Patients with “low-risk” myelodysplastic syndrome (MDS) are mostly treated with approaches aiming to reduce the negative consequences of ineffective hematopoiesis. Transfusion therapy should be tailored to allow adequate oxygenation and optimal quality of life, and may lead to the need for iron chelation therapy. Growth factors (erythropoietin and granulocyte colony-stimulating factor [G-CSF]) may induce long-lasting improvement of hemoglobin levels and does not increase the risk for leukemic transformation. Growth factors should be offered to defined subgroups of patients. Immunosuppression with anti-thymoglobulin or cyclosporine A may be an alternative for younger patients with refractory anemia (RA). The new immunomodulating compound lenalidomide, CC5013, is very active in the 5q– syndrome and is under evaluation for other low-risk MDS subtypes. “High-risk” MDS is associated with poor survival and high risk for leukemic transformation. The DNA hypomethylating compounds azacytidine and decitabine may offer improved long-term outcomes in this group of patients, although there has so far been no effect on survival rates. The efficacy of farnesyl transferase inhibitors has been evaluated in a series of phase II trials. The overall response rate was low, but the majority of responses were CRs. Finally, a number of new drugs directed to various biological and genetic targets are entering clinical trials.

Current Classifications of MDS
A thorough diagnostic evaluation is a prerequisite for therapeutic decision-making. Parallel use of the older French-American-British (FAB) and the newer World Health Organization (WHO) classifications is helpful in evaluating patients with myelodysplastic syndrome (MDS), but has led to certain problems. The WHO’s distinction between refractory anemia (RA) and refractory anemia with ringed sideroblasts (RARS), and the recognition of refractory cytopenia with multi-lineage dysplasia with or without ringed sideroblasts (RCMD+/- RS) are valuable contributions to the prediction of prognosis and response to treatment. Similarly, the creation of a new subcategory encompassing patients with isolated deletion of 5q and < 5% blasts (5q– syndrome) reflected a long-recognized clinical entity. However, the WHO classification does not address the problem of classifying patients with severe bone marrow fibrosis, which is a known negative prognostic marker, nor the issue of hypoplastic MDS. Moreover, the border between acute myeloid leukemia (AML) with tri-lineage dysplasia, and RA with excess blasts in transition (RAEB-t) remains unclear. Centers that recognize RAEB-t as MDS, as in the FAB system, will be able to assess the response to new treatment modalities specifically in this subgroup. Centers using only the WHO classification should include patients with “RAEB-t” in the group of AML with tri-lineage dysplasia, but this has not been implemented in a uniform way. A consequence is that ongoing clinical trials of MDS on the one hand and AML on the other may include patients with very similar characteristics, making interpretation of these trials extremely difficult. And, importantly, both FAB and WHO classifications are based mainly on the identification of morphological final common pathways, such as progenitor dysplasia and blast increase, rather than on specific biological and molecular markers, which will likely be the basis of the next generation of therapeutics. Therapeutic development in MDS has been rather slow compared to other hematological malignancies, and not until recently have new pathogenetic discoveries led to a number of innovative therapeutic approaches.

Risk Assessment
The decision about how to deal with the morbidity of the disease versus the potential benefits and toxicities from treatment will ultimately be made by the individual patient. This decision is based on age, personal preferences, and available information about disease biology and prognostic factors. The International Prognostic Scoring System (IPSS), based on the number of cytopenias, percentage of bone marrow blasts, and karyotype, is a fundamental tool for predicting prognosis and thus planning therapy. Usually, the immediate goal of therapy in patients with low or intermediate-1 IPSS scores is improvement of quality of life, while the immediate therapeutic goal in patients with scores of intermediate (Int)-2 or high is improvement...
in survival.

However it must be remembered that the IPSS was designed to predict the prognosis of untreated patients, and should not automatically be used as a tool for predicting the response to various treatments. More specific criteria will likely be necessary to predict the outcome to biologically targeted therapies (Table 1).

Clinical Challenges

Although the possibility of curing MDS has increased with improved transplant strategies, the majority of MDS patients will still live with, and die of, their disease. Severe anemia leading to the need for chronic transfusions and markedly reduced quality of life is often the major clinical problem for patients with WHO RA, RARS and 5q− syndrome or with IPSS stages low or intermediate-1.1,4 Progressive cytopenia, which is more common in the other MDS subtypes, may predict for transformation to AML but may also be a feature of RCMD without an increase of blasts. Severe pancytopenia is linked to markedly increased morbidity and reduced quality of life. The life expectancy of patients with high and Int-2-risk MDS is short (e.g., ≤ 1 year), and approaches to prevent transformation from low- to high-risk disease are needed as is better treatment for high-risk disease.

Supportive Care and Transfusion Therapy

The aim of supportive care is to reduce morbidity from ineffective hematopoiesis and to improve quality of life. Anemic patients with low-risk MDS who do not respond to treatment with growth factors or other treatment may be chronically transfused. Patients with chronic transfusion need should be transfused to enable an adequate tissue oxygenation, good quality of life, and physical and intellectual activity.

The optimal target hemoglobin level for transfusion varies between patients and is dependent upon factors such as age, co-morbidity, life-style and working conditions. Recent observations suggest that the use of a trigger for RBC transfusions of 8 g/dL is often insufficient to prevent severe symptoms of anemia. The management of chronic neutropenia and thrombocytopenia is not specific for MDS and there is no evidence that routine prophylaxis with cytokines, antibiotics, or pro-coagulants will improve the status or outcome of the majority of patients, although individual patients may benefit from this approach.

Iron Chelation

There are only a few recent publications describing the iron status of MDS patients.7 Most available knowledge comes from the much younger thalassemia cohort, which may be difficult to compare with the MDS population. There are no controlled trials evaluating the long-term effects of iron chelation in MDS, but current guidelines recommend that desferrioxamine treatment be considered in patients with low-Int-1 risk MDS, who have received > 20-25 units of packed RBC or who have a serum ferritin level around 1500 µg/L.6,8 However, because it must be given parenterally, administration of desferrioxamine is often impractical. Two new oral chelators, deferiprone and ICL 670, have well-documented effects in thalassemia and sickle-cell anemia patients.9,10 Ongoing and preliminary reported studies also include patients with MDS, and hopefully the eventual availability of these oral chelators will make it easier to treat iron overload in MDS.

Hemopoietic Growth Factors

It was recently reported that erythroblasts in low-risk MDS constitutively release the pro-apoptotic molecule cytochrome c from mitochondria to cytosol.11 Moreover, it was shown that mitochondrial iron in RARS accumulates in the form of aberrant mitochondrial ferritin (MtF), even during very early erythroid maturation.12 These data support a central role for mitochondria in the pathogenesis of some subtypes of MDS, in particular the sideroblastic anemias.

Erythropoietin (Epo) and granulocyte colony-stimulating factor (G-CSF) promote growth and differentiation of hemopoietic progenitors, but they are also strong inhibitors of apoptosis. Epo may improve hemoglobin level in around 20%-25% of unselected anemic patients with low-risk MDS, with a higher response rate in RA than in RARS.13 Several studies have shown that the addition of low doses of G-CSF synergistically enhances the erythroid response rate, in particular in patients with RARS.14,15 FAB-RARS shows an erythroid response rate of around 50%; however, a recent re-analysis using the WHO classification demonstrated a significantly better response rate in RARS (75%) than in RCMD-RS (9%).3 This may reflect G-CSF’s ability to strongly inhibit cytochrome c release, hence mitochondria-mediated apoptosis, in RARS erythroblasts.11 The response to treatment with Epo+G-CSF can be predicted by combining information about pretreatment transfusion need (< or ≥ 2 units per month) and serum Epo (< or ≥ 500 U/L). The predictive value of such a model was recently validated,12 and it was concluded that patients with two unfavorable factors, high transfusion need and serum Epo, had a very low

Table 1. Targeted treatments for myelodysplastic syndrome (MDS).

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Therapeutic Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition of mitochondria-mediated apoptosis</td>
<td>Erythropoietin, granulocyte colony-stimulating factor</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>Antithymocyte globulin, Cyclosporin A</td>
</tr>
<tr>
<td>Immune-modulation</td>
<td>Thalidomide, lenalidomide</td>
</tr>
<tr>
<td>Inhibitors of angiogenesis</td>
<td>VEGF inhibitors</td>
</tr>
<tr>
<td>DNA hypomethylation</td>
<td>Azacytidine, decitabine</td>
</tr>
<tr>
<td>Inhibition of histone deacetylation</td>
<td>Valproic acid, depsipeptide, MS275</td>
</tr>
<tr>
<td>Oncogene deactivation</td>
<td>Farnesyl transferase inhibitors, imatinib</td>
</tr>
<tr>
<td>Enzyme and kinase inhibition</td>
<td>TLK199, Src family kinase inhibitors</td>
</tr>
</tbody>
</table>
probability of responding to treatment (Table 2).

A recent, large, long-term follow-up of 129 patients reported a median duration of response to G-CSF plus Epo of 23 months (3-116 months) for all patients, and 28 months in patients with RA and RARS. Complete erythroid responses, defined as a stable hemoglobin value > 11.5 g/L, were more durable than partial responses (29 vs 12 months). Furthermore, the study compared long-term outcome of the G-CSF + Epo cohort in terms of survival and leukemic transformation with untreated patients from the IPSS database. Since patients in the IPSS cohort were followed from diagnosis and the G-CSF + Epo cohort from start of treatment, the analysis was biased in favor of the IPSS cohort. In spite of this, the multivariate regression analysis showed no difference between the cohorts in terms of survival and evolution to AML. It could thus be concluded that G-CSF does not enhance the risk for leukemic transformation. Importantly, use of G-CSF + Epo in patients defined by the decision model as unlikely to respond to such therapy was associated with shorter survival and a high risk for AML evolution, which further underlines that growth factor therapy is a poor therapeutic choice in this group of patients.

The long-acting Epo-analogue, darbepoetin, seems to be at least as effective as epoetins alpha and beta, according to a recently published pilot study and a preliminary reported larger phase II study. The phase II study reported a response rate of 60%, with few additional responses when G-CSF was added. Further studies are needed to explore the long-term activity of darbepoetin as well as the optimal dosing schedules. The Nordic MDS Group is currently conducting a study investigating the effect of correction of anemia, by darbepoetin or by transfusion in case of no response, on exercise capacity, cardiac function and quality of life in elderly patients with MDS.

### Immunosuppression

Anti-thymocyte globulin (ATG) administration may be an effective treatment for a subset of patients with low-risk MDS. Responses to ATG are almost exclusively seen in the FAB-RA subtype and are significantly associated with shorter survival and a high risk for AML evolution, which further underlines that growth factor therapy is a poor therapeutic choice in this group of patients.

The Nordic MDS Group is currently conducting a study investigating the effect of correction of anemia, by darbepoetin or by transfusion in case of no response, on exercise capacity, cardiac function and quality of life in elderly patients with MDS.

### Table 2. Decision-model for treating the anemia of myelodysplastic syndrome (MDS) with Erythropoietin (Epo) + granulocyte colony-stimulating factor (G-CSF).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Score</th>
<th>Value</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion need</td>
<td>&lt; 2 U/month</td>
<td>0</td>
<td>≥ 2 U/month</td>
<td>1</td>
</tr>
<tr>
<td>Serum-Epo*</td>
<td>&lt; 500 U/liter</td>
<td>0</td>
<td>≥ 500 U/liter</td>
<td>1</td>
</tr>
</tbody>
</table>

* Pre-treatment evaluation

Predicted response rate: Total score 0 = 74%, 1 = 23%, 2 = 7%

Predicted value of model $P < 0.001$ 14

Patients with score 2 do not benefit from treatment with Epo + G-CSF 17

### Thalidomide and Immunomodulatory Drugs

There is evidence for abnormal function of the marrow microenvironment in MDS. Tumor necrosis factor (TNF)-α has been suggested as a potential mediator of marrow failure, and enhanced serum TNF-α levels have been related to poor response to treatment with Epo. Abnormally expanded angiogenesis has also been implicated in the pathogenesis of MDS. Whether the dysfunctional microenvironment in MDS constitutes a primary biological event or results from other genetic and epigenetic events remains to be investigated.

The effect of thalidomide on the cytopenia of MDS has been evaluated in a number of smaller phase II trials, showing an erythroid response rate of around 20% in selected patients, but only minor effects on the other cytopenias. Interestingly, some patients who have failed treatment with Epo may respond to thalidomide. Responding patients seem to be younger and have RA, thus presenting a similar pattern as responders to ATG and CyA. However, thalidomide treatment is associated with significant side effects including fatigue, constipation, and neuropathy, leading to a high degree of patient discontinuation of the drug.

CC5013 (lenalidomide), a 4-amino-glutarimide thalidomide analogue, which is more potent than thalidomide but lacks its neurotoxic and teratogenic effects, is active in a subset of patients with MDS, in particular in patients with a deletion including 5q31. In a recently published pilot study of 43 patients, 10 of 12 patients with this cytogenetic abnormality showed an erythroid response, defined as transfusion independency, of which 9 also had a complete cytogenetic response. The response rate in 23 patients with normal karyotype was 57%, while patients with other karyotypic abnormalities responded less well (1/8). However, only 1 of 10 patients with moderate to severe thrombocytopenia had a sustained improvement of the platelet count. Neutropenia and thrombocytopenia were common adverse events (65% and 74%, respectively), and 58% of patients required interruption of treatment or a dose reduction. The effect of lenalidomide in a larger group of patients with 5q- aberration was recently the subject of a preliminary report. Among a total of 148 patients, 66% achieved an erythroid response, the majority obtaining a major or complete response as defined using International Working Group criteria. The response rate was higher in patients with the isolated 5q31 aberration than in those with additional chromosomal aberrations. After a median...
follow-up of 9.3 months, the median duration of response had not been reached. Lenalidomide caused grade III-IV neutropenia and thrombocytopenia in more than a third of the patients, and interestingly the maximum tolerated dose is clearly lower in MDS than in myeloma. Long-term results regarding response duration, AML evolution, and survival are still to be reported and will influence the role for lenalidomide in the 5q– syndrome. A third phase II lenalidomide study is evaluating the effect of the drug in low/Int-1 risk patients without 5q– aberrations. A randomized European trial evaluating the effects of two doses of lenalidomide versus placebo in 5q– patients is soon to start, followed by studies on non-5q– MDS patients and high-risk patients with 5q– aberration.

Other Therapeutic Approaches Targeting the Marrow Microenvironment

Studies evaluating the effects of anti-TNF-α antibodies on the ineffective hematopoiesis and cytopenias of MDS have reported only moderate hematological improvement in a minor subset of patients.26 This may indicate that TNF-α expression is a secondary rather than a primary disease feature in MDS. Small molecule inhibitors of VEGF receptor tyrosine kinases and other angiogenic cytokines have emerged as potential candidates for therapeutic development, but there is so far limited clinical data to report. One of the first inhibitors, SU5416, was evaluated in high-risk MDS and AML and was shown to have some biologic effect.27 Other inhibitors are under investigation.

Epigenetic Modulation

Epigenetic modulation of gene function is a very powerful cellular mechanism.28 DNA methylation leads to silencing of gene expression. Several recent reports suggest an association between methylation of the p15INK4a gene promoter and risk for AML transformation in MDS; hence, DNA hypermethylation has been suggested as one of the more important therapeutic targets in this disorder.

The DNA hypomethylating pyrimidine analogues 5-azacytidine and 5-aza-2-deoxycytidine (decitabine) may reduce hypermethylation and induce re-expression of key tumor suppressor genes in MDS. The effect of azacytidine was evaluated in a randomized phase III trial.29 Azacytidine-treated patients showed a better overall response compared to those treated with supportive care only (60% vs 5%) and a longer time to progression to AML or death, but no overall survival advantage. These results led to the licensing of azacytidine in the US in 2004, while the decision from the European authorities is still pending. The effect of azacytidine on survival and AML evolution is currently being evaluated in an international randomized phase III trial of patients with Int-2 and high-risk MDS. Patients in the control arm are treated with “doctor’s choice”; supportive care, low-dose cytosine arabinoside (ara-C) or induction chemotherapy. The Nordic MDS Group is investigating the effect of azacytidine given as long-term maintenance treatment in CR after induction chemotherapy in patients with high-risk MDS and AML following MDS. Decitabine has been evaluated in several clinical trials in high-risk MDS and has shown a favorable effect in particular in patients with high-risk MDS according to IPSS.30 The overall response rate is 25% for Int-1, 48% for Int-2 and 64% for high-risk patients, respectively, and the median survival seems to be longer than expected. Two randomized phase III trials are investigating the effect of decitabine on long-term outcome. According to the recent preliminary report of a US trial of 170 patients, AML-free survival, but not overall survival, was longer in the decitabine group, which also showed improved quality of life.31 The median number of courses to response has been noted to 3–4 with both azacytidine and decitabine. Accordingly, comparison of studies involving these drugs may be compromised if patients are taken off study at varying times. The ability to give multiple courses of decitabine may be increased by the development of low-dose schedules and is being investigated.

Histone acetylation status plays a key role in the regulation of gene transcription and is closely linked to DNA methylation. Decreased histone acetylation, i.e., by increased histone deacetylase activity (HDACs), may also lead to epigenetic silencing of tumor suppressor genes. Inhibition of histone deacetylation is another new interesting concept in the treatment of hematological malignancies.32 One clinically available oral HDAC inhibitor, valproic acid given in combination with all-trans retinoic acid, was recently reported to have an effect in a limited number of high-risk MDS and leukemia patients.33 Several HDAC inhibitors, such as MS 275, SAHA, and depsipeptide, are being evaluated in clinical trials for MDS and other hematological malignancies.

Farnesyl Transferase Inhibitors

The RAS gene family affects critical regulatory pathways in signal transduction and proliferation. The activation of these pathways is dependent on farnesylation. N-ras mutations are found in around 10% of MDS, more common in the chronic myelomonocytic leukemia subgroup, but its role in predicting prognosis in MDS has been debated.34 Compounds inhibiting farnesylation have been shown to inhibit RAS-dependent tumor growth in vitro. Oral administration of the farnesyl transferase inhibitor (FTI) tipifarnib has been investigated in high-risk MDS and AML.35 In a recently published phase II study, 3 of 27 evaluable patients with high-risk MDS responded to therapy, with 2 patients achieving a complete remission. There was no correlation between the presence of RAS mutations and response, indicating that the FTIs have a broader range of action. A randomized phase II study of 82 high-risk patients was recently reported in preliminary form.36 Twenty-eight patients (33%) responded to treatment, 6 of whom achieved a CR.
Imatinib-Responsive MDS
Reciprocal chromosomal translocations including 5q33 generate a fusion protein involving the PDGFb receptor. The fusion protein causes constitutive RTK signaling, and results in CMML with eosinophilia. All 5 reported patients achieved a rapid and complete remission after treatment with imatinib mesylate.36

Other New Drugs for MDS
Arsenic trioxide has shown reasonable toxicity but only moderate therapeutic activity in high-risk and low-risk MDS.37 Clofarabine, which has shown efficacy in a small cohort of MDS patients, continues to be evaluated in high-risk MDS and AML.38 A significant number of new compounds directed towards various cellular mechanisms are being evaluated in clinical protocols; TLK199, a glutathione analogue inhibitor of GST P1-1 for high-risk MDS, Src family kinase inhibitors and new TPO-R agonists for severe thrombocytopenia.22

Treatment Algorithms for MDS
Patients with MDS can basically be divided into low-risk and high-risk groups, although the border between these

Table 3. Algorithm for treating symptomatic patients with low and intermediate-1 risk myelodysplastic syndrome (MDS).

- High-quality transfusion and chelation therapy
- Evaluate refractory anemia (FAB or WHO) for immunosuppressive treatment
- Evaluate for curative approaches; allogeneic stem cell transplantation (intermediate-1 risk)
- Patients with 5q– aberration: lenalidomide if available
- Epo ± G-CSF according to decision model (only good and intermediate probability of response). Start with Epo, add G-CSF at 8 weeks if no response
- Other patients, and patients with no or lost response to treatment above: clinical trials/transfusion therapy/hypomethylating agents, if available

Abbreviations: FAB, French-American-British; WHO, World Health Organization; Epo, erythropoietin; G-CSF, granulocyte colony-stimulating factor

Table 4. Algorithm for treating patients with intermediate-2 and high-risk myelodysplastic syndrome (MDS).

- High-quality supportive care.
- Evaluate for curative approaches; allogeneic stem cell transplantation (could include intermediate-1 risk)
- Hypomethylating agents, if available or in clinical trials
- Evaluate for clinical trials with new therapies
- Evaluate for induction chemotherapy (individual risk analysis based on performance status, and probability of response)
- Evaluate for low-dose chemotherapy

varies with age. In order to choose treatment for an individual patient, it is important to clarify the role of licensed and established treatments, as well as make a critical evaluation of the potential of new treatment options. Allo transplantation is today the only documented curative therapy. The probability of response to induction chemotherapy and intensified treatment has been evaluated in a couple of studies, which may assist in therapeutic decision-making.39,40 Tables 3 and 4 give suggestions for therapeutic management of new patients with MDS.

References


