Overview on Pediatric Myelodysplastic Syndrome: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Review Article

ABSTRACT

Myelodysplastic syndrome (MDS) is a set of clonal bone marrow diseases in children that are characterised by peripheral cytopenia, dysplastic alterations in the bone marrow, and inefficient hematopoiesis. MDS is uncommon in children, with just 1-4 occurrences per million children afflicted. Adults, particularly the elderly, are more susceptible to the disease. Some hereditary

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disorders, such as Fanconi's anaemia, Shwachman's, and Down's syndromes, are known to predispose children to developing MDS. JCML and monosomy 7 syndrome are the two most frequent paediatric MDS types, both of which affect children in their early years. Approximately 20% of juvenile myelodysplastic syndrome (MDS) cases are discovered by chance during normal laboratory testing or during the course of a suspected hereditary bone marrow failure (IBMF). Differentiating MDS with low blast numbers from aplastic anaemia (AA) and MDS with excess blasts from AML are the two key diagnostic issues in this condition. Bone marrow transplantation and stem cell transplantation is the treatment of choice in most cases. In this article we discuss the disease epidemiology, diagnosis, and treatment.

1. INTRODUCTION

MDS is a set of clonal bone marrow diseases in children that are characterised by peripheral cytopenia, dysplastic alterations in the bone marrow, and inefficient hematopoiesis. Because of their proclivity to convert into acute myeloid leukaemia, MDS diseases have been labeled "preleukemias" (AML). Because of this danger, bone marrow transplantation is the most usual treatment [1]. MDS, on the other hand, is frequently found in children in conjunction with genetic diseases and hereditary bone marrow failure syndromes. The fact that many individuals with refractory anaemia were not detected earlier in the disease until recently, due to a lack of consensus on criteria for identifying the condition in children, is cause for worry. As a result, some people die as a result of problems that go undiagnosed. Alternatively, a small number of infants with chronic unresponsive anaemia die of frank leukaemia as the condition progresses [2].

MDS is uncommon in children, with just 1-4 occurrences per million children afflicted. Adults, particularly the elderly, are more susceptible to the disease, which can take a variety of forms, ranging from an acute, swiftly lethal sickness to a chronic, indolent condition. MDS in children is a different disease from MDS in adults. Inherited bone marrow failure syndromes and other genetic abnormalities are more typically linked with childhood MDS. MDS is diagnosed by examining blood and bone marrow for cytogenetic abnormalities and blast proportion. Once the bone marrow blast percentage grows beyond 20-30%, MDS is regarded converted to AML [1]. Pediatric MDS has a dismal prognosis since cytotoxic chemotherapies, such as those used to treat acute leukaemia, are ineffective, leaving only bone marrow transplantation as a cure. Next-generation DNA sequencing has revealed a lot about adult MDS. Recurrent mutations in genes involved in modulating the expression (e.g., TET2, ASXL1, and DNMT3A) and RNA splicing (e.g., SF3B1 and U2AF1) were discovered in many investigations of adult MDS patients. However, mutations in these genes are rare in paediatric MDS research. This is not surprising given the well-established clinical and morphologic distinctions between paediatric and adult MDS (e.g., bone marrow hypocellularity is more prevalent in children), prompting the World Health Organization (WHO) to categorise MDS in adults and children separately [3].

Anemia is rarely the only symptom of childhood MDS; neutropenia or thrombocytopenia are frequently present as well. The 2008 WHO Classification of Childhood Myelodysplastic Syndromes, as detailed below, is used to categorise childhood MDS.

The following are the characteristics of MDSs [1]:

- RCC (refractory cytopenia of children) is defined as blood blasts of fewer than 2% and bone marrow blasts of less than 5%.
- RAEB stands for refractory anaemia with excessive blasts, which includes blood blasts of more than 2% and bone marrow blasts of 5-19%.
- Acute myelogenous leukaemia with MDS-related changes (peripheral blood or blood blast >20 percent) or refractory anaemia with excess blasts in transformation (RAEB-T): Bone marrow blasts 20-29 percent, or acute myelogenous leukaemia with MDS-related changes (peripheral blood or blood blast >20 percent).

The French-American-British (FAB) group made the first systematic attempt at morphological categorization of MDS. However, in children, the FAB categorization of MDS is only partially relevant. Some forms (refractory anaemia with ring sideroblasts and chronic myelomonocytic leukaemia) are exceedingly rare or nonexistent,

and other unusual paediatric illnesses, such as juvenile chronic myelogenous leukaemia (JCML) and the monosomy 7 syndrome, are not included. Furthermore, because there is some overlap between paediatric MDS and myeloproliferative disorders, and the variants affecting young children have distinct characteristics, there is still some confusion about the nosographical definition of childhood MDS, resulting in none of the proposed classifications being widely accepted and used [4].

Treatment for juvenile MDS varies depending on the severity of the disease; for the majority of these children, allogeneic hematopoietic stem cell transplantation (HSCT) with a Human Leukocyte antigen (HLA)-identical donor is the treatment of choice. HSCT is used to treat MDS with an excess of blasts or MDS caused by treatment. For RCC patients with monosomy 7 or a complicated karyotype, as well as those with severe neutropenia or transfusion dependency, HSCT is suggested. HSCT from an HLA-haploidentical relative combined with targeted graft modification allows for a reduction in transplant-related problems [5].

Secondary or chemotherapy-related myelody-splasia is becoming more common as the number of children cured of cancer continues to rise, and these illnesses pose a tough challenge for paediatric haematologists due to their poor response to chemotherapy [4].

Pediatric myelodysplastic syndromes (MDS) account for fewer than 5% of all cancers in children. An underlying genetic predisposition syndrome is seen in 30 to 45 percent of paediatric MDS patients. Following intense treatment for an unrelated illness, a proportion of individuals develop MDS/acute myeloid leukaemia (AML). A clear diagnosis of MDS is usually only possible after a thorough clinical and laboratory examination, which typically involves additional testing in a reference laboratory [6].

2. EPIDEMIOLOGY

In Europe and Canada, the estimated annual incidence of paediatric MDS ranges from 1 to 4 cases per million, and men and females are affected equally. In children, the median age at presentation is 6.8 years. MDS is intimately linked to congenital diseases and genetic abnormalities, which affect about half of all paediatric patients. Down syndrome, trisomy 8 syndrome, Fanconi anaemia, congenital

neutropenia (Kostmann syndrome), Diamond Blackfan anaemia, dyskeratosis congenita, neurofibromatosis type 1, and acquired aplastic anaemia with prior myelosuppressive treatment are among these conditions [2,7-10].

Germline mutations in transcription factors including GATA2, RUNX1, ETV6, or CEBPA are rapidly being acknowledged as a cause of familial MDS/AML. Germline GATA2 mutations, in particular, have been found in 7% of children with primary MDS. Other studies that used targeted sequencing to find pathogenic variations in children with idiopathic bone marrow failure or MDS revealed harmful variants in only around 10% of individuals, indicating the need for more extensive sequencing. Beyond transcription factors, such as ANKRD26 and SRP72, the list of genes with germline mutations in paediatric MDS has lately begun to grow [3,11-18].

Some hereditary disorders, such as Fanconi's anaemia, Shwachman's, and Down's syndromes, are known to predispose children to developing MDS. JCML and monosomy 7 syndrome are the two most frequent paediatric MDS types, both of which affect children in their early years. The spontaneous development of granulocyte-macrophage progenitors in JCML is characterised by a marked responsiveness to granulocyte-macrophage colony-stimulating factor. Massive organomegaly is seldom seen in the historically documented variations of MDS, and the clinical presentation mirrors that of other myeloproliferative diseases [4].

In children, refractory cytopenia (RC) is the most frequent MDS subtype, accounting for around half of all MDS cases. The link between MDS and increasing blast count and de novo AML is better described by biological and clinical aspects than by blast count, according to agreement. Because monosomy 7 is the only chromosomal anomaly clearly associated with MDS, children with a low blast count and other chromosomal abnormalities or a normal karyotype must be continuously monitored before an MDS diagnosis can be made. The incidence of secondary treatment-related MDS is growing as more children survive initial cancer with chemotherapy or radiation therapy [19].

3. EVALUATION AND DIAGNOSIS

Approximately 20% of juvenile myelodysplastic syndrome (MDS) cases are discovered by

chance during normal laboratory testing or during the course of a suspected hereditary bone marrow failure (IBMF) syndrome work-up. Patients with occult cytopenias are more likely to present with symptoms such as exhaustion, fever, infection, and/or bleeding. Bicytopenias, rather than solitary anaemia, are more common in juvenile patients with MDS than in adults. Physical examination results may be useful in many cases because of the relationship with IBMF syndromes, and may indicate skeletal, cutaneous, genitourinary, cardiovascular, and/or gastrointestinal problems [6].

Findings associated with bone marrow failure can be seen in children with myelodysplastic syndrome (MDS). The symptoms might be similar to those of acute leukaemia. The general look ranges from healthy to constitutionally wasting. Anemia can cause a pale complexion and weariness. Thrombocytopenia can cause bruising and petechiae. In juvenile myelomonocytic leukaemia, hepatosplenomegaly is the most common symptom (JMML). Lymphadenopathy is prevalent in 40-76 percent of JMML patients, although it is present in fewer than 10% of adult-type MDS patients. A generalised erythematous, maculopapular rash affects around 30% of JMML patients [1].

The larger proportion of foetal haemoglobin, the more extreme reduction in platelet count, and, in rare cases, the lack of the distinctive cytogenetic abnormalities in the monosomy 7 syndrome are used to differentiate it from JCML [4].

Because the presence of cytopenias and a hypocellular bone marrow is nonspecific, the following differential diagnostic considerations should be ruled out: autoimmune and other rheumatologic disorders, such as juvenile rheumatoid arthritis; mitochondrial disorders (eg, Pearson syndrome); various metabolic disorders; inherited anemias; and IBMF syndromes; viral infections; toxin or drug exposures; autoimmune and other rheumatologic disorders, such as juvenile rheumatoid arthritis; toxin or drug exposures; autoimmune and other rheumatologic disorders, such as juvenile rheumatoid arthritis [6].

Differentiating MDS with low blast numbers from aplastic anaemia (AA) and MDS with excess blasts from AML are the two key diagnostic issues in this condition. A higher presenting mean corpuscular volume is indicative of MDS in the former, while clonal hematopoiesis is confirming in the latter. Immunohistochemistry may also be beneficial. In comparison to children with AA, children with MDS have a high expression of p53 and a low expression of survivin. If present, MDS-related cytogenetic abnormalities aid in the differentiation of RCC from AA or congenital bone marrow failure disorders [2].

4. TREATMENT

Myeloablative therapy is the sole therapeutic option with a realistic curative promise since MDS is a clonal early stem-cell condition with relatively few leftover nonclonal stem cells. At three years, hematopoietic stem cell rescue regimens result in a 30-50 percent event-free survival (EFS) rate. Children who are young and get hematopoietic stem cell rescue shortly after diagnosis have better outcomes [1].

Chemotherapy plays a minor role in the treatment of MDS. In MDS, however, remission rates with normal AML treatment are substantially lower than in AML, and resistant disease is far more prevalent. Only about a third of MDS patients who were treated with chemotherapy lived for more than three years. Chemotherapy worked better for children with monosomy 7 than for those without. Although low-dose cytarabine and oral mercaptopurine have been utilised to lower tumour burden, remission is rare [2].

Patients with low erythropoietin levels benefit from the administration of erythropoietin. The Eastern Cooperative Group (ECOG) recently released findings from a phase III adult study that demonstrated that erythropoietin therapy enhanced overall survival in patients responding to erythropoiesis-stimulating drugs when compared to the best supportive care management. The Nordic and French MDS Study Groups have similarly verified this. G-CSF (granulocyte colony-stimulating factor) was also utilised, with a temporary improvement in neutropenia. The use of growth factors has been questioned because of the known enhanced reactivity of myelodysplastic clones to granulocyte-macrophage colony-stimulating factor (GM-CSF) and reports that G-CSF treatment in children with severe aplastic anaemia is linked to the development of MDS or AML later in life [1,20].

Bone marrow transplantation: In children MDS, bone marrow transplantation (BMT) is now the only curative treatment. In most studies, the 3-

year disease-free survival percentage is about 50%. The treatment of choice for children with MDS is presently myeloablative therapy with busulfan, cyclophosphamide, and melphalan, followed by either matched family or matched unrelated donor BMT. The stage of the disease has a big impact on BMT's success. Children with refractory cytopenia have very low recurrence rates. A period of attentive waiting before BMT is typically acceptable in infants with RCC who do not have substantial cytopenia and have a normal karyotype. Furthermore, BMT plus a reduced-intensity conditioning regimen with fludarabine had equivalent results to typical myeloablative BMT in the aforementioned group, but with significantly less toxicity [1,21-24].

stem cell transplantation, which is usually recommended to all patients with MDS with an excess of blasts, MDS related to previously administered chemoradiotherapy, and RCC associated with monosomy 7, complicated karyotype, severe neutropenia, or transfusion dependency. Immunosuppressive therapy may be an option for RCC patients with hypocellular bone marrow and no monosomy 7 or complex karyotype, albeit the response rate is lower than in severe aplastic anaemia, and a significant number of these patients will require HSCT for nonresponse or recurrence [25].

5. DISCUSSION

Various studies have discovered an abnormal karyotype in 30 percent to 50 percent of all children with MDS, with the majority of these being numerical chromosome anomalies; fewer than 10% of these children have structural abnormalities, compared to the karyotype in patients with AML, where structural abnormalities are more common. Monosomy is the most prevalent cytogenetic abnormality in children with MDS, occurring in 30 percent of cases. The next most prevalent trisomies are chromosomes 8 and 21, which may not be clinically visible in some cases but should be checked for in all patients meeting the diagnostic criteria for MDS. Children are nearly never affected by the 5q-abnormalities, which is so frequent in adults [26-39].

According to literature, Hispanic youngsters have a high rate of secondary AML. From 1989 to 1999, patients with t-MDS/AML treated under Children's Cancer Group protocol 2891 have male-to-female ratio (71 percent vs. 68 percent). A larger number of patients were

Hispanic, according to the research, although the link was not statistically significant. Hispanics made up 9% of the overall population in 1990 and 12.5 percent in 2000, according to the United States census. In the 1990 and 2000 censuses, Hispanics made up 25.5 percent and 32 percent of the population of Texas, respectively. The male and Hispanic majority cannot be explained entirely by bias in the referral population. Obesity or genetic polymorphisms influencing medication clearance, both of which are common in the Hispanic community, may predispose these juvenile patients to t-MDS/AML. Although the underlying mechanism is uncertain, a retrospective study of BMI and survival in Children's Cancer Group-2961 revealed a worse result due to greater treatment-related mortality among the obese [30-37].

6. CONCLUSION

Myelodysplastic syndrome (MDS) uncommon in children, with just 1-4 occurrences per million children afflicted. Adults, particularly the elderly, are more susceptible to the disease. Being such rare disease and with interference of it's clinical features with other similar condition, diagnosis is not that easy and thus using of differentiating diagnosis is important. The most effective treatment so far is bone marrow transplantation, stem cell transplantation can also be effective. There's also some conditions where administrating of erythropoietin or Granulocyte colony-stimulating factor (G-CSF) can be effective.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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