

## Pediatric MDS

Charlotte M. Niemeyer

Division of Pediatric Hematology and Oncology, Department of Pediatrics and Adolescent Medicine, University of Freiburg, Germany

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### Classification

Myelodysplastic syndromes (MDS) in children and adolescents are a heterogeneous group of rare disorders with an annual incidence of 3.6/million. It accounts for less than 5% of hematopoietic neoplasia in childhood. It has become evident that there are significant differences between MDS in children and adults. In children, refractory anemia (RA) with ringed sideroblasts and MDS associated with del(5q) chromosome are exceedingly rare. In addition, the importance of multilineage dysplasia in RA is unknown. Anemia is generally the main presenting symptom in adults with RA, but in childhood cases, neutropenia and thrombocytopenia are frequently observed. Therefore, "refractory cytopenia" (RC) was felt to be a more suitable term for pediatric MDS without excess blasts. Furthermore, in children there are no data to indicate whether a blast threshold of 20% is better than the traditional 30% to distinguish MDS from de novo AML. To accommodate these characteristics of pediatric MDS, a simple classification scheme based on morphological features and conforming with the WHO suggestions was proposed. It recognizes 3 diagnostic groups: RC (BM blasts <5%), RA with excess blasts (RAEB) (BM blasts 5-20%) and RAEB-T (BM blasts 20-30%). Auer rods are no longer a discriminator for classification. The dysplastic prodrome of AML in Down syndrome is classified within myeloid leukemia in Down syndrome and excluded from population-based studies of MDS.

MDS can arise in an otherwise healthy child, when it may be named "primary". It may also develop in a child with a known predisposing condition, when it is referred to as "secondary". Secondary MDS is seen in patients a) with

inherited bone marrow failure b) with acquired aplastic anemia c) with familial myeloid neoplasia, and d) after chemo- or radiation therapy. It is to be recognized, however, that children with so-called primary MDS may have an underlying yet unknown genetic defect predisposing them to MDS at young age.

The concept of monosomy 7 representing a distinct hematologic disorder has been abandoned. Monosomy 7 is the most common acquired abnormality noted in hematopoietic cells of children with MDS often occurs as a sole abnormality. The frequency of the different karyotypic alterations varies among MDS subtypes.

### Primary MDS

In primary MDS the main diagnostic challenges are to differentiate low grade MDS from aplastic anemia or congenital bone marrow failure syndrome, and high grade MDS from AML. Both issues will be dealt with in some details.

### Primary MDS without increase in blast count (refractory cytopenia)

MDS with less than 5% blasts in the bone marrow is particularly difficult to diagnose, because dysplasia of hematopoietic cells is frequently observed in association with infections, metabolic disorders, nutritional deficiencies, and a variety of other diseases. In the absence of a cytogenetic marker, the clinical course will have to be carefully evaluated before a diagnosis of RC can be established. RC is the most common subtype of childhood MDS accounting for about half of the cases.

Like in adults, MDS without increase in blast count in children and adolescents can present with cytopenia and a hyperplastic bone

marrow. In childhood, more than 50% of cases have, however, a decreased cell content in the bone marrow. This observation together with a low rate of leukemic transformation raises the question whether some of these children have an unrecognized congenital disorder with dysplasia and marrow failure rather than acquired MDS.

Karyotype is the most important factor for progression to advanced MDS and survival. The median time to progression for children with RC and monosomy 7 is less than 2 years. In contrast to monosomy 7, patients with trisomy 8 and other karyotypes may experience a long stable course of their disease.

HSCT from a MRD or MUD is the treatment of choice for patients with monosomy 7 early in the course of their disease. In view of the low transplant-related mortality observed in patients transplanted from a sibling donor, HSCT can also be recommended for all other patients if a suitable MRD is available. An expectant approach with careful observation may be reasonable for patients without a MRD in the absence of transfusion requirements, severe cytopenia or infections.

Therapies like hematopoietic growth factors, differentiating agents or hypomethylating agents are generally felt not to be indicated in children and adolescents with RA, because none of these approaches has been shown to prolong survival. Whether immunosuppression can result in sustained responses in a substantial number of children with RC is currently unknown.

#### **Primary MDS with increased blasts (refractory cytopenia with excess blasts and Excess blasts in transformation)**

There is consensus that the relationship between MDS and de novo AML is better defined by biological and clinical behavior than by blast count. Consequently, myeloid disease with low blast count and cytogenetic abnormalities typically associated with de novo AML is classified as AML. Because monosomy 7 is the only chromosomal abnormality strongly suggestive of MDS, children presenting with a low blast count and other chromosomal aberrations or normal karyotype have to be followed closely before a

diagnosis of MDS can be established. Disease with rapid increase in marrow blasts or organ infiltration should be considered de novo AML, which is by far the more common disorder. To allow for the interface between MDS and de novo AML, RAEB-T was retained in the pediatric classification until new data becomes available.

The most appropriate therapy for children with RAEB or RAEB-T is unknown. Although most investigators agree that HSCT can improve survival, the importance of cytoreductive therapy prior to grafting remains controversial. Data from the European Working Group of MDS in Childhood (EWOG-MDS) indicate that intensive chemotherapy prior to HSCT will not improve survival. In this study of advanced primary MDS, the probability of survival was about 50% and not influenced by marrow blast percentage at the time of transplantation. Hopefully, well controlled international clinical trials will resolve the issues on pre-HSCT remission induction therapy, optimal preparative regimen and stem cell source in the future.

#### **Secondary MDS**

##### **MDS in congenital bone marrow failure**

Among the congenital bone marrow failure disorders Fanconi anemia is most frequently followed by hematopoietic neoplasia. MDS or AML develop in as many as 50% of the patients with Fanconi anemia before the age of 40 years. Because most patients with Fanconi anemia have a dysplastic bone marrow and the definition of clonality is problematic, we currently choose to diagnose MDS in Fanconi anemia only in the presence of an increased blast count. Because the natural history and therapy differ between MDS in Fanconi anemia and other patients therapy results should be reported separately. For patients with congenital severe neutropenia (Kostmann syndrome) a crude rate of MDS/AML development of about 15% has been reported. In most SCN patients with MDS/AML acquired mutations in the G-CSF receptor are noted, and partial or complete loss of chromosome 7 is found in more than half. MDS may occur in as many as one third of those with Shwachman-Diamond syndrome,

but has only occasionally been described in patients with Diamond-Blackfan anemia. It is noteworthy, that not all bone marrow failure syndromes predispose to the development of MDS, e.g. patients with dyskeratosis congenita develop bone marrow failure in 95% of the cases but MDS is rare.

#### **MDS after acquired aplastic anemia**

MDS develops in 10-15% of those children with aplastic anemia not treated with HSCT. Most cases of MDS in children have been diagnosed within the first three years from presentation with aplastic anemia. The fast progression to MDS raises the question whether at least some of the patients had MDS from the beginning. One might also speculate that there is a biological overlap between aplastic anemia and hypoplastic RC.

#### **Familial MDS**

Familial occurrence of MDS, especially with -7/7q-, has been reported in a number of cases. Some families show discordance for -7; therefore, it is uncertain whether -7 per se increases the risk for familiar cases. The inherited predisposing locus in familial MDS or AML with -7/7q- may not be located on chromosome 7. Familial MDS does also occur without -7/7q-.

#### **Therapy-related MDS**

New intensive treatment protocols may lead to an increased risk of therapy-related diseases. Children with MDS secondary to chemo- or radiation therapy generally have a poor survival. Even if remission can be achieved with AML-type therapy, only very few patients remain disease free and only SCT offer cure in about a third of the patients.