Introduction

Myelodysplastic syndrome is the most common hematologic malignancy of the elderly. It is an acquired primitive stem cell disorder resulting in ineffective hematopoiesis manifested by variable degrees and numbers of cytopenias, and an increased risk of transformation to acute leukemia (35-40%). MDS usually develops in older adults with a median age of 72-76 years in most series [1, 2]. It is more common in males than in females and in Caucasians than in Asians and American Indians. MDS is relatively common with a reported incidence of 3.5-4.9 per 100,000. The incidence increases to 28-36/100,000 beyond age 80, making it as common as CLL or myeloma in this age group [3].

Pathogenesis

Biology of MDS

In MDS there is abnormal regulation of proliferation, maturation and survival of pluripotential hematopoietic stem cells due to genomic alterations and clonal interactions within the microenvironment. Tumor promotion and clonal expansion lead to ineffective hematopoiesis arising from accelerated proliferation and apoptosis. With disease progression, stem cell maturation is further impaired with a decline in programmed cell death associated with enhanced survival of myeloblasts. This leads to expansion of the leukemic clone. Thus, in low-risk MDS abnormal cytokine release, increased angiogenesis and autoimmunity predominate, the apoptotic index is increased and cells undergo premature intramedullary cell death. In high-risk MDS, gain of RAS activity, increased VEGF/R signaling and epigenetic changes, that include hypermethylation of tumor suppressor genes and chromatin remodeling, predominate. In high-risk MDS, the apoptotic index is decreased [4].

Causes of MDS

Environmental or therapeutic exposure to benzene, ionizing radiation, and chemotherapeutic agents are known to predispose to the development of MDS. However, a history of such exposures can be elicited in only a small minority of patients with MDS and in the great majority of patients this disease is idiopathic.

MDS is a Stem Cell Disorder

Several lines of evidence support the idea that MDS is a disease of the hematopoietic stem cell. Not only are patients with MDS frequently pancytopenic, but also the characteristic clonal cytogenetic changes associated with MDS can be identified in lymphocyte populations as well [5]. Corroborating this is the observation that, while MDS frequently evolves into acute myelogenous leukemia, it may also in rare cases progress to acute lymphoblastic leukemia [6]. Finally, investigators have recently succeeded in transplanting human MDS into severely immunocompromised mouse hosts by means of stem cell transplantation [7, 8].
Underlying Genetic and Epigenetic Changes

Although the mechanisms through which the complex cellular phenotype of MDS develops remain poorly understood, a growing number of genetic changes associated with this disease have been catalogued. Large-scale clonal cytogenetic changes are observed in over 50% of patients with MDS. These are typically chromosome gains or losses, the most common of which are -5/del5q (10-20% of MDS patients), +8 (10%), and -7/del7q (5-10%). Cytogenetic abnormalities have great value in assessment of prognosis (discussed below) [9]. Certain specific molecular genetic changes have also been observed in MDS patients. Point mutations in AML1 (25% of patients), NRAS (10-15%), FLT3 (10%), and p53 (5-10%) all likely play a part in the development or progression of MDS, but their impact on disease prognosis has not yet been fully evaluated [10, 11].

Epigenetic changes are defined as heritable changes in gene expression that do not entail changes in DNA sequence, and included methylation and acetylation of chromatin and histones. In MDS the phenomenon of regional hypermethylation is thought to lead to the loss of expression of tumour suppressor genes, which in turn contribute to the development or progression of MDS. While the specific genes deregulated in this manner have not been exhaustively studied, this observation has led to the development of therapeutic agents that target methylation (see below) [12].

The Role of Autoimmunity in MDS Pathogenesis

Several laboratory and clinical observations support the idea that abnormalities in regulation of the immune response contribute to the pathogenesis of MDS. Alteration of CD4:CD8 T cell ratios is common in MDS, and molecular genetic studies have shown a high frequency of oligoclonal T-cell expansion. These observation, along with the similarity of the hypoplastic variant of MDS to aplastic anaemia, a disease with well-established autoimmune pathology, have led to the successful use of T-cell immunosuppressive therapy in some patients with MDS (see below). In addition, autoimmune complications may be associated with MDS in 10-13% of patients and may respond to immunosuppressive therapies [13, 14]. They can be classified into acute systemic vasculitis or autoimmune disorders, chronic or isolated autoimmune phenomena, classical connective tissue disorders (Sjögren’s, PMR, SLE, RA, relapsing polychondritis), immune mediated hematological abnormalities (ITP, AIHA) and asymptomatic serological immunological abnormalities [15].

PNH has been associated with myelodysplastic syndromes (MDS). In a study of 90 MDS patients compared with 20 healthy controls CD55- and CD59-deficient granulocytic populations were detected in 15.5% of MDS patients compared to 2.8% of normal individuals [16].

Diagnosis

Patients with MDS typically present with peripheral blood cytopenias, which are recognized incidentally when a complete blood count is performed or which result in symptoms reflecting anaemia, neutropenia, or thrombocytopenia. Although anaemia is common in older adults, a diagnosis of MDS should be considered in anaemic elderly patients, particularly when accompanied by other cytopenias, or an increase in the MCV or RDW. The diagnosis of MDS is dependent on demonstration of dysplastic features in the peripheral blood and marrow. Flow cytometry of bone marrow cells can show characteristic abnormalities in MDS and this technique has an emerging role in MDS diagnosis, but has not yet been fully validated for this purpose. While MDS is most commonly associated with increased bone marrow cellularity, myelofibrotic [17] and hypoplastic variants [18] are also reported. Classically, MDS has trilineage dysplasia, but occasionally dysplasia may be confined to 1 or 2 lines. The differential diagnosis includes [19]:

- Vitamin B12 or folate deficiency
- Proven exposure to heavy metals
- Recent cytotoxic therapy
- HIV
- Autoimmune diseases
- Chronic liver diseases and/or chronic alcohol use
MDS has until recently been classified from the French-American-British (FAB) system [20]. Recently the World Health Organization (WHO) system has become the international standard [21]. The criteria for these two systems are summarized in the table below. Major distinguishing features include recognizing differences between morphologic dysplasia restricted to one cell lineage or all cell lineages, deeming the 5q-syndrome to be an entity of its own, creating the entities MDS unclassifiable and MDS/MPD and lowering the diagnostic BM blast percent for AML from 30% to 20%.

Table 1- Myelodysplastic Syndromes (MDS) [22]

<table>
<thead>
<tr>
<th>FAB subtype</th>
<th>WHO subtype [23]</th>
<th>Bone marrow blasts (%)</th>
<th>Blasts in peripheral blood (%)</th>
<th>Monocytes &gt;1000/µl in peripheral blood</th>
<th>Ringed sideroblasts &gt;15%</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>RA without ringed sideroblasts a</td>
<td>&lt;5</td>
<td>&lt;1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RARS</td>
<td>RA with ringed sideroblasts a</td>
<td>&lt;5</td>
<td>&lt;1</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Refractory cytopenia with multilineage dysplasia a</td>
<td>&lt;5</td>
<td>&lt;1</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td>5q-syndrome</td>
<td>&lt;5</td>
<td>&lt;1</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>RAEB</td>
<td>RAEB-1</td>
<td>5-10%</td>
<td>&lt;5</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td>RAEB-2</td>
<td>11-20%</td>
<td>&lt;5</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td>MDS unclassifiable</td>
<td>&lt;1-20</td>
<td>&lt;5</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>CMML</td>
<td>CMML&lt;13,000 leukocytes/µl</td>
<td>&lt;1-20</td>
<td>&lt;1-20</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>RAEB-T</td>
<td>AML</td>
<td>21-30</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
</tbody>
</table>

Myelodysplastic Syndromes/myeloproliferative Disorders

| CMML >13,000 leukocytes/µl | 0-20% | <1-20% | + | +/- |

AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; RA, refractory anemia; RAEB, refractory anemia with excess of blasts; RAEB-T, refractory anemia with excess of blasts in transformation; RARS, refractory anemia with ringed sideroblasts.

Table 1 adapted from Verbeek, W. and A. Ganser, Evolving treatment options of myelodysplastic syndromes. Ann Hematol, 2001. 80(9): p. 499-509. Copyright 2001 Oxford University Press. All rights reserved, used with permission.

Prognosis & Staging (for CMML see page 14)

MDS is a heterogeneous group of diseases with variable outcome [19, 24, 25]. Factors that predict outcome include:

- WHO subtype
- Complex karyotype [24]
- Chromosome 5 or 7 abnormalities [24]
- Increased CD34 expression [26, 27]
- Abnormal localization or immature precursors (ALIP) [27]
- Therapy related MDS
- Fibrosis [28]
- Mutational status [29]
- Increased VEGF and microvessel density [30]
- Beta-2 microglobulin [31]
- Transfusion dependence [32]

Prognosis

The WHO classification has independent prognostic value in MDS [33], but does not account for the prognostic value of cytogenetics. The IPSS is most commonly used for risk stratification, can only be applied if cytogenetics analysis has been performed and was recently validated prospectively [34]. Its limitation is that it is calculated at the time of diagnosis and may not provide sufficient prognostic information at the initiation of treatment. The WHO classification-based prognostic scoring system (WPSS) is a more dynamic prognostic
model that can be applied to MDS patients at any time during their clinical course. It marries characteristics from the WHO classification and the IPSS and inserts a new variable into the prognostic equation: transfusion dependence [35]. In the WPSS, the most important variables for the prognostic model are WHO subgroups, karyotype and transfusion requirement. The WPSS classifies patients into five risk groups showing different survivals and probabilities of leukemic evolution at any time during follow-up.

### Table 2. WHO Classification-Based Prognostic Scoring System for MDS [35]

<table>
<thead>
<tr>
<th>Variable</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO Category</td>
<td>RA, RARS, 5q-</td>
<td>RCMD, RCMD-RS</td>
<td>RAEB-1</td>
<td>RAEB-2</td>
</tr>
<tr>
<td>Karyotype*</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>—</td>
</tr>
<tr>
<td>Transfusion requirement†</td>
<td>No</td>
<td>Regular</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Note. Risk groups were as follows: very low (score = 0), low (score = 1), intermediate (score = 2), high (score = 3 to 4), and very high (score = 5 to 6).

Abbreviations: MDS, myelodysplastic syndrome; RA, refractory anemia; RARS, refractory anemia with ringed sideroblasts; 5q-, myelodysplastic syndrome with isolated del(5q); and marrow blasts less than 5%; RCMD, refractory cytopenia with multilineage dysplasia; RCMD-RS, refractory cytopenia with multilineage dysplasia and ringed sideroblasts; RAEB-1, refractory anemia with excess of blasts-1; RAEB-2, refractory anemia with excess of blasts-2.

*Karyotype was as follows: good: normal; -Y del(5q); poor: complex (> three abnormalities), chromosome 7 anomalies; and intermediate: other abnormalities.

†RBC transfusion dependency was defined as having at least one RBC transfusion every 8 weeks over a period of 4 months.

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Table 3 - The International Prognostic Scoring System (IPSS)

<table>
<thead>
<tr>
<th>BM Blast %</th>
<th>&lt;5</th>
<th>5-10</th>
<th>11-20</th>
<th>21-30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>+ 0</td>
<td>+ 0.5</td>
<td>+1.5</td>
<td>+ 2</td>
</tr>
<tr>
<td>Karyotype</td>
<td>Normal, -Y,5q-,20q-</td>
<td>Other abnormalities</td>
<td>Complex, or chromosome –7 abnormalities</td>
<td></td>
</tr>
<tr>
<td>Score</td>
<td>+ 0</td>
<td>+ 0.5</td>
<td>+ 1</td>
<td></td>
</tr>
<tr>
<td>Cytopenias (# of lineages involved)</td>
<td>0/1</td>
<td>2/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score</td>
<td>+ 0</td>
<td>+ 0.5</td>
<td>1.5-2</td>
<td>&gt;2</td>
</tr>
<tr>
<td>Total Score</td>
<td>0</td>
<td>0.5-1</td>
<td>1.5-2</td>
<td>&gt;2</td>
</tr>
<tr>
<td>Risk Group</td>
<td>Low</td>
<td>Intermediate 1</td>
<td>Intermediate 2</td>
<td>High</td>
</tr>
<tr>
<td>Median Survival (Years)</td>
<td>5.7</td>
<td>3.5</td>
<td>1.2</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Baseline Investigations

The following should be performed in most patients with MDS at time of initial assessment:

- CBC, differential
- Blood film
- Retic count
- Direct antiglobulin test (DAT)
- Bone marrow aspirate and biopsy with cytogenetics
- Vitamin B12, red cell folate, ferritin, iron saturation
- TSH
- Serum EPO level
- Liver and renal profile
- 2-D echo and 12-lead ECG
- HLA DR 15 testing should be ordered if patient being considered for immunosuppressive therapy
- HFE testing in patients without RARS who present with elevated ferritins in the absence of transfusions
- JAK2 mutational testing in patients with myeloproliferative features e.g. thrombocytosis or leukocytosis
- PNH testing by flow cytometry
- TEL/PDGFRbeta and Hip1/PDGFRbeta fusion proteins by nested PCR or t(5;12) and del(4q12) by FISH in patients with CMML

In Toronto and the metro area, send cytogenetics to:

Cancer Cytogenetics
The Banting Institute (Room 77) 100 College Street
Toronto, Ontario, M5G 1L5 Telephone #: 416-978-3333

Or

Cancer Cytogenetics
North York General Hospital 4001 Leslie Street
Toronto, Ontario M2K 1E1 Telephone # 416- 756-6438

If patient has secondary MDS, then specific chromosomal abnormalities (e.g. chromosome 5, 7 or 11) may be requested by FISH if conventional cytogenetics fail to show dividing cells.
Treatment

MDS can be divided into low-risk (IPSS L, LI) and high-risk (IPSS HI, H) categories. Two thirds of MDS patients have low risk disease. Low-risk MDS patients have the longest survival and the primary therapeutic goals in these patients should be to improve ineffective hematopoiesis, quality of life and limit iron toxicity. The primary therapeutic goal in high-risk MDS patients should be to extend survival and delay transformation to acute leukemia.

For patients that are high-risk the following treatment options exist:

A. Stem Cell Transplantation

Allogeneic transplant is the only known curative therapy for MDS. In a registry study of 885 patients with MDS or secondary AML who received HLA matched sibling donor transplants, 3-year relapse-free survival was 53% for RA, 46% for RAEB, and 38% for RAEB-T/sAML [36]. Non-relapse mortality can be as high as 39% for older patients (55-66) [37]. Predictive factors of good outcome include: younger age, shorter disease duration, HLA compatibility, primary MDS, < 10% blasts, good risk cytogenetics and low IPSS score. In more advanced FAB subtypes non-myeloablative (mini) transplants are being investigated, and have extended the age limit to 65-70 but its place remains to be determined in view of its higher relapse rate [38]. A decision analysis of allogeneic BMT for MDS found that delaying transplantation in low-risk MDS maximized overall survival. Immediate transplantation for high-risk MDS was associated with maximal life expectancy [39]. A recent study showed a strong association between elevated pre-transplant serum ferritin concentration and poor post-transplant outcome in MDS patients, suggesting that iron chelation therapy (see below) may be of value prior to transplant in these patients. Because some patients with MDS can have cytogenetically normal polyclonal hematopoiesis after treatment with chemotherapy, autologous transplantation is an experimental option [40] and shows some promise [38, 41]. Nevertheless, ABMT should only be performed within the context of a clinical trial.

B. AML-type Chemotherapy

AML-type chemotherapy is capable of inducing complete responses in 40-50%, but they are rarely durable. The response to anti-AML therapy is similar in high risk MDS and AML [42]. Historically, CR rates appear lower than for de-novo AML, but may be similar for highly selected patients with favorable characteristics (Age < 45 with normal karyotype) [43]. Early mortality ranges from 8-24% with median survivals of 9-24 mo [44]. RAEB-T in the FAB classification is now considered AML and should be treated as AML. Estey, et al. from the MD Anderson has found that the widespread use of intense chemotherapy regimens in the 1990’s for MDS has not changed outcome [45].

C. Low Intensity Therapy

Epigenetic Therapy: DNA Methyl Transferase Inhibitors

Hypermethylation of specific gene promoters, resulting in suppression of gene transcription, is a frequent feature of cancer and has been implicated in the pathogenesis of MDS and the progression to AML. DNA methyltransferase inhibitors show activity in both low and high risk MDS and may alter the natural history of the disease. The two most studied agents are listed below and summary data of efficacy are included in table 4. Observations common to both include median time to response of 4-6 cycles (less for decitabine 5 day schedule) and myelosuppression. Given their temporary biological effects on global methylation, these drugs should be administered as close to schedule with growth factor support and antibiotic prophylaxis if necessary.

5-Azacitidine (5-Aza, VidazaTM)

5-Azacitidine (5-Aza, VidazaTM) undergoes conversion to 5-deoxy-azacitidine before incorporation into DNA and binding to and depleting methyltransferases. In a phase III multicenter study of the CALGB [46], 5-AZA given subcutaneously 7 out of 28 days was studied against observation in a crossover model. The overall response rate was 60% (7% CR, 16% PR, 37% Improved) compared with 5% in control arm. Median time to leukemic transformation was 21 months in the 5-AZA arm, versus 13 months in supportive care arm (P =
0.003) suggesting that the drug decreased the rate of transformation to AML. There was no significant difference in survival, likely because of the crossover. No difference in response rate was observed in different MDS risk groups. Quality of life was enhanced in responding patients [47]. Based on these data, azacitidine received approval by the FDA for use in MDS patients and is in widespread use in USA and Europe. A survival benefit to Vidaza versus conventional care was recently demonstrated by an international RCT (n=358) of Vidaza versus conventional care (including LDAC, BSC or standard chemotherapy) in higher risk MDS patients (10-29% marrow blasts). Median survival for Vidaza was 24 months versus 15 months for CCR (p=.0001) [48]. In the pooled analysis of 3 CALGB trials (8421, 8921 and 9221) of 5-Aza re-analyzed according to WHO criteria for response in MDS, the CR rate was 10-17% and 23-36% achieved HI. The median number of cycles to first response was three and 90% of responses were seen by cycle 6. The median duration of response was 13.1 months (2-166+ months)[49].

5-Aza-2-Deoxycytidine (Decitabine, DacogenTM)

Decitabine is a more DNA-specific nucleoside analog and potent hypomethylating agent. Results of a US multicenter phase III MDS trial (n = 170) were recently presented at the 2004 ASH Annual Meeting. Decitabine, administered IV every 8 hours for 3 days/month was effective in delaying time to AML progression or death, especially in high-risk patients. The overall response rate was significantly higher compared to the supportive care arm. Using the IWG response criteria, 9% of patients had a complete response and 8% had a partial response. 13% had hematologic improvement for an overall response rate of 28%. There was a 50% reduction in transfusion requirements and a delay until leukemia and death in higher risk MDS subtypes. The median duration of response was 8.7 months [50]. Decitabine dosed as 20 mg/m² IV daily for 5 days/28d schedule is associated with higher response rates [51-53] and this schedule has currently been validated in a multi-center phase II study[54] Decitabine may offer improved survival compared with cytarabine-based intensive chemotherapy in high risk MDS in one retrospective study[55].

Availability of Hypomethylating Agents

Although both 5-Azacytidine and Decitabine are of proven benefit, have received FDA approval and are part of routine care for MDS in the U.S.A., neither has been submitted for approval by Health Canada. Both agents may be obtained through the Health Canada Special Access Program on an individual case-by-case basis, with the drug costs being borne by the patient.

Table 4 – Summary of Key Clinical Trials of Hypomethylating Agents in MDS

<table>
<thead>
<tr>
<th></th>
<th>Vidaza CALGB 922113</th>
<th>Vidaza Updated CALGB 922113</th>
<th>Dacogen Randomized Phase 3</th>
<th>Dacogen 5-day schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>99</td>
<td>99</td>
<td>89</td>
<td>95</td>
</tr>
<tr>
<td>CR, No. (%)</td>
<td>7 (7)</td>
<td>10 (10)</td>
<td>8 (9)</td>
<td>32 (34)</td>
</tr>
<tr>
<td>PR, No. (%)</td>
<td>16 (16)</td>
<td>1 (1)</td>
<td>7 (8)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>HI, No. (%)</td>
<td>37 (37)</td>
<td>36 (36)</td>
<td>12 (13)</td>
<td>13 (13)</td>
</tr>
<tr>
<td>ORR, No. (%)</td>
<td>60 (60)</td>
<td>47 (47)</td>
<td>27 (30)</td>
<td>46 (48)</td>
</tr>
</tbody>
</table>

D. Low Dose Chemotherapy

Low dose cytosine arabinoside (Ara-C) is the most extensively studied agent in this category. Although low dose Ara-C has been reported to induce complete or partial remissions in approximately 30% of patients with RAEB, RAEBT and MDS, the only prospective randomized phase III comparing low dose ara-C with supportive care failed to show improvement in survival [56, 57]. Responses may be as high as 55% in patients with platelet counts >150, or without ringed sideroblasts, cellularity >70%, or complex karyotype [58]. Low dose melphalan (2 mg/day) has been studied in two small series with response rates of 38% and 40% [59, 60], but responses may not be durable and may be associated with the development of 17p deletion.
E. Angiogenesis Inhibitors

Angiogenesis, the process by which new blood vessels are formed, is increased in the bone marrow in MDS [30, 61-63]. Studies suggest a correlation between increased VEGF and progression to leukemia possibly via autocrine and paracrine stimulation [64-67]. This process is therefore a logical target for therapy. Anti-angiogenic agents being studied in MDS include thalidomide, thalidomide analogues (CC-5013) (see below) as well as VEGF receptor antagonists and matrix metalloproteinase inhibitors to name a few [68-70]. Combination approaches of thalidomide with other agents are being explored. SU5416, a VEGF receptor antagonist has also shown some success in MDS [71] and its successor S6668 and others are currently in clinical trials.

F. Histone Deacetylase Inhibitors

Histones are very important for chromatin architecture and gene transcription. When histones are acetylated, gene transcription is enhanced. Histone deacetylation by HDACs leads to chromatin condensation and suppression of gene transcription. In MDS, this may lead to transcriptional silencing of tumor suppressor genes. Several HDAC inhibitors are now undergoing investigation in MDS trials, including phenylbutyrate, valproic acid (VPA) and other. In one small phase II study, (n=18), 44% of patients responded to VPA monotherapy, including one partial remission [72]. HDACI’s may act synergistically with hypomethylating agents to improve response rates [73]. Emerging data suggest that responses to VPA as a single agent may be more frequent in low risk MDS [74, 75].

G. Arsenic Trioxide (ATO, Trisenox™)

Arsenic may function as an inhibitor of angiogenic signaling and autocrine signaling in AML. In one recent study, HI rates were 34% and 39% in lower-risk patients, and 6% and 9% in higher-risk patients, respectively; the overall major HI rates were 20% and 22%. Transfusion independence or reduction by $\geq 50\%$ occurred in 33% of patients dependent on RBC transfusions. The overall median duration of HI was 6.8 months (range, 2 to 40 months). Toxicity was moderate [76]. In another study, the overall rate of hematologic improvement (intent-to-treat) was 24 (19%) of 115 patients with MDS, 16% of RBC transfusion-dependent patients and 29% of platelet transfusion-dependent patients became transfusion independent. Toxicity was mild to moderate [77]. Arsenic in combination with other agents is currently undergoing clinical evaluation on trial for MDS.

H. Farnesyl Transferase Inhibitors (FTI’s)

FTIs represent a class of signal transduction inhibitors that disrupt the signals, which promote proliferation in leukemic or myelodysplastic cells. Approximately 10-30% of patients with MDS have an activating mutation in one of the Ras family proteins. FTI’s disrupt Ras protein activity by preventing the addition of a farnesyl group, hence preventing membrane attachment and activation. Tipifarnib and Lonafarnib are the FTIs most studied in MDS. In small studies, their activity in MDS is associated with response rates that range from 11-29%, but tipifarnib was associated with greater toxicity and discontinuation rates [78, 79]. A multicenter phase 2 study evaluated the use of tipifarnib (R15777) in patients with poor-risk myelodysplastic syndrome (MDS; French-American-British classification). Patients (n = 82) received tipifarnib 300 mg orally twice daily for the first 21 days of each 28-day cycle. Twenty-six patients (32%) responded to tipifarnib: 12 (15%) complete responses (CRs) and 14 (17%) hematologic improvements; (modified International Working Group criteria, 2006). Among the 12 CRs, the median response duration was 11.5 months (range, 2.0-21.9 months), the median time to progression was 12.4 months (range, 3.9-23.8 months), and 7 were still alive at time of analysis (all > 3 years). Median overall survival was 11.7 months (95% CI, 9.4-15.0). Grade 3-4 neutropenia (18%) and thrombocytopenia (32%) were the most common treatment-related adverse events; severe nonhematologic adverse events were rarely reported. In this study, durable responses and acceptable side effects were observed [80]. Lonafarnib seems to be particularly active in MDS patients with plt. transfusion dependence (24% HI and 26% plt transfusion independence). Gastrointestinal toxicity was significant with 19% of patients discontinuing therapy due to diarrhea, nausea and/or anorexia [81]. The optimal doses and schedules of these FTI’s are still being explored in clinical studies.
For patients that are low-risk the following treatment options exist:

A. Hematopoietic Growth Factors

Anemia is very common in MDS. More than 50% of patients are anemic (hgb < 10g/dl) at presentation and more than 80% of patients require RBC transfusions during their course of disease.

Erythropoietin and Granulocyte Colony Stimulating Factor (G-CSF)

Erythropoietin and G-CSF have been extensively studied in MDS and is the subject of a NCCN evidence-based guidelines and a meta-analysis [82]. In a randomized trial erythropoietin resulted in an improvement in transfusion requirement compared to placebo [83]. Used alone, erythropoietin may alleviate anemia in 15-20% of patients. The addition of G-CSF to erythropoietin appears to increase erythroid response, particularly in RARS patients [84, 85] with responses as high as 75% reported if there was unilineage dysplasia [86]. Responses to erythropoietin appear to be greater in patients with a serum erythropoietin level <500 and/or a requirement of ≤ 2 units of red blood cells per month (see Table 5 below for Nordic MDS Study Group predictive scoring model). This has been validated by the same authors in a prospective test sample of 53 patients [87], using doses of erythropoietin of 10,000 units SQ for 5/7 days and Neupogen 75, 150 or 300 µg tiw dose adjusted to keep ANC of 6-10. Median durations of CR and PR responses were 29 months and 5.5 months. Recommended starting doses of erythropoietin are 40,000-units/week, but up to 70,000 units/week may be needed. They can be given in multi or single weekly schedules [88, 89]. Retrospective analysis of Groupe Francophone des Myelodysplasies (GFM) trials evaluating epoetin or darbepoetin +/- G-CSF in 403 MDS patients demonstrated the median response duration to growth factor therapy to be 20-24 months. Higher response rates were observed with < 10% blasts, low and Int-1 IPSS, RBC transfusion independence, serum EPO level < 200 IU/L and shorter interval between diagnosis and treatment. Longer response durations were associated with major responses, IPSS low-Int-1, blasts < 5% and absence of multilineage dysplasia. Provocatively, the cohort of ESA treated MDS patients compared with untreated MDS cohort used to design the IPSS (IMRAW database) suggested that epoetin or DAR treatment may have a favourable survival impact in MDS [90]. A similar survival benefit (HR 0.57, p=.015) with no adverse effect on leukemia evolution of ESA therapy in patients with lower transfusion needs has been observed by the Nordic MDS group [91].

<table>
<thead>
<tr>
<th>Erythropoietin</th>
<th>Score</th>
<th>RBC Transfusion needed</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100</td>
<td>+2</td>
<td>&lt; 2 units/month</td>
<td>+2</td>
</tr>
<tr>
<td>100-500</td>
<td></td>
<td>≥ 2 units/month</td>
<td></td>
</tr>
<tr>
<td>&gt; 500</td>
<td>- 3 points</td>
<td></td>
<td>- 2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Score</th>
<th>&gt; +1</th>
<th>±1</th>
<th>&lt; -1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>74%</td>
<td>23%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Duration of Use

Although most trials of growth factors are 8-16 weeks, there is evidence from a Greek MDS study of 281 patients that prolonged administration (i.e. > 26 weeks) is associated with higher response rates (18% at 12 weeks and 45% at 26 weeks) [92].

There is no role for prophylactic G-CSF or GM-CSF for severe neutropenia, although its use may be considered during an episode of sepsis. G-CSF should not be used as priming prior to cytotoxic chemotherapy for high risk MDS.
Darbepoetin

Recent studies have shown that longer-acting hyperacetylated forms of erythropoietin (e.g., darbepoetin, Aranesp™) given less frequently (q 1-3 weeks) can yield an erythropoietic response comparable to that achieved with erythropoietin + G-CSF [93-96]. An open-label, phase II non-randomized trial was conducted with darbepoetin (DAR), an erythropoiesis-stimulating factor with prolonged half-life, at a weekly dose of 300 mcg subcutaneously in 62 anaemic patients with myelodysplastic syndrome (MDS) with an endogenous erythropoietin (EPO) level < 500 mU/ml. Most of the patients were classified as low or intermediate 1 according to the International Prognostic Scoring System. After 12 weeks, 44 (71%) patients had an erythroid response (34 major and 10 minor), including eight of 13 patients who were previous non-responders to conventional EPO. Median dose of DAR required to maintain response was 300 µg every 14 d [97].

Although growth factors do decrease transfusion dependence in responders, their impact on overall quality of life and cost effectiveness is controversial [93, 98, 99].

Other growth factors such as IL-11 for thrombocytopenia have mild efficacy in MDS, but have troublesome side effects [100]. AMG 531, a thrombopoietin (TPO) receptor agonist, has been studied in a phase 1-2 study for thrombocytopenic MDS patients. The ORR was 41% with a median duration of response of 23 weeks. A larger phase III placebo-controlled study is planned [101].

B. Immunosuppressive Therapy (IST)

Immune mechanisms have been implicated in the pathogenesis of marrow failure in MDS [102]. In addition to restricted or clonal T-cell populations, monocytes have been found to be activated in patients with myelodysplastic syndromes that may contribute to bone marrow failure through CD40-CD40L interactions with T helper cells. This was more commonly seen in younger patients and those with trisomy 8 [103].

Immunosuppressive therapy has activity in MDS [104-106]. Options studied included antithymocyte globulin (ATG) and cyclosporin A. Previous smaller phase II studies of ATG have demonstrated activity in all three lineages and improved survival in responders compared with non-responders. Median response durations were 10 months but 76% of responders maintained transfusion independence for 32 months [104, 107, 108]. Cyclosporin A (3-5 mg/kg) has been studied alone and in combination with ATG for hypoplastic or normocellular MDS [105, 106, 109]. Pooled results from case series with a total of 72 patients demonstrated a RR of 61% [110].

In the largest published study to date from the NIH, one hundred twenty-nine patients with MDS received IST with a median follow-up of 3.0 years (range, 0.03 to 11.3 years), were treated with antithymocyte globulin (ATG) or cyclosporine (CsA) in combination or singly. Variables affecting response and survival were studied and outcomes were compared with those of 816 patients with MDS reported to the International Myelodysplasia Risk Analysis Workshop (IMRAW) who received only supportive care. RESULTS: Thirty-nine (30%) of 129 patients receiving IST responded either completely or partially: 18 (24%) of 74 patients responded to ATG, 20 (48%) of 42 patients responded to ATG plus CsA, and one (8%) of 13 patients responded to CsA. Thirty-one percent (12 of 39) of the responses were complete, resulting in transfusion independence and near-normal blood counts. In multivariate analysis, younger age was the most significant factor favoring response to therapy. Other favorable factors affecting response were HLA-DR15 positivity and combination ATG plus CsA treatment (P = .001 and P = .048, respectively). In multivariate analysis of the combined IMRAW and IST cohorts, younger age, treatment with IST, and intermediate or low International Prognostic Scoring System score significantly favored survival. In summary, IST produced significant improvement in the pancytopenia of a substantial proportion of patients with MDS and was associated with improved overall and progression-free survival, especially in younger individuals with lower-risk disease.

A recent predictive model has been developed to help identify patients most likely to respond to immunosuppression. The predictive model is as follows: Patients who are DR15+ whose age (y) added to red cell transfusion dependence [(RCTD) (mo)] is less than or equal to 71 have a high probability of response (41%-100%). DR15+ patients whose age (y) + RCTD (mo) is less than or equal to 57 also have a high probability of response (41%-100%). All other patients have low predicted probabilities of response and should not be offered immunosuppressives as therapy. Roughly 35% of patients are DR15+. These authors suggested that only low/low-intermediate IPSS-risk patients should be considered for immunosuppressive therapy because of the possibility that T cell suppression may promote progression to AML in higher-risk cases [111].
In another series from Germany, low IPSS score and bone marrow hypocellularity in MDS patients predicted hematological responses to ATG [112].

C. Cytokine Inhibition

Marrow and serum levels of TNF-α, interferon-α, IL-1β, TGF-β, and interferon-γ are increased in MDS. Amifostine, Remicade, pentoxifylline, dexamethasone and ciprofloxacin appear to inhibit the production of these cytokines and have been studied in small series with modest results [113-118].

D. Differentiating Agents

Polyclonal CD34(+) stem cells have been identified in PBPC harvests [40]. Retinoids including 13-cisretinoic acid, vitamin D₃, interferons, hematopoietic growth factors, and ATRA have been studied and demonstrate either minimal activity or, absence of benefits in overall survival (OS) or leukemia free survival (LFS) [119-126].

E. Thalidomide

In a recently published clinical trial of 83 patients with MDS treated with thalidomide (100-400 mg/day)[68] and in an updated series of 248 un-selected patients [127], the response rate was 19-21% with a large drop-out rate from side effects (28%) Responses were greater in patients with low risk disease, lower blast counts and higher platelet counts. Few patients with RAEB responded. Responses may take 3-5 months to be seen and lower doses with slower dose escalation (100 up to 400 mg/day) are required.

F. Lenalidomide, Revlimid ™, Revimid ™

Lenalidomide is a thalidomide analog with a distinct clinical profile that has demonstrated erythroid responses leading to RBC transfusion independence, particularly in del(5q) MDS [128], but also in some patients with Low or Int-1 MDS lacking the del(5q) chromosomal abnormality [129]. Although the exact mechanism of action is yet to be defined, lenalidomide has many biological activities including anti-angiogenesis, immunomodulation, anti-cytokine and direct toxic effect on malignant bone marrow cells [130].

In a small phase II study, List et al showed that this agent is very active in low-risk MDS patients unresponsive to EPO therapy or unlikely to respond to EPO therapy. Erythroid responses occurred in 56% of patients and cytogenetic response was observed in 75% of del5q patients [131]. Two subsequent multi-phase II multi-center trials of over 360 patients have been completed and are summarized in the table below. Based upon this report, this exciting immunomodulatory (ImiD) drug has received January 2008 provisional notice of compliance by Health Canada for use in patients with del 5q MDS with or without additional cytogenetic abnormalities.

Analysis of MDS-003 has shown that the induction of early cytopenias on lenalidomide correlates with a response to lenalidomide. Longer TI duration was associated with lower IPSS score, lower karyotype complexity and 5q- syndrome. A comparison of overall survival by karyotype complexity suggests that lenalidomide may favorably impact survival in patients with greater cytogenetics complexity. Median survival was 96 months among patients with isolated del 5q (n=128) compared to 67 months in patients with ≥ 1 additional chromosomal abnormality. These data suggest that lenalidomide may favorably impact survival in higher risk patients. These data also suggest that the mechanism of action of lenalidomide is karyotype dependent, acting through suppression of the abnormal clone in del 5q patients while directly promoting erythropoiesis in patients with alternate karyotypes [132].
Table 6 – Lenalidomide in MDS with and without del5q

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Raza et al. [129]</th>
<th>List A. et al.[128]</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS 002: Multicenter Phase 2</td>
<td>MDS003: Multicentre Phase 2</td>
<td></td>
</tr>
<tr>
<td><strong>Patient Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusion dependent low or int-1 risk MDS without deletion 5q with plt count &gt; 50k and at least 2 units over preceding 8 weeks</td>
<td>Transfusion dependent low or int-1 risk MDS with deletion 5q with plt count &gt; 50k and at least 2 units over preceding 8 weeks</td>
<td></td>
</tr>
<tr>
<td><strong>Sample Size</strong></td>
<td>214</td>
<td>148</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>10 mg po daily or on 21/28 day schedule</td>
<td>10 mg po daily or on 21/28 day schedule</td>
</tr>
<tr>
<td><strong>Transfusion Independence (TI)</strong></td>
<td>26%</td>
<td>67%</td>
</tr>
<tr>
<td><strong>Median Time to Response</strong></td>
<td>4.8 weeks (1-39)</td>
<td>4.6 weeks (1-49)</td>
</tr>
<tr>
<td><strong>Median Duration of TI</strong></td>
<td>41 weeks</td>
<td>Not reached at 2 years</td>
</tr>
<tr>
<td><strong>50% Reduction in Transfusions</strong></td>
<td>17%</td>
<td>9%</td>
</tr>
<tr>
<td><strong>Overall HI</strong></td>
<td>43%</td>
<td>76%</td>
</tr>
<tr>
<td><strong>Cytogenetics Remission</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>19%</td>
<td>85%</td>
</tr>
<tr>
<td>Partial</td>
<td>4/9</td>
<td>45%</td>
</tr>
<tr>
<td>5/9</td>
<td></td>
<td>28%</td>
</tr>
<tr>
<td><strong>Toxicity</strong></td>
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<td></td>
</tr>
<tr>
<td>Grade ≥ neutropenia</td>
<td>30%</td>
<td>55%</td>
</tr>
<tr>
<td>Grade ≥ thrombocytopenia</td>
<td>25%</td>
<td>44%</td>
</tr>
<tr>
<td><strong>Bone Marrow Response</strong></td>
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<td></td>
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<tr>
<td>Resolution of dysplasia</td>
<td>N/A</td>
<td>36%</td>
</tr>
<tr>
<td>Normalization of blast count</td>
<td>7%</td>
<td>74%</td>
</tr>
<tr>
<td>Resolution of ringed sideroblasts</td>
<td>16%</td>
<td>64%</td>
</tr>
<tr>
<td>Progression to higher grade/AML</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Dose adjustments required</strong></td>
<td>55%</td>
<td>84%</td>
</tr>
<tr>
<td><strong>Discontinuation for adverse events</strong></td>
<td>N/A</td>
<td>20%</td>
</tr>
</tbody>
</table>

**Practical Aspects of Lenalidomide Use**

Detailed recommendations for the use of lenalidomide have recently been published [133]. Lenalidomide is recommended in the treatment of patients with low- or intermediate-risk MDS and -5/del5q, whether as a solitary abnormality or in combination with other chromosome changes. The recommended starting dosage is 10 mg PO OD, 21 days out of 28. Neutropenia and thrombocytopenia are very common, both occurring in >50% of patients. Support with G-CSF (300 μg twice weekly) is recommended for patients with absolute neutrophil counts < 1.0, while platelet transfusions may be given to permit continued administration of the drug in patients with thrombocytopenia. Venous thromboembolism (VTE) is rare in MDS patients on lenalidomide, but because of the strong association between lenalidomide and VTE in multiple myeloma, physicians should consider VTE prophylaxis with low molecular weight heparin in patients with prior history of VTE. The commonest non-hematologic adverse effects of lenalidomide are diarrhea and rash, each occurring in ~30% of patients. These conditions tend to be benign and self-limited, and seldom require dose adjustment or discontinuation of lenalidomide therapy.

**G. Hypomethylating Agents**

Hypomethylating agents have also been shown to be active in low risk MDS. See section above.
Supportive Care

Transfusion

Frequent RBC transfusions may cause significant complications such as transfusion reactions, infections and iron overload. A substantial number of patients with MDS become red cell transfusion dependent and this rate increases with IPSS risk category (low risk 39%; Int-1: 50%; Int-2: 63% high risk: 79%) [134]. In the Pavia study, the transfusion frequency as measured by the number of transfusions per month associated with a proportional decline in both overall and leukemia-free survival [33]. In MDS patients, there is a positive correlation between Hb level and health related quality of life [135]. Red cell transfusion can effectively palliate fatigue in patients with MDS. No single threshold should be used for all patients, but a symptomatic threshold should be identified for each patient. Transfusion reactions are common in MDS with approximately 35% of patients developing antibodies. Phenotyping MDS patients before they become RBC transfusion dependent is recommended with transfusion of phenotype matched units if possible. Because of platelet allo-immunization, platelet transfusion should be reserved for patients with excessive bleeding or bruising. Tranexamic acid may be used to minimize mucosal bleeding (1 g PO BID-TID).

Iron Chelation

A detailed review of the pathophysiology of iron overload in MDS and Canadian consensus guidelines for iron chelation therapy in this disease has recently been published [136]. The Pavia study has suggested that transfusion-related iron-loading is associated with unfavorable disease outcome through the inherent risks for organ complications. The presence of secondary iron overload as measured by serum ferritin concentration threshold greater than 1000 µg/ml was associated with a significant decrease in overall survival in patients with RA or RARS (HR 1.51; p < .001) [33]. Patients with good risk myelodysplastic syndrome projected to live 3.5 years or more who are transfusion dependent are at risk of transfusional iron overload. Each unit of blood (400 cm³) contains 200 mg of iron. Secondary hemochromatosis can develop when total body iron reaches 7-15 g. Desferrioxamine (deferoxamine, Desferal™) administered by subcutaneous pump 30-40 mg/kg daily for 5 days via CADD pump or 1 g bolus twice daily subcutaneously is the only licensed iron chelator in Canada. Patients on Desferal should have yearly audiology and ophthalmology assessments. ICL670 (Exjade™, Novartis) is an oral iron chelator with high iron-binding potency and selectivity. A large multi-center phase III study of once daily oral ICL670 (n=296) vs. deferoxamine (n=291) in patients with β-thalassemia and transfusional hemosiderosis demonstrated that Exjade at doses of 20 and 30 mg/Kg produced decreases in liver iron content comparable to deferoxamine. The most common adverse events included rash, gastrointestinal disturbances, and mild nonprogressive increases in serum creatinine. No agranulocytosis, arthropathy, or growth failure was associated with deferasirox administration [137]. In this study, patient-reported satisfaction and convenience were significantly higher for the once-daily, oral ICT deferasirox than for DFO infusions [138]. Gattermann et al recently reported the preliminary results of an open-label, multicentre, phase II study of 47 patients with MDS and transfusion-dependent anemia, who were treated with varying doses (5, 10, 20, or 30 mg/kg) of deferasirox (DSX) for 12 months, based on starting hepatic iron content. DSX produced an overall dose-dependent reduction in liver iron content (LIC) of 5.7 mg Fe/g dry weight and an overall dose dependent decline in serum ferritin of 267 µg/L. Generally mild to moderate side effects were reported by 45 patients; the most frequent adverse event was mild, transient gastrointestinal disturbance. Based on these results, DSX appears to be a convenient, effective, and well-tolerated oral chelator for iron overload in MDS patients [139, 140].

Exjade is currently licensed in Canada and available if private drug insurance is available. It is available via the Section 16 mechanism if the patient has an allergy or contraindication to Desferal. Exjade is also available or subsidized by Novartis depending on economic need via the Exjade assistance program. Call 1-866-395-2334 for more information or visit www.novartis.ca for more information.
CMML

CMML shares features both of MDS and a chronic myeloproliferative disorder and can be divided into dysplastic (MDS CMML) and proliferative (MPD CMML) forms. Patients with MPD CMML typically have hepatosplenomegaly, high leukocyte counts (>12 x 10⁹/L) and an elevated LDH [141]. There is no significant difference in survival between the two groups. Patients with MDS CMML should be treated similarly to other patients with MDS. It is important to note that the IPSS score excluded CMML patients with white counts more than 12,000 and is not relevant to most forms of CMML [142]. The MD Anderson has published and validated a CMML risk score based on the following 4 adverse prognostic markers. These include hemoglobin < 12 g/dl (RR 1.68), absolute lymphocyte count > 2.5 x 10⁹/L (RR 1.71), peripheral immature myeloid cells > 0% (RR 1.4) and increased LDH (RR 1.64). Median survivals for the resultant 4 risk categories were 34 months low (0-1 RF), 16 months intermediate 1 (2 RF), 8 months intermediate 2 (3 RF) and 7 months for high-risk (4 RF) [143]. Response to hydroxyurea is 60% and is superior to VP-16 [83]. Responses can be durable (median 24 mo). Responses and survival are inferior for patients with unfavorable karyotype or severe anemia. Patients with MPD CMML who are symptomatic should be treated with hydroxyurea (1-4 g/day). Dose should be titrated to maintain WBC (10-15 x 10⁹/L) and platelet count >30 x 10⁹/L. JAK2V617F activating mutation occurs in 7.8%-13% of chronic myelomonocytic leukemia [144] and should be checked at baseline in patients. Chronic myelomonocytic leukemia (CMML) is a myelodysplastic syndrome that has been associated with the expression of platelet-derived growth factor B receptor (PDGFRbeta) fusion proteins, namely TEL/PDGFRbeta. These fusion proteins possess a constitutive PDGFRbeta tyrosine kinase activity, leading to aberrant PDGFRbeta signaling and cellular transformation. TEL/PDGFRbeta and Hip1/PDGFRbeta fusion proteins have been observed in CMML at low frequency (4% each respectively) [145], but should be sought by nested PCR or t(5;12) and del(4q12) by FISH in patients with CMML in order to identify potential candidates for Gleevec. 5-AZA and DAC, albeit less studied, have impressive activity in CMML (ORR 25%-58%) [51, 146, 147], but are not currently available off study. Patients in whom hydroxyurea is ineffective can be offered low dose ara-C or melphalan.

Algorithm for MDS Management

The NCCN Clinical Practice Guidelines in Oncology for Myelodysplastic Syndromes V.I.2007 (www.nccn.org) were recently updated. Although not all of the drugs recommended are available in Canada, we expect that some may soon be licensed or available on compassionate release. Whenever possible, a referral for clinical trial is highly recommended.

References

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