bone marrow is $<5\%$ (indicating RAEB-1)—and with 5%-19% blasts in the peripheral blood or 10%-19% blasts in the bone marrow are classified in the highest grade of the WHO classification, RAEB-2.[10]

A retrospective comparison of the WHO classification (2003) and the pediatric WHO adaptation (2008) for MDS/MPD has shown that the latter classification is better able to effectively categorize childhood MDS than the more general WHO classification and that children meeting the poor prognosis criteria in this system are more likely to progress to AML or death.[11] Presently, the pediatric WHO adaptation (2008) is being used worldwide and applies to more than 99% of all childhood MPD cases.

PATHOPHYSIOLOGY

MDS, a clonal disease arising in a progenitor cell restricted to the myeloid, erythroid, or megakaryocytic series, causes serious disturbances in the normal maturation of these cells. About 30% of all children with MDS have a known constitutional disorder. Many others may also have unrecognized alterations in their

Table 2. Revised World Health Organization Classification of Childhood Myelodysplastic Syndromes (2008)

Myelodysplastic Syndromes
Refractory cytopenia (blood blasts $<2\%$, bone marrow blasts $<5\%$)
Refractory anemia with excessive blasts (blood blasts $>2\%$, bone marrow blasts 5%-19%)
Refractory anemia with excess blasts in transformation (bone marrow blasts 20%-29%) or acute myelogenous leukemia with MDS-related changes (peripheral blood or blood blasts $>20\%$)
Myelodysplastic/Myeloproliferative Disease
Juvenile myelomonocytic leukemia
Down Syndrome Disease
Transient abnormal myelopoiesis
Myeloid leukemia of Down syndrome

genotype that may predispose them to the disease.[12] Mutations of the recently identified tumor suppressor gene *TET2* are seen in 20% of all patients with MDS, while mutations in the *TP53* and *FMS* genes are found in 30% of adult MDS patients. Mutations in the protooncogenes such as *Ras*, *p53*, or *WT1* or karyotypic changes such as monosomy 7 are now considered part of the final pathway of disease evolution.[13]

CYTOGENETICS

Various studies have found an abnormal karyotype in 30%-50% of all children with MDS[14] and most of these are numerical anomalies of the chromosomes; fewer than 10% show structural abnormalities compared to the karyotype in patients with AML where structural abnormalities predominate. Monosomy 7 is the most common cytogenetic abnormality seen in childhood MDS cases and occurs in 30% of these patients.[14] Trisomies of chromosomes 8 and 21 are the next most common, may not be clinically obvious in some instances, and hence should be tested for in all cases fulfilling the diagnostic criteria of MDS.[15] The 5q- abnormality, so common in adults, is almost never seen in children.[16]

CLINICAL AND LABORATORY FEATURES

The clinical features of MDS include pancytopenia and the consequences of deficiencies of red blood cells, white blood cells, and platelets. Anemia, recurrent infections, and bleeding episodes are usually why patients seek medical attention. Single-lineage pancytopenia may be the presenting characteristic. However, not all children with refractory cytopenia have anemia. Indeed, isolated refractory anemia is uncommon in children with MDS, in whom

Table 3. Differences Between Myelodysplastic Syndromes (MDSs) in Adults and Children[20,21]

Criteria	Adult MDS	Childhood MDS
Incidence (million/yr)	>30	0.5-4
Refractory anemia with ring sideroblasts (RARS)	20%-25%	<2%
Cytogenetic aberrations (seen in)	30%-50%	50%
Mutation of *Ras* gene	Common	Rare
5q- aberration (seen in)	20%	<2%
Monosomy 7 abnormality (seen in)	8%-10%	30%
Aim of therapy	Usually palliative	Usually curative

the common presenting feature is usually thrombocytopenia and/or neutropenia, often accompanied by a hypocellular bone marrow. Hepatosplenomegaly is not a prerequisite for diagnosis. The white blood cell count is usually low, and if leukocytosis is persistently documented, the diagnosis of MDS must be reconsidered. In most cases, the peripheral smear, usually more contributory to the diagnosis than the marrow, reveals macrocytosis and thrombocytopenia. The bone marrow cellularity is variable but hypocellularity is more common in children than in adults. Both peripheral blood and bone marrow reveal characteristic dysplastic features with megaloblastic erythropoiesis, bizarre small or unusually large megakaryocytes, and dysgranulopoiesis. The abnormal localization of immature precursor (ALIP) cells in the bone marrow, characteristic in adults, is not essential for the diagnosis in children. Elevated levels of fetal hemoglobin are also commonly seen. Children with monosomy 7 MDS may have a skin rash similar to that of histiocytosis. Flow cytometry is not very specific for diagnosis but may be of benefit in identifying the disease, especially when bone marrow smears are of suboptimal quality.[17]

DIFFERENTIAL DIAGNOSIS

The two main diagnostic challenges in this disorder are to differentiate MDS with low blast counts from aplastic anemia (AA) and MDS with excess blasts from AML. In the former, a higher presenting mean corpuscular volume is suggestive of MDS and clonal hematopoiesis is confirmatory. Further, immunohistochemistry may also be useful. Children with MDS show a high expression of *p53* and low expression of survivin compared to children with AA.[18] MDS-related cytogenetic abnormalities, if present, also help to differentiate between RCC and AA or congenital bone marrow failure syndromes.

AML is a major differential diagnosis of MDS. A low total leukocyte count, multilineage dysplasia of the hematological cells, clonal hematopoiesis, and numerical rather than structural cytogenetic anomalies indicate MDS. A marrow blast count of <20% also indicates MDS, although biological features rather than a cutoff blast count value are more important. The presence of monosomy 7 strongly suggests MDS irrespective of clinical features and morphology. However, for patients with equivocal cytogenetics and marrow blast counts between 20% and 30%, clinicians may want to repeat the marrow test after 2-4 weeks and, if the blast count has increased to >30%, treat the child for AML. Children with clinical and morphological features of MDS but with the cytogenetic features typical of AML—t(8;21)(q22;q22)/t(15;17)(q22;q12)—must also be treated as having AML.[19]

Dysplasia in bone marrow cells may also occur in a variety of clinical situations with different etiologies, including infections, drug therapy, and chronic disease. Parvovirus, herpes virus, and human immunodeficiency virus infections, as well as deficiencies of B_{12} and copper, can give rise to similar cellular morphology. Metabolic disease and rheumatoid arthritis in older children may also confuse the inexperienced clinician. Rare congenital abnormalities, such as congenital dyserythropoietic anemia and Pearson syndrome, should also be excluded before diagnosing MDS.

MINIMUM DIAGNOSTIC CRITERIA FOR MDS

The minimum criteria for the diagnosis of MDS[4] should include at least 2 of the following:

- Sustained unexplained cytopenia
- Bilineage morphological myelodysplasia: at least 10% of the cells of at least 1 myeloid bone marrow cell line—ie, erythroid, granulocyte, or megakaryocyte—must show unequivocal dysplasia for the lineage to be considered dysplastic
- Acquired clonal cytogenetic abnormality
- Increased blasts (>5%)

Table 3 summarizes the differences between childhood and adult MDS.[20,21]

TREATMENT

Chemotherapy

Chemotherapy has a limited role in treating MDS. The remission rates with standard AML chemotherapy are, however, much lower in MDS than in AML, while resistant disease is more common. Fewer than 30% of MDS patients treated with chemotherapy survived for more than 3 years.[22] Children with monosomy 7 had better outcomes with chemotherapy than those without.[23] Low-dose cytarabine and oral mercaptopurine have been used to reduce the tumor load but rarely achieve remission.

Cytokines

Various trials with granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor, and interleukin 3 are in progress, some in association with low-dose cytarabine. G-CSF improves neutropenia, but concerns about accelerating progression to frank leukemia exist.[24] Differentiating agents such as cis-retinoic acid have been used in adults with some success, but they cannot be justified in childhood protocols where cure is the aim of management.

Bone Marrow Transplant

Bone marrow transplant (BMT) is currently the only curative option in childhood MDS. The 3-year disease-free survival rate is around 50% in most series.[25,26] Myeloablative therapy with busulfan, cyclophosphamide, and melphalan, followed by either matched family or matched unrelated donor BMT, is currently the treatment of choice for children with MDS.

The stage of the disease is vital to the outcome of BMT. Very low relapse rates are seen in children with refractory cytopenia. For children with RCC in whom profound cytopenia is absent and a normal karyotype is present, a period of watchful waiting before BMT is often justified.[27] Further, in the aforementioned population, BMT and a reduced-intensity conditioning regimen with fludarabine resulted in comparable outcomes to standard myeloablative BMT but with far less toxicity.[28]

Other Modalities

Immunosuppressive therapy with antithymocyte globulin and cyclosporine has been tried in a few children. Overall survival appears encouraging, although long-term results are not yet available. Because hypermethylation occurs in many children with MDS, methyltransferase inhibitor drugs such as azacitidine and decitabine appear to hold promise as an alternative therapy. However, the use of these drugs in children has yet to be studied. Not only do serious safety concerns exist, but also enhanced and extensive supportive care is often necessary in patients on therapy with these agents.[29] Additionally, the monoclonal antibody alemtuzumab has recently been tested in adult patients with promising results.[30] Trials in children must follow.

PROGNOSIS

The prognosis in children with MDS depends on the stage of the disease, the presence of congenital anomalies, and the karyotype. Monosomy 7 in children is not associated with poor prognosis, unlike in adults; however, a few studies have suggested that children with monosomy 7 progress earlier to AML. Children with RCC tend to have better outcomes than those without. In some cases, no treatment is advocated, especially in earlier stages of the disease.

CONCLUSION

MDS is a rare condition in childhood and often progresses to AML. The classification of the disease in childhood has been simplified and is applicable to more than 99% of cases of childhood MDS. Abnormal cytogenetics occurs frequently in these children and plays a role in response to therapy and outcome. BMT is currently the only viable therapy option and should be performed early in the illness, although newer agents are in the trial phase.

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