MYELODYSPLASTIC SYNDROME

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Key Words  classification, clinical features, diagnosis, molecular alterations, treatment

Abstract  During the past 15 years, important progress has been made in the understanding of the biology and prognosis of myelodysplastic syndrome (MDS). MDS is a clonal disorder characterized by ineffective hematopoiesis, which can lead to either fatal cytopenias or acute myelogenous leukemia (AML). Risk-adapted treatment strategies were established because of the high median age (60–75 years) of the MDS patients and the individual history of the disease (number of cytopenias, cytogenetic changes, transfusion requirements). Allogeneic bone marrow transplantation currently offers the only potentially curative treatment, but this form of therapy is not available for the typical MDS patient, who is >60 years of age. Therapy with erythropoietin and G-CSF has improved the quality of life of selected patients. The development of small molecules directed against specific molecular targets with minimal adverse effects is the hope for the future. Innovative uses of immunomodulatory agents and the optimizing of cytotoxic treatment should continue to help in the treatment of MDS.

CLASSIFICATION

Myelodysplastic syndrome (MDS) is a clonal disorder characterized initially by ineffective hematopoiesis and subsequently by frequent development of acute myelogenous leukemia (AML). Peripheral blood cytopenias in combination with a hypercellular bone marrow exhibiting dysplastic changes are the hallmark of MDS. In 1982, the French-American-British Cooperative Group classified five subentities of MDS (1): refractory anemia, refractory anemia with excess of blasts (RAEB), refractory anemia with excess of blasts in transformation (RAEB-T), refractory anemia with ringed sideroblasts (RARS), and chronic myelomonocytic leukemia (CMML). This classification based on morphological criteria was recently revised, resulting in the World Health Organization (WHO) classification (2–6) (Table 1). Because of the better prognosis of patients with an isolated cytogenetic aberration at 5q, the WHO classification includes the 5q– syndrome as...
TABLE 1  World Health Organization classification of myelodysplastic syndromes∗

<table>
<thead>
<tr>
<th>Category</th>
<th>Peripheral blood</th>
<th>Bone marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>Anemia</td>
<td>Blasts &lt;5%</td>
</tr>
<tr>
<td></td>
<td>Blasts &lt;1%</td>
<td>Ringed sid. &lt;15%</td>
</tr>
<tr>
<td></td>
<td>Mono &lt;1000/mm³</td>
<td></td>
</tr>
<tr>
<td>RARS</td>
<td>Anemia</td>
<td>Blasts &lt;5%</td>
</tr>
<tr>
<td></td>
<td>Blasts &lt;1%</td>
<td>Ringed sid. ≥15%</td>
</tr>
<tr>
<td></td>
<td>Mono &lt;1000/mm³</td>
<td></td>
</tr>
<tr>
<td>RCMD</td>
<td>Cytopenias (bi- or pancytopenia)</td>
<td>Dysplasia ≥10% of cells</td>
</tr>
<tr>
<td></td>
<td>Blasts &lt;1%</td>
<td>Blasts &lt;5%</td>
</tr>
<tr>
<td></td>
<td>Mono &lt;1000/mm³</td>
<td>Ringed sid. &lt;15%</td>
</tr>
<tr>
<td>RCMD-RS</td>
<td>Cytopenias (bi- or pancytopenia)</td>
<td>Dysplasia ≥10% of cells</td>
</tr>
<tr>
<td></td>
<td>Blasts &lt;1%</td>
<td>Blasts &lt;5%</td>
</tr>
<tr>
<td></td>
<td>Mono &lt;1000/mm³</td>
<td>Ringed sid. ≥15%</td>
</tr>
<tr>
<td>RAEB-I</td>
<td>Cytopenias</td>
<td>Multilineage dysplasia</td>
</tr>
<tr>
<td></td>
<td>Blasts &lt;5%</td>
<td>Blasts 5%–9%</td>
</tr>
<tr>
<td></td>
<td>Mono &lt;1000/mm³</td>
<td></td>
</tr>
<tr>
<td>RAEB-II</td>
<td>Cytopenias</td>
<td>Multilineage dysplasia</td>
</tr>
<tr>
<td></td>
<td>Blasts 5%–19%</td>
<td>Blasts 10%–19%</td>
</tr>
<tr>
<td></td>
<td>Mono &lt;1000/mm³</td>
<td>Auer rods ±</td>
</tr>
<tr>
<td></td>
<td>Auer rods ±</td>
<td></td>
</tr>
<tr>
<td>MDS–U</td>
<td>Cytopenias</td>
<td>Unilineage dysplasia</td>
</tr>
<tr>
<td></td>
<td>Blasts &lt;1%</td>
<td>Blasts &lt;5%</td>
</tr>
<tr>
<td>MDS, isolated</td>
<td>Anemia</td>
<td>Blasts &lt;5%</td>
</tr>
<tr>
<td>del(5q)</td>
<td>Blasts &lt;5%</td>
<td>Isolated del(5q)</td>
</tr>
<tr>
<td></td>
<td>Platelets normal or increased</td>
<td>Normal or increased mega.</td>
</tr>
</tbody>
</table>

Abbreviations: RA, refractory anemia; RARS, RA with ringed sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RCMD–RS, RCMD with ringed sideroblasts; RAEB, RA with excess blasts; MDS–U, myelodysplastic syndrome unclassifiable; Mono, monocytes; Sid., sideroblasts; mega., megakaryocytes.

a separate entity. The initial chromosomal aberration, the age of the patient, and the number and severity of the cytopenias are important to evaluate the prognosis of MDS, as summarized in the International Prognostic Scoring System, IPSS (7) (Table 2). The median survival of MDS patients according to this classification ranges from 6 years for low-risk to 6 months for high-risk patients.

Secondary MDS

Secondary MDS is a term that we use to emphasize that the MDS results from exposure to a mutagen. This could occur as a consequence of therapy for another disease (treatment-related MDS) or exposure to a toxic material, such as benzene. MDS has been described following therapy of malignancies (e.g., Hodgkin’s disease, non-Hodgkin lymphomas, multiple myeloma), including autologous transplantation.
MYELODYSPLASTIC SYNDROMES

3

TABLE 2 International prognostic scoring system for myelodysplastic syndromes

<table>
<thead>
<tr>
<th>Score value</th>
<th>Bone marrow blasts (%)</th>
<th>Karyotype</th>
<th>Cytopoenias (lineages affected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;5</td>
<td>Normal, sole; −Y, del 5q, del 20q</td>
<td>0 to 1</td>
</tr>
<tr>
<td>0.5</td>
<td>5–10</td>
<td>Others</td>
<td>2 to 3</td>
</tr>
<tr>
<td>1.0</td>
<td>11–20</td>
<td>Complex(^b) and/or chromosome 7 anomalies</td>
<td></td>
</tr>
<tr>
<td>1.5</td>
<td>21–30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)The prognostic score is determined by the sum of the single scoring values. The risk groups are determined as follows (brackets: median survival): Low = 0 points (5.7 years); Intermediate-1 = 0.5–1.0 points (3.5 years); Intermediate-2 = 1.5–2.0 points (1.2 years); High \(\geq\) 2.5 points (6 months).

\(^b\)\(\geq3\) chromosomal abnormalities.

(8–10). Alkylating chemotherapy most frequently is implicated as the causative class of agents (11). The highest incidence of secondary MDS/AML occurs 3–8 years after treatment of the antecedent malignancy (12).

After therapy with DNA topoisomerase II inhibitors, secondary MDS/AML develops within a period of about 2–3 years (12). Recently, several single reports have indicated that the NUP98 gene on chromosome 11p15 is one of the targets for chromosomal translocations in patients with therapy-related MDS after exposure to poly-chemotherapy including topoisomerase II inhibitors (13).

5q– Syndrome

This clinically distinct entity involves a deletion of the long arm of chromosome 5 and is characterized by a female preponderance, thrombocytosis, prominent megaloblastoid erythroid hyperplasia in the bone marrow, and megakaryocytes that are unusually large (often >30 \(\mu m\) in diameter) and often have a single, eccentric, round nucleus (14). Interestingly, the rate of leukemic transformation in individuals with 5q– syndrome is only 25% after an observation period of 15 years, as compared to about 40% in patients with a normal karyotype (7). The underlying molecular targets in 5q– syndrome are still unknown. The critical segment may be at chromosome 5q31 (15, 16). The human GRAF (GTPase regulator associated with focal adhesion kinase) gene located in this region can fuse to the MLL (mixed lineage leukemia) gene, disrupting both alleles (17), but the significance of this gene in the 5q– syndrome is unclear. Also, the loss of one allele on 5q (haploinsufficiency) could contribute to the 5q– abnormality, similar to what occurs in the familial platelet disorder with predisposition to AML (see below).

In striking contrast to this syndrome is the loss of chromosome 5 or 5q– in therapy-related MDS, which presages an almost inevitable leukemic
transformation. This may be associated with loss of regions of 5q other than the region lost in the 5q− syndrome.

**Hypoplastic MDS**

Usually, patients with MDS have a hypercellular bone marrow. In ~10% of cases, peripheral blood cytopenia is associated with a hypoplastic bone marrow. In such cases distinguishing MDS from aplastic anemia may be difficult, but the presence of cytogenetic changes can help to identify malignant clonal cells, supporting the diagnosis of MDS. The pathophysiology of hypoplastic MDS is not known; autoreactive and clonal-involved T-cells are believed to suppress normal hematopoietic cells by secretion of inhibitory cytokines. This subtype is most likely to respond to immunosuppressive agents.

**CLINICAL FEATURES**

MDS occurs primarily in the elderly population, with a median age between 60 and 75 years and a surprisingly high incidence of about 15–50 cases per 100,000 individuals over the age of 70 per year (18, 19). Despite this predominance of elderly patients, MDS occasionally occurs in younger individuals and even in children. In recent years, the incidence of MDS appears to be rising, perhaps partly owing to increased diagnostic awareness. The sex distribution is balanced (18), despite earlier reports that indicated a male preponderance. The exception is CMML, which has a clear male preponderance (20).

Fatigue and exertional dyspnea may develop over a prolonged period, often exceeding 6–12 months. These symptoms may be misinterpreted as either cardiac failure or pulmonary disease, particularly in elderly patients. Approximately half of the individuals are asymptomatic at the time of initial diagnosis and are usually diagnosed after a routine blood count. Progressive hematopoietic failure leading to anemia, thrombocytopenia, and leukopenia, either alone or in any combination, is the dominant finding in MDS. Anemia is an almost universal characteristic at the time of initial diagnosis; more than 80% of patients present with a hemoglobin concentration below 10 g/dl. The reticulocyte count usually is reduced.

The peripheral blood leukocyte count is low in ~25%–30% of individuals with MDS, but because the blast cells replace more of the bone marrow, 40% of RAEB cases and 80% of RAEB-T cases can have leukopenia. Granulocytes may exhibit a reduced segmentation and either diminished or absent granulation. Approximately one third of the individuals have recurrent infections. These occur not only because of granulocytopenia but also as a result of defects of neutrophil function, including impaired chemotaxis and reduced phagocytic activity.

Signs of bleeding, mainly petechiae, gingival bleeding, or hematoma following trivial injuries, are surprisingly uncommon, given the frequency of thrombocytopenia. Fewer than 10% of patients will present initially with serious bleeding,
e.g., gastrointestinal hemorrhage, macrohematuria, or retinal or central nervous system hemorrhage.

**CYTOGENETICS AND MOLECULAR ALTERATIONS**

The cytogenetic changes found in MDS are not unique to the disease. Both structural and numerical cytogenetic changes may occur (reviewed in References 21 and 22). The most frequent chromosomal abnormalities in MDS involve deletions of chromosomes 5, 7, 11, 12, and 20 and/or trisomy 8 (Table 3). The incidence of chromosomal abnormalities is about 30%–50% in primary MDS and 80% in mutagen-related MDS. The latter often features complex changes that frequently involve deletions of chromosomes 5 and/or 7. Translocations are rare in MDS. MDS-related chromosomal deletions imply alterations in tumor suppressor genes or DNA repair genes. Usually these changes require two hits: mutation of the target gene and loss of the second allele through deletion, duplication, or recombination.

The underlying causes of primary MDS are still being defined. Analysis of cytogenetic abnormalities, G6PD isoenzymes, restriction-linked polymorphisms, and X-linked DNA polymorphisms of the androgen receptor have shown that MDS is a clonal abnormality of the hematopoietic stem cell characterized by defective maturation and, in advanced stages, uncontrolled proliferation (23). Lymphocytes are probably not involved in the clonal hematopoiesis in MDS (24), but precursors of erythrocytes, platelets, neutrophils, monocytes, eosinophils, and basophils are members of the abnormal clone. Figure 1 proposes a multistep pathogenesis of MDS. After initial damage of the progenitor cell by a toxin or spontaneous mutation, several additional alterations may affect these cells, providing them with a growth advantage. These alterations can influence expression of cell cycle-related genes, transcription factors, and tumor suppressor genes.

| TABLE 3 | Most frequent chromosomal aberrations in MDS patients (frequency of chromosomal aberration is given in brackets) |
|-----------------|-----------------|-----------------|
| Numerical       | Translocations  | Deletions        |
| +8 (19%)        | inv 3 (7%)      | del 5q (27%)    |
| −7 (15%)        | t(1;7) (2%)     | del 11q (7%)    |
| +21 (7%)        | t(1;3) (1%)     | del 12q (5%)    |
| −5 (7%)         | t(3;3) (1%)     | del 20q (5%)    |
|                 | t(6;9) (<1%)    | del 7q (4%)     |
|                 | t(5;12) (<1%)   | del 13q (2%)    |

*Symbols: −, loss of chromosome; +, additional chromosome; inv, inversion; t, translocation; del, deletion.*
Multistep pathogenesis in MDS. The initial genetic insult to the hematopoietic stem cell can be caused by chemicals, radiation, cytotoxic drugs, or random endogenous mutations. The accumulation of several alterations that may affect cell cycle control, transcription, or tumor suppressors results in the expansion of the MDS clone. The progression to leukemia probably does not depend on the order of occurrence of genetic alterations but depends on which genes are altered. The final step, leukemic transformation, may be enhanced by alteration of additional genes, including tumor suppressor genes, and/or by hypermethylation of critical targets. The later stage of leukemogenesis is associated with decreased apoptosis.

Recent studies have suggested that microarray analyses can provide sufficient data to detect genes or gene patterns associated with alterations of specific cellular pathways or signal cascades in MDS (25). The prediction of prognosis or risk type of MDS from gene expression data is a long way from practice (26, 27), but it may have a strong impact in the future on classification and risk definition in MDS.

TREATMENT

Patients with MDS are mainly older individuals suffering from accompanying diseases. Therefore, various strategies have been used to treat patients with MDS. Rather than to offer a cure, the main therapeutic goals in patients with MDS are often to improve hematopoiesis and to ensure an age-related quality of life. Low-intensity therapies, defined as treatments that permit outpatient management, are often directed at patients with low-risk MDS (IPSS low and intermediate-1). Such strategies are not necessarily associated with either improved survival or progression-free survival.

Patients with high-risk MDS (IPSS intermediate-2 and high) need high-intensity therapies (aggressive antileukemic chemotherapy and/or stem cell transplantation) to eliminate the expanded clonal cells and to induce hematological responses. Because of the high median age of patients with MDS, only about one third of high-risk MDS patients can receive intensive cytotoxic treatment. For patients...
who do not qualify for intensive therapy, experimental treatments to suppress, differentiate, or eradicate the malignant clone are under investigation.

Supportive Care

Supportive care generally is the mainstay of therapy. Patients should be treated with erythrocytes for symptomatic anemia. To reduce the risk of iron overload in patients who receive >10 erythrocyte transfusions per year, therapy with an iron chelator should be used, e.g., by bolus subcutaneous administration (28). An optimal hemoglobin level is not known, but usually symptoms such as fatigue and dyspnea occur if the hemoglobin level drops below 8 g/dl, prompting erythrocyte transfusions. Individuals with a history of coronary heart disease have to be transfused more aggressively. To minimize the risk of myocardial infarction in these patients, the hemoglobin level should be 10 g/dl or greater.

Platelet transfusions are restricted to bleeding complications because repeated platelet transfusions are associated with alloimmunization, which results in refractoriness to donor platelets. In cases of refractoriness to either pooled or single-donor platelet transfusions, administration of antifibrinolytic agents or vasopressin may stop minor bleeding, such as from the nose or gingiva.

In the event of documented infections, as well as in the case of fever of unknown origin, antibiotics must be given early. The danger of sepsis from common infections is greater in neutropenic patients than in normal individuals, and intravenous antibiotics are often necessary.

Allogeneic Transplantation

Allogeneic bone marrow transplantation (BMT) or peripheral blood progenitor cell transplantation (PBPCt) is a curative therapy for MDS. The results of allogeneic transplantation vary considerably depending on the subtype of disease and other clinical factors (29). The overall long-term disease-free survival is 60% for IPSS low, 40% for IPSS intermediate-2, and 20% for IPSS high individuals (30–32). Several important factors can improve the outcome after allogeneic transplantation (33), including age (increased survival in patients aged <37 years), low number of cytopenias (<2 is associated with good prognosis after allotransplantation), low IPSS, matched sibling donor, short disease duration (<3–6 months), bone marrow blast cells <5%, and the achievement of complete remission (CR) before transplantation (Table 4). The non-relapse mortality (NRM) after 3 y in this setting ranges from 12% to 30% for both sibling and unrelated matched transplants, but it is up to 50% in unrelated HLA-nonidentical transplants. This considerable therapy-associated mortality is related to a high incidence of graft-versus-host disease (GVHD), which is often associated with severe bacterial or fungal infections including disseminated aspergillosis (32).

“Mini-transplantation” may be an alternative treatment option in MDS patients aged >60 years (34). These individuals receive partial hematopoietic and
immune ablation, and the transplantation results in a chimerism to encourage a graft-versus-MDS/AML effect. This approach is still investigational.

The use of peripheral blood progenitor cells for transplantation is associated with a rapid hematopoietic recovery. This significantly reduces the number of days of fever, as well as the need for parenteral antibiotics, antifungal therapy, and transfusion of erythrocytes and/or platelets. Total duration of hospitalization is also decreased, compared with that of a historical matched bone marrow transplantation group (35).

### Autologous Transplantation

The high toxicity of allogeneic transplantation and the advanced age of most patients have prompted many investigators to evaluate the feasibility of autologous transplants in high-risk MDS. Early results of PBPCT indicate that survival rates, but not disease-free survival, may approach those of allogeneic transplantation because of the low mortality associated with the autotransplant itself (36). A retrospective analysis of 79 patients autografted for MDS showed an overall survival of 39% and a disease-free survival of 34% at 2 years (37, 38).

### Hematopoietic Growth Factors

Eighty-five percent of MDS patients have elevated serum erythropoietin levels. Despite this fact, the rationale to treat MDS patients with recombinant erythropoietin (Epo) is the possibility that pharmaceutical doses may enhance the defective proliferation and differentiation of the erythroid precursors. In ∼25% of low-risk MDS patients receiving Epo, erythrocyte mass increases and/or transfusion requirements are reduced. Factors associated with response to Epo include serum Epo level below 200 U/L, absence of transfusion requirement, and absence of ringed sideroblasts (39). Long-term Epo responders have been described (40).

Interestingly, the combination of Epo with either granulocyte-colony stimulating factor or granulocyte macrophage-colony stimulating factor (G- or GM-CSF)
has a synergistic effect in patients with MDS (41–46). In particular, RARS patients who have almost no response to Epo have a 40% response rate (increased erythrocyte mass) if they receive the combination of Epo and G-CSF. The clinical role for thrombopoietin in MDS patients with low platelet counts (<20,000/µl) must be further defined by careful, controlled clinical trials that evaluate bleeding events, side effects, and particularly the risk of development of neutralizing antibodies.

Demethylating Agents

Many genes have regions in their promoter (CpG islands) that can be methylated at the 5’ position of cytosine, which silences expression of these genes. Theoretically, demethylation of methylated genes that are important in differentiation and/or apoptosis could have clinical applications. For example, p15INK4b, a cell cycle brake, is frequently methylated in MDS but not in normal myeloid cells (47). Both 5-azacytidine (Azacitidine; Vidaza™, Pharmion Corp., Boulder, CO) and 5-aza 2’-deoxycytidine (Decitabine, SuperGen, Inc., Dublin, CA) reduce DNA methyltransferase activity and therefore can cause DNA hypomethylation (48, 49). Whereas Azacitidine is incorporated mostly into mRNA and tRNA, Decitabine is incorporated solely into DNA, possibly accounting for the somewhat different toxicity profile of these two drugs.

Initial pilot trials with low-dose Azacitidine (50) and low-dose Decitabine (51) provided encouraging results. A multicenter study of Azacitidine (52) confirmed its efficacy. Recently, results of a multicenter phase II trial with low-dose intravenous 5-aza 2’-deoxycytidine (45 mg/m² for 3 days every 6 weeks) were reported for 66 mostly elderly patients with advanced MDS (IPSS: 24% intermediate-1, 38% intermediate-2, 38% high) (53). The overall hematologic response rate was 49%, which included a response of 64% for high-risk individuals. The actuarial median response duration was 31 weeks, with a response duration of 39 weeks and 36 weeks for patients who reached a PR or CR, respectively.

Immunosuppressive Agents

Immunosuppressive therapy has been proposed for the past 15 years as a treatment option for MDS to reverse bone marrow failure by inhibiting intramedullary secretion of proapoptotic cytokines. In a pilot study, 42 transfusion-dependent MDS patients received antithymocyte globuline (ATG, 40 mg/kg/d for 4 days) (54, 55). Remarkably, erythrocyte transfusion independence occurred in 16 individuals, and platelets increased in 14 of them. Three individuals with refractory anemia had a complete remission. The response rate was 64% in the low-risk individuals and 33% in those with high-risk MDS. The median response duration was 10 months, ranging from 3 to 38 months. A recently published update of this nonrandomized, single-treatment study (56) reported an overall frequency of transfusion independence of 34% in a total of 61 patients with MDS. Parameters to predict a good
response to ATG treatment are low IPSS and a short history of erythrocyte transfusions (57).

Several small studies used cyclosporin A (CSA) for MDS patients (58–60) with variable results. A predictive marker for a good response may be the expression of the HLA-DRB1*1501 allele (61). Of a total of 10 patients studied, 6 patients responded to CSA, all of whom had the 1501 allele. Four patients did not show any response and did not have this human leukocyte antigen. It remains unclear how ATG and/or CSA improves hematopoiesis in MDS, and why many months of therapy are needed before a response occurs. Several multicenter trials using ATG and/or CSA for MDS are ongoing.

### Intensive Cytotoxic Treatment

At the present time, long-term benefit for individuals with MDS can be achieved only by eradication of the abnormal clone and restoration of normal hematopoiesis. Recent studies in which intensive cytotoxic treatment was administered to younger individuals with high-risk MDS have produced remission rates ranging from 22% to 79%. As a consequence of the further improved supportive care in patients receiving intensive cytotoxic treatment, the remission rate achieved in high-risk MDS patients is comparable with those for patients with de novo AML. On the other hand, in a recently published study that evaluated intensive chemotherapy alone compared to chemotherapy followed by transplantation in a total of 269 patients with high-risk MDS, neither the chemotherapy nor the transplantation showed a clear benefit (62).

The decision whether to pursue aggressive treatment should include stratification according to the patient's risk factors using the IPSS (7). The use of hematopoietic growth factors permits more patients to receive intensive cytotoxic treatment. Nevertheless, the duration of remission often is short, usually about 12 months (63). Long-term remissions are associated with restoration of polyclonal hematopoiesis (64), and the achievement of a partial remission after induction therapy may be of clinical benefit for high-risk patients.

### Arsenic Trioxide (As₂O₃)

Arsenic compounds have been used therapeutically for at least a millennium in China. In the West, arsenic in the form of “Fowler’s solution” was used in the middle of the nineteenth century to treat fever of unknown origin. Most recently, As₂O₃ has produced very good response in acute promyelocytic leukemia (65–67). Clinical studies to evaluate As₂O₃ in MDS are under way (68).

### Future Experimental Approaches

Farnesyl transferase inhibitors showed in vivo efficacy in the treatment of patients with AML, conceivably by inhibiting the Ras pathway. The role of these agents in the treatment of high-risk MDS patients who are not qualified to receive
intensive treatment is not yet established, but they may be a future option (69).

The bone marrow of individuals with MDS contains an abnormally high number of blood vessels (70, 71). This has encouraged the investigation of inhibitors of angiogenesis, such as SU5416 and thalidomide, and of inhibitors of vascular endothelial growth factor (VEGF) for individuals with either AML or MDS. Thalidomide was initially developed as a “sleeping pill,” but it was found to have activity in the treatment of patients with multiple myeloma. In MDS, treatment with thalidomide as a single agent (72) resulted in 30%–40% of MDS patients showing a hematopoietic response, usually improved erythropoiesis. Further studies of antiangiogenic drugs, including the new thalidomide analogue CC-5013 (Revimid™; Celgene, Warren, NJ) which may have immunomodulatory efficacy in patients with 5q– syndrome (A. List, personal communication), and anti-TNFα therapeutics are ongoing. Ultimately, we will define the genetic lesion of the patient and have in our armamentarium a therapy specific for that molecular abnormality.

**Overall Treatment Approach in MDS**

The treatment decision should take into consideration the patient’s disease risk according to IPSS, age, and performance status. Based on these factors, possible treatment strategies are as follows:

1. **Individuals up to the (biological) age of ~55–60 years are candidates for allogeneic transplantation from an HLA-matched (sibling or unrelated) donor.** The patients should be carefully informed about the risks of the allogeneic stem cell transplantation. The alternative treatment options (see below) should be discussed.

2. **Patients with IPSS low or intermediate-1 MDS who have no HLA-identical donor, or are older than 60 years and have good clinical performance, should receive either supportive care or, when necessary, a trial of erythropoietin.** For nonresponders to erythropoietin, the combination therapy of erythropoietin with G-CSF may be effective. Alternatively, immunosuppressive therapy or other experimental approaches should be considered. As their disease progresses, various therapies might be evaluated in the context of an ongoing clinical study.

3. **Patients with IPSS high or intermediate-2 MDS, older than 60 years and having a good clinical performance, are candidates for intensive cytotoxic therapy, followed by consolidation therapy and perhaps autologous transplantation.**

4. **Individuals who are elderly and/or in poor clinical condition should receive supportive care.** If possible and desired by the patient, investigational, outpatient-based therapy (e.g., demethylating drugs or thalidomide) should be offered.
LITERATURE CITED


37. de Witte T, van Biezen A, Hermans J,


chronic leukemias and myelodysplastic syndromes. Blood 96:2240–45


CONTENTS

MYELODYSPLASTIC SYNDROME, Wolf-K. Hofmann and H. Phillip Koeffler 1
G Protein Polymorphisms in Hypertension, Atherosclerosis, and Diabetes, Winfried Siffert 17
Post-Transplant Lymphoproliferative Disorders, Stephen Gottschalk, Cliona M. Rooney, and Helen E. Heslop 29
Metabolic Syndrome: A Clinical and Molecular Perspective, David E. Moller and Keith D. Kaufman 45
New Anticoagulant Therapy, Lori-Am Linkins and Jeffrey I. Weitz 63
Endothelial Progenitor Cells, Aarif Y. Khakoo and Toren Finkel 79
Aromatase Inhibitors: Rationale and Use in Breast Cancer, Cynthia Osborne and Debu Tripathy 103
Andropause: Is Androgen Replacement Therapy Indicated for the Aging Male?, Rabih A. Hijazi and Glenn R. Cunningham 117
Surgical Therapy for Metastatic Disease to the Liver, David J. Bentrem, Ronald P. DeMatteo, and Leslie H. Blumgart 139
New Strategies in the Treatment of the Thalassemias, Stanley L. Schrier and Emanuele Angelucci 157
New Concepts in Von Willebrand Disease, J. Evan Sadler 173
Genetics of Longevity and Aging, Jan Vijg and Yousin Suh 193
Progress Toward an HIV Vaccine, Norman L. Letvin 213
Therapeutic Intervention and Targets for Sepsis, Todd W. Rice and Gordon R. Bernard 225
Management of Peripheral Vascular Disease, I. Baumgartner, R. Schainfeld, and L. Graziani 249
Role of Magnetic Resonance Imaging and Immunotherapy in Treating Multiple Sclerosis, Jingwu Zhang and George Hutton 273
Definition and Clinical Importance of Haplotypes, Dana C. Crawford and Deborah A. Nickerson 303
Approaches to Therapy of Prion Diseases, Charles Weissmann and Adriano Aguzzi 321
CONTENTS

ENDOMETRIOSIS: NEW GENETIC APPROACHES AND THERAPY,  
David H. Barlow and Stephen Kennedy  345

SEVERE ACUTE RESPIRATORY SYNDROME (SARS): A YEAR IN  
REVIEW, Danuta M. Skowronski, Caroline Astell, Robert C. Brunham,  
Donald E. Low, Martin Petric, Rachel L. Roper, Pierre J. Talbot,  
Theresa Tam, and Lorne Babiuk  357

GENE-ENVIRONMENT INTERACTIONS IN ASTHMA AND OTHER  
RESPIRATORY DISEASES, Steven R. Kleeberger and David Peden  383

THE SILENT REVOLUTION: RNA INTERFERENCE AS BASIC BIOLOGY,  
RESEARCH TOOL, AND THERAPEUTIC, Derek M. Dykxhoorn  
and Judy Lieberman  401

MANAGEMENT OF ADULT IDIOPATHIC THROMBOCYTOPENIC PURPURA,  
Douglas B. Cines and Robert McMillan  425

MONOGENIC OBESITY IN HUMANS, I. Sadaf Farooqi  
and Stephen O’Rahilly  443

APPLICATION OF MICROBIAL GENOMIC SCIENCE TO ADVANCED  
THERAPEUTICS, Claire M. Fraser and Rino Rappuoli  459

ATRIAL FIBRILLATION: MODERN CONCEPTS AND MANAGEMENT,  
Ashish Agarwal, Meghan York, Bharat K. Kantharia,  
and Michael Ezekowitz  475

DNA REPAIR DEFECTS IN STEM CELL FUNCTION AND AGING,  
Youngji Park and Stanton L. Gerson  495

HEMATOPOIETIC STEM AND PROGENITOR CELLS: CLINICAL AND  
PRECLINICAL REGENERATION OF THE HEMATOLYMPHOID SYSTEM,  
Judith A. Shizuru, Robert S. Negrin, and Irving L. Weissman  509

INHERITED SUSCEPTIBILITY TO COLORECTAL CANCER, Peter T. Rowley  539

APTMERS: AN EMERGING CLASS OF THERAPEUTICS,  
Shahid M. Nimjee, Christopher P. Rusconi, and Bruce A. Sullenger  555

GENE THERAPY FOR SEVERE COMBINED IMMUNODEFICIENCY,  
Marina Cavazzana-Calvo, Chantal Lagresle, Salima Hacein-Bey-Abina,  
and Alain Fischer  585

INDEXES

Subject Index  603
Cumulative Index of Contributing Authors, Volumes 52–56  637
Cumulative Index of Chapter Titles, Volumes 52–56  640

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