ABSTRACT

Myelodysplastic syndromes (MDS) are clonal disorders of the multipotent hematopoietic stem cell characterized by ineffective hematopoiesis and associated with marrow hypercellularity, increased intramedullary cell death and peripheral cytopenias of varying severity. Patients with myelodysplasia have a propensity (20% to 30% of cases) to undergo transformation into acute myeloid leukemia (AML), and a large body of evidence indicates that MDS represent steps in the multiphasic evolution of AML. Progression of the disease is characterized by expansion of the abnormal clone and inhibition of normal hematopoiesis leading to deterioration of the blood cell count and/or development of AML. MDS are relatively unusual in childhood, representing only 3% of pediatric hematological malignancies, although it has been reported that up to 17% of pediatric AML cases may have a previous myelodysplastic phase. The first systematic attempt at morphological classification of MDS was provided by the French-American-British (FAB) group. However, the FAB classification of MDS is only partially applicable in children. Some variants are extremely rare or absent (refractory anemia with ring sideroblasts and chronic myelomonocytic leukemia), and other peculiar pediatric disorders, represented by juvenile chronic myelogenous leukemia (JCML) and the monosomy 7 syndrome, are not included. Moreover, since there is a partial overlap between pediatric MDS and myeloproliferative disorders and the variants occurring in young children have rather specific features, some confusion still surrounds the nosographical definition of childhood MDS, so that none of the proposed classifications are widely accepted and used. Characteristically, some genetic conditions such as Fanconi’s anemia, Shwachman’s and Down’s syndromes predispose to the development of MDS in childhood. The most common variants of childhood MDS are represented by JCML and the monosomy 7 syndrome, both disorders typically occurring in young children. JCML is characterized by a spontaneous growth of granulocyte-macrophage progenitors that show a striking hypersensitivity to granulocyte-macrophage colony-stimulating factor. Clinical presentation resembles that of some myeloproliferative disorders, with massive organomegaly usually not observed in the classically reported variants of MDS. Clinical features of the monosomy 7 syndrome resemble those observed in JCML and a differential diagnosis between these two entities relies upon the higher percentage of fetal hemoglobin, the more pronounced decrease in platelet count and, in some cases, the lack of the peculiar cytogenetic abnormality in the latter. With the number of children being cured of cancer constantly rising, a significant increase in secondary or chemotherapy-related myelodysplasia is being observed, and these disorders represent a formidable challenge for pediatric hematologists due to their poor response to chemotherapy. As a matter of fact, owing to their biological heterogeneity and aggressive clinical course in childhood, all MDS variants pose serious difficulties for successful management. If a compatible donor is available, allogeneic bone marrow transplantation (BMT) becomes the treatment of choice and should be performed during the early stages of the disease. Supportive therapy, differentiative treatments and low-dose chemotherapy, while valuable alternative therapeutic options in adults, have limited application in pediatric patients. The role of intensive chemotherapy and autologous BMT has not yet been clearly defined, and the use of hematopoietic growth factors does not seem to have a significant influence on the natural history of the disease. In the future, new insights into the events leading to progressive genetic changes in the clonal population and into the molecular basis of these genetic lesions could result in interesting new therapeutic approaches directed either at the oncogenes involved in the pathogenesis of the disease, or at the cytokines and/or their receptors causing the abnormal differentiation and proliferation of the myelodysplastic clone.

Key words: myelodysplastic syndromes, bone marrow transplantation, monosomy 7, juvenile chronic myelogenous leukemia, oncogenes
Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal disorders involving the multipotent or pluripotent hemopoietic stem cell and are usually characterized by ineffective hematopoiesis with increased intramedullary cell death that determines peripheral blood cytopenia. Infection or bleeding due to marrow failure and a propensity (20% to 30% of cases) to undergo transformation into acute myeloid leukemia (AML) represent the main cause of death for these patients. In fact, a large body of evidence indicates that MDS represent steps in the multiphasic evolution of AML. Studies of clonality have shown a variable pattern of clonal proliferation in MDS: most of the patients studied demonstrated clonality limited to the granulocytic-monocytic series, but some possessed clonal pluripotent progenitors capable of both myeloid and lymphoid differentiation. This heterogeneity has also been observed in AML, thus supporting the preleukemic nature of MDS. In addition, patients with MDS have been found to carry the same molecular lesions observed in AML, in particular point mutations in cellular proto-oncogenes or genes relevant for cell proliferation and cell death (i.e. RAS genes, c-fms, p53 suppressor gene). Different combinations of these molecular lesions probably explain the variable clinical course of these patients.

MDS are typical disorders of the elderly, the reported median age at presentation being 60-65 years. Even though the precise frequency in pediatrics is still unclear, Blank and Lange suggested that up to 17% of pediatric AML cases have a preleukemic phase, and MDS seem to account for about 2-3% of childhood hematological malignancies. MDS can be primary or develop following exposure to myelotoxic agents. The incidence of MDS appears to be increasing with the use of intensive chemo-radiotherapy, which, though curing the majority of pediatric patients with cancer, may cause secondary or therapy-related MDS. An increasing number of secondary AML and MDS, most frequently in children previously treated for Hodgkin disease but also after other hematological and non-hematological malignancies, have recently been reported.

Our knowledge of the pathophysiological mechanism of MDS has improved considerably in recent years. Studies of G-6PD polymorphism in heterozygous females, DNA polymorphisms at X-linked loci, as well as cytogenetic analysis of bone marrow (BM) progenitor cells have made it clear that these disorders result from clonal expansion of a multipotent or pluripotent hemopoietic progenitor. Mounting evidence indicates that at least two steps are involved in the pathogenesis of MDS: an early step that leads to expansion of a genetically unstable stem cell clone and a later one, often characterized by the acquisition of chromosome aberrations, conferring some selective growth advantage. Factors including host susceptibility related to specific hereditary factors, age and exposure to leukemogenic agents (benzene, alkylating drugs and radiation) seem to play a major role in the early event by causing somatic mutations of growth regulatory genes, such as RAS genes and c-fms. However, activation of individual proto-oncogenes appears to be insufficient for conferring a malignant phenotype and at this stage the disease is often clinically silent. Additional events, namely chromosome abnormalities, reflecting the genetic instability of the affected clone, are necessary mediators of the neoplastic change. As mentioned above, different combinations of molecular lesions may also explain the variable clinical course and biological behavior of the disease in patients with identical MDS variants.

Classification of MDS in childhood

Due to their heterogeneity at presentation and in their natural history, in the past MDS were given various names, e.g. smoldering acute leukemia, preleukemic anemia, refractory anemia, refractory anemia with excess of myeloblasts, etc. In 1982, the French-American-British (FAB) Cooperative Group categorized MDS into five morphological subtypes: refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess of blasts (RAEB), RAEB in transformation to acute leukemia (RAEB-t) and chronic myelomonocytic leukemia (CMML), according to the criteria reported in Table 1.
years later, the Morphologic, Immunologic and Cytogenetic (MIC) Cooperative Study Group provided additional cytogenetic data that allowed further refinement. Several studies highlighted that the less aggressive subtypes, RA and RARS, are extremely rare in children, whereas the majority of children with MDS fall into the bad risk categories (RAEB, RAEB-t). Moreover, the applicability of the FAB classification to childhood MDS is not completely satisfactory or comprehensive of all disorders classically included in the group of pediatric myelodysplasias. In fact, the FAB classification does not include two of the most common variants of pediatric MDS described in the literature, namely juvenile chronic myelogenous leukemia (JCML) and the monosomy 7 syndrome, which share clinical and biological features found in both MDS and myeloproliferative disorders (MPD). Thus, it is clear that some overlap between MDS and MPD exists and this is particularly evident in childhood. On the basis of these considerations, a tentative and arbitrary classification of childhood MDS which includes the peculiar pediatric variants and thus implements the FAB classification is reported in Table 2.

**Juvenile chronic myelogenous leukemia**

JCML is considered to be the pediatric equivalent of adult CMML because it shares similar clinical and biological characteristics, as well as karyotype abnormalities. JCML is a rare hematopoietic malignancy of early childhood representing less than 2% of all childhood leukemias. A higher incidence of the disease in males and in patients with type 1 neurofibromatosis (NF-1) has been reported. At diagnosis, most of the patients are under two years of age and over 90% have not yet reached the age of four. Patients are often difficult to diagnose because of their clinical heterogeneity. Splenomegaly, hepatomegaly, generalized lymphadenopathy and skin manifestations (eczematous rash, xanthomata) are common clinical features. Leukemic infiltration of the lungs may determine a clinical picture characterized by cough, tachypnea and bronchospasm, with an interstitial radiological pattern.

<table>
<thead>
<tr>
<th>Peripheral blood blasts (%)</th>
<th>RA</th>
<th>RARS</th>
<th>RAEB</th>
<th>RAEB-t</th>
<th>CMML</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal marrow blasts (%)</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;5</td>
<td>5-20</td>
<td>5-20</td>
</tr>
<tr>
<td>Ringed sideroblasts &gt;15%</td>
<td>-</td>
<td>+</td>
<td>±</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Auer rods</td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Peripheral blood monocytosis</td>
<td>(&gt; 1 x 10^9/L)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

RAEB-t is diagnosed in the presence of i) Auer rods, ii) >5% blasts in the peripheral blood, or iii) 20-30% of blasts in the bone marrow.

Leukocytosis (usually under 100×10^9/L), monocytosis, anemia, variable normoblastemia and thrombocytopenia represent the peripheral blood pattern most frequently reported at the onset of the disease. Other laboratory findings include an increased synthesis of hemoglobin F (associated with reversion to fetal hematopoiesis), elevated serum levels of muramidase, vitamin B12, and serum IgG, IgA and IgM. The presence of autoantibodies is also common. Leukocyte alkaline phosphatase cannot be regarded as a specific marker of the disease since 60% of patients have a normal or even increased score. The Philadelphia chromosome is always absent, even though other chromosomal abnormalities have been reported in 18% of the cases described.

JCML is characterized by an aggressive clinical course and, even though patients rarely undergo transformation to a frank blast crisis, median survival time is less than 10 months from diagnosis. Variables demonstrated to be associated with a shorter survival are: age greater than two years at presentation, hepatomegaly, bleeding, thrombocytopenia, high counts of normoblasts and blast cells in the peripheral blood. In particular, children diagnosed before the age of two...
may have a more indolent course and a prolonged survival without intensive treatment. The response to agents employed for the treatment of adult type CML (busulfan, hydroxyurea and interferon-\(\alpha\)) is poor\(^3\) and even intensive combination chemotherapy has produced only suppression, but not eradication, of the malignant clone.\(^{33,34}\) Allogeneic bone marrow transplantation (BMT) appears to be the only curative strategy for the disease at this time.\(^{35}\) Sanders and colleagues\(^{35}\) reported that six out of 14 patients who received an allogeneic BMT (six from an HLA-identical sibling and eight from a partially-matched family donor) have remained in remission for as long as 11 years after transplantation.

Spontaneous growth of granulocyte-macrophage progenitors (CFU-GM) and inhibition of normal hematopoietic progenitors seems to represent the main pathogenetic mechanism of JCML. A number of in vitro studies aimed at elucidating the biological behavior of hematopoietic progenitors from JCML patients have found that: i) JCML CFU-GM can proliferate in semisolid cultures in the absence of added growth factors;\(^{36}\) ii) spontaneous CFU-GM growth depends on the presence of monocytes-macrophages since it can be suppressed by adherent cell depletion;\(^{37}\) iii) the spontaneous CFU-GM growth is determined by granulocyte-macrophage colony stimulating factor (GM-CSF) that acts as an autocrine-paracrine growth factor;\(^{38}\) iv) CFU-GM growth is attributable to a striking hypersensitivity of CFU-GM to GM-CSF and not to cytokine overproduction.\(^{39}\) The primary pathogenetic mechanism of JCML also seems to involve the autocrine production and release of tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)). In fact, TNF-\(\alpha\) plays a central role in determining the inhibition of normal hematopoiesis and directly determines the proliferation of malignant monocytes-macrophages and GM-CSF production. This, in turn, further promotes replication of GM-CSF hypersensitive cells, with interleukin-1 (IL-1) representing an important accessory factor that augments the effect of GM-CSF and TNF-\(\alpha\).\(^{40}\) Recently, we demonstrated that allogeneic BMT, which leads to the eradication of the malignant clone and its substitution with the normal hematopoiesis of the donor, interrupts the autocrine-paracrine loop of JCML cell replication and also brings about the disappearance of the growth-inhibitory effect of cytokines on normal hematopoiesis.\(^{41}\) The crucial role played by GM-CSF in the pathogenesis of JCML makes this cytokine and its receptor attractive therapeutic targets for receptor-specific monoclonal antibodies or growth factor analogues.

**Monosomy 7 syndrome**

Monosomy and partial deletion of chromosome 7 have been described in primary AML and MDS and, especially, in secondary or therapy-related AML and MDS. All these conditions are exquisitely characterized by recurrent bacterial infections, attributable to a defect in neutrophil chemotaxis.\(^{42}\) However, they also characterize a distinct variant of hematological malignancy in childhood, the monosomy 7 syndrome.\(^{43,44}\) This syndrome most often affects boys under 2 years of age and its clinical presentation resembles that observed in some myeloproliferative disorders, in particular JCML. It can be distinguished from this latter entity because patients with the monosomy 7 syndrome usually have higher platelet counts, normal fetal hemoglobin and a greater propensity to undergo transformation to AML. Familial forms of monosomy 7 have also been described, with some subjects carrying the cytogenetic lesion without any clearly evident clinical or hematological abnormality.\(^{45,46}\) In the report published by Shannon and co-workers,\(^{46}\) in 2 out of 3 pairs of siblings with monosomy 7, the presence of different parental chromosomes 7 invalidated the hypothesis that the Knudson model of oncogenesis (2 mutational events affecting tumor suppressor genes) represented the pathogenetic basis of this abnormality. The possibilities proposed by the authors that the loss of the long arm of chromosome 7 is an incidental finding in MDS, unrelated to the development and progression of the disease, or alternatively that chromosome deletions are necessary for but not sufficient to produce MDS (thus at least one more genetic lesion would be required) stimulated intensive research aimed at
clarifying how deletion of chromosome 7 contributes to leukemogenesis. In this regard, a recently published report proposed a model in which chromosome 7 deletions participate in the development of MDS/MPD by gene dosage.\textsuperscript{47} One practical consideration for this condition is that children with the monosomy 7 syndrome should not receive a marrow transplant from an HLA-identical sibling until it has been clearly and unequivocally shown that the potential donor does not present the cytogenetic abnormality.

Cytogenetic and molecular findings in MDS

Cytogenetic analysis of bone marrow cells is an essential step in the diagnostic process for all children with suspected or documented myelodysplasia. Sequential examinations are also strongly recommended in order to detect possible clonal evolution which is frequently encountered during the progression of the disease. The MIC Cooperative study group demonstrated that about 60\% of patients with idiopathic MDS and more than 90\% of those affected by secondary myelodysplasia show an abnormal karyotype.\textsuperscript{24} The most frequently detected cytogenetic abnormalities include monosomy of chromosome 7 (see above), trisomy of chromosome 8, monosomy of chromosome 5, deletions of the long arm of chromosome 7 or 5 and, more rarely, abnormalities involving chromosomes 11, 19, 20 and 21. Detection of monosomy 7 or complex cytogenetic abnormalities have been associated with poor prognosis, and patients with secondary or therapy-related MDS are more likely to present karyotype abnormalities predictive of unfavorable outcome. The frequent involvement of chromosomes 5 and 7 in MDS has suggested intriguing hypotheses regarding the role of hematopoietic growth factors and some of their receptors in the pathogenesis of these disorders. In fact, the long arm of chromosome 5 contains genes coding for GM-CSF, interleukin-3 (IL-3), interleukin-4, interleukin-5, monocyte colony-stimulating factor (M-CSF) and the c-fms oncogene, which codes for the M-CSF receptor, whereas the genes for erythropoietin, multiple drug resistance 1, multiple drug resistance 2, \textit{met} oncogene and T-cell receptor \(\beta\) and \(\gamma\) chains have been found on the long arm of chromosome 7.\textsuperscript{48} The common involvement of 5q or 7q lesions in MDS, together with the concentration in these regions of genes involved in hematopoiesis, is suggestive, although their role in the development of the preleukemic state has not been clearly defined. It can be hypothesized that an abnormal structure or an altered regulation of the expression of these genes, while not constantly observed in MDS, might play an essential part in the leukemogenic process by conferring a proliferative advantage or by predisposing to additional genetic lesions by increasing genetic instability.\textsuperscript{49} Nevertheless, it cannot be excluded that the loss of a normal allele may unmask a recessive mutant of an anti-oncogene on the remaining chromosome.

It must be mentioned that several studies have pointed out the role of mutations of the RAS gene family (H-RAS, K-RAS and N-RAS, three 21-kD guanine nucleotide-binding proteins involved in the control of cellular proliferation and differentiation) in the pathogenesis of MDS. In the active state \textit{RAS} is bound to guanosine triphosphate (GTP) and transmits signals from the external \textit{milieu} of the cell to its interior, whereas \textit{RAS} becomes inactive when GTP is hydrolyzed to guanosine diphosphate (GDP). Mutations in codons 12, 13 and 61 have been described in about 30\%-40\% of patients with MDS and these usually determine increased levels of RAS-GTP.\textsuperscript{49-51} In particular, \textit{RAS} activation seems to favor malignant progression through a selective growth advantage presented by the cells in which the mutation occurs and through interference with their genetically established differentiation program. Identification of molecular lesions at the level of \textit{RAS} or c-fms oncogenes can also contribute to documenting MDS in patients whose clinical and laboratory findings do not permit a certain diagnosis and for whom the use of X-linked DNA polymorphisms does not provide useful information.

Shannon \textit{et al.}\textsuperscript{52} recently demonstrated that loss of the normal \textit{NF1} allele from the bone marrow of children with \textit{NF1} may predispose to the development of MDS. In fact, neurofi-
bromin, encoded by the NFI gene, is a GTPase-activating protein that binds to RAS and accelerates the hydrolysis of GTP to GDP. Since GTPase-activating proteins regulate the process of signal transduction involving RAS genes, loss or inactivation of a GTPase-activating protein such as NFI could lead to elevated levels of RAS-GTP and this could represent an essential step in malignant transformation. Shannon et al. also documented a loss of heterozygosity for the NFI gene in bone marrow samples from 5 out of 11 children with NFI in whom malignant myeloid disorders developed, thus providing evidence that the NFI gene acts as a tumor suppressor in myeloid cells in vivo. The role of NFI in the pathogenesis of MDS in children who do not have NFI is still unclear, even though the same authors analyzed 25 children with myeloid disorders and monosomy 7 and found that all bone marrow samples retained parental alleles.

**Treatment strategies for pediatric MDS**

Clinical and biological heterogeneity is an intrinsic characteristic of myelodysplasia; some subtypes are associated with short survival and others with a more indolent prolonged course. Due to the wide variation in survival and propensity to undergo transformation to AML (Table 3) among patients belonging to the same FAB subgroup of MDS, alternative attempts at assessing prognosis and refining the prognostic value of the FAB classification have been elaborated. Prognostic factors reported to be associated with short survival include pancytopenia (particularly anemia and thrombocytopenia), high peripheral blood and bone marrow blast counts, abnormal localization of immature precursors (ALIP) on marrow trephine biopsy, increased percentage of CD34+ cells in the bone marrow, karyotype abnormalities (especially the more complex ones) and RAS oncogene activation, which seems to play a role in malignant progression to AML (Table 4).

As mentioned above, myelodysplasia in children is often characterized by an aggressive clinical course, the virtual absence of some subgroups (i.e. RARS) and by the presence of peculiar variants (i.e. JCML and the monosomy 7 syndrome). These observations must be held in due consideration when choosing the optimal therapeutic strategy. Moreover, on the basis of the longer life expectancy of children as compared to adults, data available on the different treatment options referring mainly to adult patients are only partially applicable to the management of pediatric MDS. In fact, the primary aim of the pediatric hematologist should be a definitive cure or at least a durable stabilization of the clinical and hematological situation of the patient, achievable through the eradication or alternatively the differentiation of the malignant clone, leading to a reconstitution of normal hematopoiesis.

**Supportive therapy**

Since bleeding and infection are more common causes of death than progression to AML, transfusions and antibiotic therapy are still the mainstay of treatment.

Pyridoxine, folic acid, corticosteroids and androgens seem to be of little utility in patients with MDS. In particular, clinical trials on the use of corticosteroids have shown little efficacy, with only minor and transient increments in hemoglobin levels. Prolonged therapy with corticosteroids is associated with an increased risk of side effects that outweighs their possible benefits. In randomized trials, androgen therapy improved neither the hematological picture nor the overall survival of patients affected by RAEB-t.

In conclusion, while supportive therapy alone is a reasonable approach in the elderly, the
longer life expectancy, better response to aggressive treatment and superior results of marrow transplant when performed in the early stages of MDS should be adequately considered in younger patients.

Differentiative treatments

Certain drugs in vitro can induce maturation of a clone of cells arrested at an earlier stage of development, and this observation has significant relevance in the treatment of MDS. The most intensively studied agents are 13-cis retinoic acid, 1,25-dihydroxyvitamin D₃, α-interferon and low-dose cytosine arabinoside (Ara-C). Encouraging results were reported in the first pilot studies of 13-cis retinoic acid in myelodysplasia, but two subsequent randomized trials failed to confirm its efficacy.66,67 Likewise, the use of 1,25-dihydroxyvitamin D₃ did not modify the clinical course of the disease.68 Low-dose Ara-C causes significant cytopenia in patients with myelodysplasia, probably because it acts as a chemotherapeutic agent rather than a differentiating drug. In two published studies a considerable proportion of treated patients presented a partial or complete response, even though this effect was obtained at the cost of an increased incidence of infectious complications and toxic death.69,70 Low-dose Ara-C failed to demonstrate clinical benefit when compared to supportive therapy in an intergroup study.71

Therapy with low-dose etoposide (VP-16), a drug with differentiative capacity on human leukemic cell lines at low concentrations in vitro, has recently been shown to be valuable in inducing partial or complete hematological response in patients with MDS.72 Three mechanisms were hypothesized by the authors to explain the effects of VP-16: i) its cytotoxic effect; ii) its ability to cause differentiation of malignant cells, and iii) prolongation of blood cell survival by destruction of the reticuloendothelial system. Nevertheless, these preliminary results must be confirmed in larger, randomized clinical trials before VP-16 can be considered an attractive alternative option for patients without an HLA-identical donor and those with a stable clone.

High-dose chemotherapy

The observation that most pediatric MDS are characterized by an extremely aggressive clinical course has justified the use of intensive treatment aimed at eradicating the malignant clone and reconstituting normal hematopoiesis.73 Chemotherapy has been found to induce hematological remission in a percentage of young patients similar to that observed in cases of primary AML.74-76 However, the response to chemotherapeutic agents is limited and complicated by prolonged periods of aplasia, and the duration of remission has generally been short.

Autologous BMT, theoretically questionable in a disorder involving the multipotent hematopoietic stem cell, was recently proposed by the Childrens Cancer Group after a conditioning regimen consisting of busulfan and cyclophosphamide. In this trial, which included patients with both AML and MDS, children lacking an HLA-identical sibling received intensively timed induction therapy followed by 4-hydroperoxycyclophosphamide-purged autologous marrow transplantation. The reported results are encouraging, but they should be considered preliminary and need to be confirmed in a larger randomized study able to distinguish the role of the intensively timed induction therapy from the role played by the myeloablative doses of chemotherapy used for autologous BMT.

Busulfan and hydroxyurea with or without splenectomy, while effective in Philadelphia chromosome-positive chronic myelogenous leukemia (CML), have not proved to be particularly effective in children with JCML. On the
contrary, these patients are reported to benefit from treatment with oral 6-mercaptopurine alone or in combination with subcutaneous Ara-C. Nonetheless, Castro-Malaspina et al. found that none out of 33 patients affected by JCM/L and given chemotherapy achieved complete remission.

There is no widely accepted agreement on the treatment for the infantile monosomy 7 syndrome. Two out of 6 children with this syndrome given combination chemotherapy were reported to be in remission 4 and 5 years, respectively, after the end of treatment.

Hematopoietic growth factors

The hematopoietic growth factors most commonly used in clinical trials on patients with myelodysplasia are GM-CSF, granulocyte colony-stimulating factor (G-CSF) and recombinant human erythropoietin (rHuEPO). Hematopoietic growth factors are employed in an attempt to reverse the defective proliferation and differentiation of hematopoietic precursors within the MDS marrow and, consequently, to modify the dominant cytopenias with their related morbidities. Both GM-CSF and G-CSF have proven to be effective in increasing granulocyte production in 75-90% of neutropenic patients, even though no study specifically addressed treatment of pediatric MDS. Studies on the clonality of hematopoiesis after treatment with cytokines suggest that GM-CSF and G-CSF do not preferentially stimulate normal hematopoiesis, but rather induce differentiation of the abnormal clone without having the capacity to eradicate the clone itself. G-CSF and GM-CSF therapy can also contribute to the resolution of infections in those patients who experience a substantial increase in their neutrophil count. GM-CSF and G-CSF did not improve platelet and reticulocyte production in the reported trials of MDS patients.

Concern about possible risks inherent in stimulating the proliferation of leukemic cells and the consequent evolution of myelodysplasia to AML was raised in an early study of GM-CSF. However, since an increase in blasts is part of the natural history of MDS, no firm conclusion can be drawn about the impact of cytokine therapy on transformation to acute leukemia.

The long-term effects of both GM-CSF and G-CSF on the natural history and survival of MDS patients remain to be established, and randomized controlled studies are awaited to determine whether colony stimulating factors can really ameliorate the duration and/or the quality of life of patients with myelodysplasia.

In some patients with MDS, serum erythropoietin levels are lower than would be expected relative to the degree of anemia; this observation has led to trials investigating the use of rHuEpo to correct the hyporegenerative anemia. Several studies have been published and it can be concluded that no more than 10-25% of myelodysplastic patients benefit from treatment with rHuEpo.

Recent studies have demonstrated in vitro synergy between G-CSF and rHuEpo for normal and MDS erythropoiesis. Leary et al. showed that G-CSF enhanced the development of early precursors into erythropoietin-responsive progenitors cells. A clinical trial document ed a synergistic in vivo effect of G-CSF and rHuEpo on the anemia of patients with myelodysplasia, with a substantial percentage of subjects presenting both erythroid and myeloid improvement. Responses were more frequent in patients with less advanced pancytopenia and lower endogenous erythropoietin levels, but the durability of these increases must still be clearly assessed.

IL-3 has been shown to be effective in increasing granulocyte, reticulocyte and platelet production in about 50% of MDS patients. However, the improvement in neutrophil count was not as significant as that observed after treatment with G-CSF or GM-CSF, and the effects on the other cell lines were likewise limited. The therapeutic role of IL-3 in association with other hematopoietic growth factors, as well as the efficacy of the c-kit ligand have yet to be clarified definitively.

Allogeneic bone marrow transplantation

Considering that children with MDS have a high risk of death due to cytopenia or clonal evolution to AML and that conventional chemotherapy has not proven effective, those
with an HLA-histocompatible sibling should be considered elective candidates for allogeneic BMT. Allogeneic marrow transplantation represents the only curative treatment for myelodysplasia in young patients at present, and reports have emphasized that a significant percentage of these patients can be cured with marrow transplant.97-103

In the study reported by DeWitte et al. for the European Bone Marrow Transplant Group,98 disease-free survival was about 50% and the best results were observed in patients affected by MDS with low proliferative capacity, i.e. RA and some cases of RAEB, and in patients with a more advanced stage of disease but in complete hematological remission at the time of transplant.

In the largest and most recent update of the Seattle data101 involving 93 patients treated for MDS with an allogeneic BMT from HLA-identical siblings or partially-matched family donors, the probability of disease-free survival, relapse, and non-relapse mortality at 4 years was 41%, 28% and 43%, respectively. Young age (under 40), absence of an excess of blasts, and short disease duration were found to be good prognostic factors.

Although a few pediatric cases were included in some of the previously published studies, there are only two reports specifically addressing the question of BMT in children with MDS. In the first study published by Guinan et al.99 in 1988, eight children with MDS were transplanted with an HLA-identical sibling after a conditioning regimen consisting of fractionated total body irradiation (TBI) and chemotherapy. Both the drugs employed and the doses of radiotherapy delivered differed among the patients, and GVHD prophylaxis was heterogeneous. There were no relapses and four out of the eight children became long-term disease-free survivors; four patients died of rejection and acute or chronic GVHD.

Recently, we reported on eight children with MDS who received allogeneic BMT with homogeneous myeloablative therapy and GVHD prophylaxis.104 Myeloablative therapy consisted of the classic little busulfan-cyclophosphamide (BU, Cy) regimen proposed by Tutschka et al.105 to which melphalan (L-PAM) was added, since we speculated that by adding this drug the killing of malignant cells could be further increased. Moreover, a conditioning regimen consisting of three alkylating drugs with non-cell-cycle-active action appears to be potentially capable of eradicating stem cell disorders in which at least a portion of the clonogenic cells are dormant out of cycle. This conditioning regimen was well tolerated. Only one patient died of transplant-related interstitial pneumonia of unclear etiology and another with RAEB-t and monosomy 7 relapsed 11 months after BMT, whereas the other 6 children became disease-free survivors. The three children affected by JCML obtained a complete remission and are now alive and disease free.

Our experience with patients having this variant of MDS, which represents, albeit with some distinctive features, the pediatric counterpart of adult CMML compares favorably with that of the Seattle Group mentioned above,35 in which three of six children given a transplant from an HLA-identical sibling and three of eight receiving a partially-matched graft after a TBI-containing regimen are alive and in hematological remission. Our data seem to suggest that a conditioning regimen consisting of BU, Cy and L-PAM is sufficient to permit achievement of remission in JCML and probably to eradicate the single genetically altered clone that dominates blood cell production. Since there have been several reports about the long-term morbidity of TBI,106-108 avoiding radiotherapy in the conditioning regimen would also have the advantage of reducing the risk of radiation-induced severe growth retardation, endocrine disorders, cataract development and neuropsychological sequelae.

Data on mismatched family and unrelated donor transplant for patients with MDS are still not conclusive. Some authors109 report encouraging results after BMT using a partially-matched family donor, whereas Kernan et al.109 found 18% 2-year actuarial disease-free survival for 32 patients given unrelated-donor transplant, with the donors being supplied through the National Marrow Donor Program. Therefore, at present, BMT with mismatched
family and unrelated donors should not be considered routine therapy, but should be evaluated in the context of clinical trials that weigh the biological and clinical features together with the relative prognostic implications of each individual patient.

Conclusions

Myelodysplasia in childhood usually runs an aggressive course with a great proportion of patients succumbing in the first 1-2 years after diagnosis. Available evidence indicates that BMT currently represents the only curative strategy for myelodysplastic children.

Therefore, on the basis of the reduced transplant-related mortality and morbidity in childhood and the better results achievable in patients with less advanced disease, children with all different variants of MDS and a suitable HLA-identical donor should be offered allogeneic marrow transplantation as early as possible in the course of the disease.

In children without an HLA-identical sibling and those having MDS variants associated with poorer prognosis (JCML, monosomy 7 syndrome, RAEB and RAEB-t), the possibility of using donors other than HLA-matched siblings could increase the applicability of BMT. For patients with a stable clone and low proliferative capacity MDS (i.e. RA), clonal manipulation to overcome abnormalities in cellular maturation, with consequent amelioration of cytopenia, and to eliminate more malignant subclones could represent an attractive alternative, especially if our knowledge of the cellular differentiation pathways improves.

In the future, pediatric hematologists should pay more attention to childhood myelodysplasia in order to better define the biological, clinical, therapeutic and prognostic implications of the pediatric variants of MDS. The peculiar pediatric variants in particular should be studied in order to arrive at a more widely accepted classification that will permit prognostic and therapeutic comparisons. Moreover, fundamental information deriving from these investigations could provide insights into other hematological/oncological disorders as well.

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