MYELODYSPLASTIC SYNDROMES

Effective Date: November, 2009

The recommendations contained in this guideline are a consensus of the Alberta Provincial Hematology Tumour Team synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.
BACKGROUND

Myelodysplastic syndromes (MDS) are a collection of clonal neoplastic bone marrow disorders characterized by ineffective hematopoiesis, cytopenias, and frequent cytogenetic abnormalities.1,2 MDS occurs most frequently in the elderly, with a median age at diagnosis of 65-70 years, and the population prevalence increases with age.1,3 Progression to acute leukemia is seen in approximately 30 percent of patients; there is a spectrum of disease between myelodysplastic syndromes and acute leukemia with common cytogenetic abnormalities. While some patients have relatively slow disease progression, others will experience progressive cytopenias that will eventually result in death.1,3

The etiology of MDS is most commonly idiopathic; risk factors include exposure to benzenes, phenols, other industrial chemicals including heavy metals, and cigarette smoke. MDS is frequently secondary to exposure to ionizing radiation or chemotherapy, such as alkylating agents and topoisomerase-II inhibitors. In a minority of patients, MDS is associated with prior hematologic disorders such as aplastic anemia or paroxysmal nocturnal hemoglobinuria. A familial genetic link is frequent in children and rare in adults.4 MDS can arise out of constitutional genetic disorders (trisomy 21, trisomy 8 mosaicism, familial monosomy 7), congenital neutropenias (Shwachman-Diamond or Kostmann’s syndrome), or defective DNA repair (Fanconi’s anemia, ataxia-telangiectasia, Bloom’s syndrome).5 Cytogenetic abnormalities are found in 40-70 percent of de novo MDS and contribute to a less favourable prognosis.6-7

GUIDELINE QUESTIONS

- To identify the diagnostic criteria for MDS.
- To identify the management options for MDS, including supportive care and disease-modifying therapy.
- To outline prognostic markers for MDS.

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial Hematology Tumour Team. Members of the Alberta Provincial Hematology Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Hematology Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook.

This guideline was originally developed in November, 2007. This guideline was revised in November, 2009.

SEARCH STRATEGY

For this guideline update, the MEDLINE, PubMed, Cochrane Database of Systematic Reviews, Cochrane Register of Controlled Trials, and EMBASE databases were searched for publications between January 2008 and November 2009. In addition, the 2008 and 2009 ASCO and ASH Abstracts and Proceedings were reviewed. Search terms included Myelodysplastic Syndrome* AND [practice guidelines OR systematic review* OR review OR trial* OR clinical trial] AND [treatment OR management OR therapy OR
chemotherapy OR diagnosis OR prognosis]. In addition, the updated search yielded relevant clinical practice guidelines published by the National Comprehensive Cancer Network (NCCN), American Society of Hematology, (ASH), American Society of Clinical Oncology (ASCO), and the British Committee for Standards in Haematology (BCSH).8-11

RECOMMENDATIONS

**Diagnosis and Prognosis:**

1. The hallmark of diagnosis is dysplasia in >10% of cells in at least 1 cell lineage on bone marrow aspiration and biopsy. In patients with hypocellular marrow, the presence of dysplasia and cytogenetic abnormalities support the diagnosis of MDS over aplastic anemia.

2. Immunophenotyping and quantification of blasts by flow cytometry and full karyotype cytogenetic testing should be performed on the bone marrow.

3. In hypoplastic patients, paroxysmal nocturnal hemoglobinuria (PNH) screening should be performed on bone marrow or peripheral blood (flow cytometry for CD55 and CD59).

4. Causes of marrow dysplasia other than MDS should be ruled out before making a diagnosis of myelodysplasia, including viruses, drugs, and vitamin deficiencies.

5. All patients should have prognostication based on calculation of IPSS and WHO prognostic scales.

**Treatment:**

6. Hematopoietic stem cell transplantation (HSCT) is the only curative therapy available for MDS.
   - Sibling typing should be initiated in transplant-eligible patients who are Int-1 IPSS score or higher.
   - *Low or Int-1 risk disease:* eligible patients with significant symptomatic cytopenias and/or evidence of transforming disease should be considered for allogeneic HSCT.
   - *Int-2 or High risk disease:* allogeneic HSCT should be offered as first line therapy to eligible patients, especially those age<40 and/or with sibling donors.
   - In patients with known myelodysplasia and increasing blasts, including those with blasts>20%, induction chemotherapy is not necessary prior to allogeneic transplantation.
   - In patients with a blast count ≥10%, total body irradiation (200 cGy x 2 doses) should be added to FLUBUP conditioning to reduce relapse risk.
   - Options for relapsed disease include palliation, DLI or second transplant.

7. As a majority of the patients are elderly and not eligible for HSCT, the goals of therapy range from symptom control and improved quality of life to reducing development of acute leukemia and prolongation of survival.
Supportive Care:

8. Transfusions:
   - Red cell transfusions should be employed as required to treat and prevent significant symptoms of anemia; unnecessary transfusions should be avoided to prevent symptomatic iron overload.
   - Platelet transfusions as required to prevent bleeding due to symptomatic thrombocytopenia.
     - Single donor platelets are preferred in patients with expected prolonged platelet transfusion dependency to decrease risk of HLA sensitization and platelet antibody production.
   - CMV negative blood products are suggested for CMV negative transplant candidates.

9. Infections: Antibiotic therapy for infections and neutropenic fever should be used as clinically indicated to advance the above goals of therapy.

10. Bleeding: Tranexamic acid therapy can be considered for severely thrombocytopenic patients with mucosal bleeding. ASA, NSAIDs, and systemic anticoagulation should be avoided in patients with platelets less than 50 or significant bleeding.

11. Vitamin Supplementation: B12 and folate therapy should be performed in patients with nutritional deficiencies.

12. Iron Chelation:
   - Iron chelation should be considered in patients with a life expectancy of greater than 1 year, and either ferritin >1000, >20 units blood transfused or documented organ iron overload, especially if red cell transfusions are ongoing or iron stores are increasing due to ineffective erythropoiesis.
   - Iron chelation is indicated in patients with increased iron stores who are planning HSCT.
   - Transfusion dependent or iron overloaded patients should be encouraged to avoid iron-containing supplements and multivitamins.
   - Chelation can be initiated with deferoxamine (20-50 mg/kg/day by subcutaneous or intravenous infusion over 8-12 hours or bid sc bolus injections 5 days/week) or deferasirox 20-30 mg/kg orally daily.
   - Monitor for complications of iron overload and complications of drug therapy while administering iron chelation.

13. The patient’s psychosocial situation should be monitored, and consultation made to social work, psychosocial services, home care or other supportive agencies as required.

Therapeutic Options for IPSS Low and Int-1 Myelodysplasia:

14. In patients with Low or Int-1 IPSS myelodysplasia, erythropoietin levels <500 U and transfusion requirements of less than 2 U/month, combination erythropoietin (40,000-60,000 U subcutaneous 1-3 times/week) or darbopoietin (150-300 µg/week subcutaneous or extended interval dosing) + G-CSF (3-5 µg/kg subcutaneous 3 times/week) therapy is recommended.
   - Target Hb on growth factor support is no greater than 120g/L
   - Alternative therapy is chronic transfusion

15. Growth factor therapy should be maintained for at least 12 weeks and up to 26 weeks before lack of response is concluded.
16. Patients on growth factors should have iron stores assessed to ensure they are iron replete prior to and throughout therapy.

17. Immunomodulators
   - Patients with Low or Int-1 IPSS scores and a del (5q) abnormality, with or without other cytogenetic abnormalities, and symptomatic anemia should be given first-line treatment with lenalidomide 10 mg/d 21 days per month or 10 mg daily.
   - Patients receiving lenalidomide should be monitored for the development of cytopenias with weekly CBCs for the first 8 weeks and dose reductions introduced as necessary.
   - Dose reductions should be made in patients with renal insufficiency.
   - Lenalidomide is the treatment option for all patients with Low or Int-1 risk IPSS myelodysplastic syndrome who are red cell transfusion dependent regardless of del (5q) status, using a treatment regimen of 10 mg/d 21 days/month or 10 mg daily dosing.

18. Immune Suppression: In patients with Low and Int-1 IPSS MDS, especially in the presence of a hypocellular marrow, PNH clone, and/or HLA-DR15 (DR2) positivity, and a short duration of red cell transfusion dependence, consider a course of immunosuppression with ATG 40 mg/kg/d IV over 4-6 days ± cyclosporine starting at 5 mg/kg/d for a 6 month period.

**Therapeutic Options for Int-2 and High Risk Myelodysplasia:**

19. Demethylation Agents
   - In patients with Int-2 or High Risk IPSS MDS who are not candidates for intensive chemotherapy and HSCT, or Int-1 IPSS patients with significant cytopenias, therapy with azacytidine or decitabine should be considered.
   - Azacytidine dose is 75 mg/m² per day sc for seven consecutive days every 28 days, with a minimum of 4 cycles before assessment of response. Treatment is continued for duration of clinical response.
   - Decitabine dose is 20 mg/m² IV daily x 5 days every 28 days and is continued for the duration of response.

20. Chemotherapy: Intensive chemotherapy for MDS with excess blasts may be useful in patients with rapidly increasing blast counts as a bridge to hematopoietic cell transplantation; clinical trials are needed.

**Additional Considerations for Chronic Myelomonocytic Leukemia:**

21. At diagnosis, all patients should have a full cytogenetic profile performed and FISH performed for t(5:12) where available.

22. Patients with t(5:12) or other PDGFRβ mutations should be offered therapy with imatinib mesylate.
DISCUSSION

Pathophysiology

MDS is associated most commonly with a hypercellular bone marrow, with increased proliferation of neoplastic cells and either increased or defective apoptosis. Eight to 28 percent of patients have hypocellular marrows. MDS likely develops from a number of heterogeneous pathways. DNA damage is a common factor, with evolution of clonal cytogenetic abnormalities and frequent abnormalities in DNA methylation and epigenetics. Certain genetic abnormalities are associated with MDS, such as the inactivation of the p53 tumour suppressor gene. Interaction between neoplastic cells and the microenvironment is increasingly recognized as key for the survival and proliferation of the abnormal clone; cytokine release/response and abnormalities in immune suppression are also associated with the disease. Some patients have an overlap syndrome with characteristics of both myelodysplasia and myeloproliferative disease.

Diagnostic Criteria

Family history of anemia, MDS or hematologic disease, evidence of congenital abnormalities, or exposures to chemotherapy, radiation, or toxic environmental or occupational exposures should be elicited. MDS is a diagnosis of exclusion, as dysplasia can be the result of factors other than a clonal disorder. All patients should be assessed for an effect on marrow function from drugs (including chemotherapy drugs), viral infections (i.e., parvovirus), nutrient deficiencies, alcohol ingestion, heavy metal exposure (i.e., arsenic) and recovery from other recent toxin exposures. Symptoms are those of bone marrow failure and include symptoms of anemia, infections and bleeding. Less commonly, fever and weight loss are observed.

Investigations

- CBC and differential, reticulocytes, peripheral blood smear, B12 and folate levels.
- HIV testing for those with risk factors. In patients undergoing immunosuppressive or myelosuppressive treatment, screen for viral hepatitis with hepatitis C antibody, hepatitis BsAb, hepatitis BsAg, and hepatitis C core antibody.
- In hypoplastic patients, paroxysmal nocturnal hemoglobinuria (PNH) screening should be performed on bone marrow or peripheral blood (flow cytometry for CD55 and CD59).
- Bone marrow aspirate and biopsy including a 500 cell count with morphology, reticulin staining for fibrosis and iron stains for assessment of ringed sideroblasts.
- Immunophenotyping and quantification of blasts by flow cytometry and full karyotype cytogenetic testing should be performed on the bone marrow.
- Serum erythropoietin levels in patients for whom erythropoietin treatment is being considered.
- Assessment of iron stores including Fe, total iron binding capacity (TIBC), and ferritin for evidence of iron overload.
- Human leukocyte antigen (HLA) DR typing should be performed if considering immunosuppressive therapy.
  - Increased response with HLA DR15 (HLA DR2).
- HLA-A, B, C, DR, and DQ tissue typing in patients who are HSCT transplant candidates.
The hallmark of diagnosis is dysplasia in >10% of cells in at least 1 cell lineage on bone marrow aspiration and biopsy. In patients with hypocellular marrows the presence of dysplasia and cytogenetic abnormalities support the diagnosis of MDS over aplastic anemia. In hypoplastic patients, PNH screening should be performed on bone marrow or peripheral blood (flow cytometry for CD55 and CD59). Causes of marrow dysplasia other than myelodysplastic syndromes should be ruled out before making a diagnosis of myelodysplasia, including viruses, drugs, and vitamin deficiencies.

**Classification**

The French-American-British (FAB) classification system has been largely replaced by the World Health Organization (WHO) classification system; it is included here because many studies still refer to these criteria. The WHO classification eliminates the RAEB-T category by replacing it with the diagnosis of acute leukemia when blasts are >20%. This includes some cytogenetic information, and considers CMML with the myeloproliferative disorders. Tables 1 and 2 describe the components of both classification systems.

**Table 1. FAB Classification of MDS**

<table>
<thead>
<tr>
<th>FAB Classification</th>
<th>% Blasts BM</th>
<th>% Blasts PB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory anemia (RA)</td>
<td>&lt; 5</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Refractory anemia with ringed sideroblasts (RARS)*</td>
<td>&lt; 5</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts (RAEB)</td>
<td>5-20</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>RAEB transformation (RAEB-T)</td>
<td>21-30 or</td>
<td>&gt; 5</td>
</tr>
<tr>
<td>Chronic myelomonocytic leukemia (CMML)</td>
<td>&lt; 20</td>
<td></td>
</tr>
</tbody>
</table>

*Ringed sideroblasts >15% nucleated marrow erythroid cells

**Table 2. WHO Classification of MDS**

<table>
<thead>
<tr>
<th>WHO Classification</th>
<th>% Blasts BM</th>
<th>% Blasts PB</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA/RARS*</td>
<td>&lt; 5</td>
<td>none/rare</td>
</tr>
<tr>
<td>Refractory cytopenia with multi-lineage dysplasia (RCMD)/ RCMD-RS* (bi-lineage or tri-lineage dysplasia)</td>
<td>&lt; 5</td>
<td>none/rare</td>
</tr>
<tr>
<td>RAEB-1</td>
<td>&lt; 5</td>
<td>5-9</td>
</tr>
<tr>
<td>RAEB-2</td>
<td>5-19</td>
<td>10-19</td>
</tr>
<tr>
<td>MDS – unclassified</td>
<td>&lt; 5</td>
<td>none/rare</td>
</tr>
<tr>
<td>MDS with isolated del(5q)</td>
<td>&lt; 5</td>
<td>&lt; 5</td>
</tr>
</tbody>
</table>

Female predominance, transfusion-dependent anemia; normal or increased platelet counts with hypolobulated micromegakaryocytes in the hyperplastic marrow; low incidence of transformation into acute leukemia

*Ringed sideroblasts ≥15% of nucleated marrow erythroid cells

**Prognosis**

The International Prognostic Scoring System (IPSS) for MDS was developed to predict prognosis for adult patients at the time of diagnosis. It was developed based on the FAB classification system; patients with 20-30% blasts would now be considered to have AML. Patients with extensive prior chemotherapy treatment and secondary MDS were not included in the development or validation of this scoring system. It is not validated for use at time points after diagnosis.
Table 3. International Prognostic Scoring System

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Blasts</td>
<td>&lt;5</td>
<td>5-10</td>
<td>-</td>
<td>11-20</td>
<td>20-30</td>
</tr>
<tr>
<td>Karyotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good risk: normal, isolated del(5q), -Y, isolated del(20q)</td>
<td>good</td>
<td>intermediate</td>
<td>poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor risk – complex abnormalities (&gt;3), abnormalities of chromosome 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate – all others</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytopenias (Hb &lt;100g/L, neutrophils &lt;1500/µL, platelets &lt;100)</td>
<td>0-1</td>
<td>2-3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

As shown in Table 4, age is a major predictor of overall survival and AML transformation in patients with low risk MDS at diagnosis. Median survival of all patients with MDS is 1-3 years, however this varies greatly by disease subtype. For example, median survival for patients with RAEB-II (9 months) is significantly shorter than with RAEB-I (16 months), and the risk of developing AML is higher (40% compared to 22%).

Table 4. Overall Survival and Time-to-AML Based on Total IPSS Score

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Total IPSS Score</th>
<th>OS (years) Age &gt; 60 years</th>
<th>OS (years) Age &lt; 60 years</th>
<th>Time to 25% AML Progression Age &gt; 60 years</th>
<th>Time to 25% AML Progression Age &lt; 60 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>4.8</td>
<td>11.8</td>
<td>9.4</td>
<td>&gt;9.4 (NR)</td>
</tr>
<tr>
<td>INT-1</td>
<td>0.5-1</td>
<td>2.7</td>
<td>5.2</td>
<td>2.7</td>
<td>6.9</td>
</tr>
<tr>
<td>INT-2</td>
<td>1.2-2</td>
<td>1.1</td>
<td>1.8</td>
<td>1.3</td>
<td>0.7</td>
</tr>
<tr>
<td>High</td>
<td>≥2.5</td>
<td>0.5</td>
<td>0.3</td>
<td>0.2</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Abbreviations: NR = not reached

The WHO system, shown in Table 5, has been integrated into a new prognostic system, which has been validated in a large cohort of patients and includes the need for transfusions as a negative prognostic factor. It is a time-dependent scale that is valid at time points after diagnosis.

Table 5. WHO Prognostic Scoring Scale

<table>
<thead>
<tr>
<th>Variable</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO classification</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>Transfusions</td>
<td>No</td>
<td>Regular</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Table 6. Overall Survival and Time-to-AML Based on the WHO Prognostic Scoring Scale

<table>
<thead>
<tr>
<th>Risk</th>
<th>Score</th>
<th>Standardized Mortality Ratio</th>
<th>Overall Survival (months)</th>
<th>2 year AML Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>0</td>
<td>1.8</td>
<td>141</td>
<td>0.03</td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
<td>3.47</td>
<td>66</td>
<td>0.06</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
<td>4.9</td>
<td>48</td>
<td>0.21</td>
</tr>
<tr>
<td>High</td>
<td>3-4</td>
<td>16.18</td>
<td>26</td>
<td>0.38</td>
</tr>
<tr>
<td>Very high</td>
<td>5-6</td>
<td>30.55</td>
<td>9</td>
<td>0.80</td>
</tr>
</tbody>
</table>

The frequency of cytogenetic abnormalities generally increases with increasing severity of disease.
Other negative prognostic factors in MDS:
- Mutation and loss of heterogeneity in p53 gene
- Increased B2 microglobulin
- Mutations in FLT3
- CD34 positivity of nucleated bone marrow cells
- Increased expression of Wilms tumour gene WT1
- Therapy-related secondary MDS
  - 75% of patients have abnormalities in chromosomes 5 and/or 7
  - Higher proportion with p53 abnormalities

All patients should have prognostication based on calculation of IPSS and WHO prognostic scoring scale.

Treatment

The dilemma with myelodysplastic syndromes lies largely in the fact that this is a disease of the elderly. The majority of patients are not eligible for hematopoietic stem cell transplantation (HSCT), the only curative therapy. Disease that has progressed to acute leukemia has a lower response rate to chemotherapy than \textit{de novo} leukemia, and is more likely to relapse.\textsuperscript{19} The development of a blast count >20% does not mandate treatment for acute leukemia, and therapeutic decisions must account for a patients’ age, comorbidities, trajectory of disease development, and overall prognosis with therapy in addition to the patients’ treatment goals. Goals of therapy range from symptom control and improved quality of life to reducing development of acute leukemia and prolongation of overall survival. A select few patients are candidates for potentially curative therapy with stem cell transplantation. \textit{HSCT is the only curative therapy available for MDS.}

Supportive Care for All Patients with MDS

Transfusions:
- Red cell transfusions should be employed as required to treat and prevent significant symptoms of anemia; unnecessary transfusions should be avoided to prevent symptomatic iron overload.
- Platelet transfusions to prevent bleeding due to symptomatic thrombocytopenia
- Single donor platelets are preferred in patients with expected prolonged platelet transfusion dependency to decrease risk of HLA sensitization and platelet antibody production.
- CMV negative blood products are suggested for CMV negative transplant candidates.

Infections: Antibiotic therapy for infections and neutropenic fever should be used as clinically indicated to advance the above goals of therapy.

Bleeding: Tranexamic acid therapy can be considered for severely thrombocytopenic patients with mucosal bleeding. ASA, NSAIDS, and systemic anticoagulation should be avoided in patients with platelets less than 50 or significant bleeding.

Vitamin supplementation: Vitamin B12 and folate therapy should be performed in patients with nutritional deficiencies.

Iron chelation: Iron overload is common in MDS as a result of increased intestinal iron absorption, ineffective hematopoiesis and iron infused during packed red cell transfusions (each unit of iron contains
200-250 mg of iron, well above the 1-2 mg/day excreted by the body). In transfusion-dependent thalassemia, prospective data confirms improved survival in patients given iron chelation. Transfusion dependency in MDS has been associated with complications of iron overload including heart failure and conduction/rhythm disturbance, diabetes, and liver dysfunction. In a retrospective review, a ferritin level of >1000 µg/L was significantly associated with decreased overall survival, with a hazard ratio increasing by 30% for every 500 µg/L rise in ferritin >1000 µg/L. In addition, a Canadian retrospective review found that predictors of survival in MDS were the IPSS score and iron chelation therapy, with a significantly longer overall survival in patients receiving chelation. Chelation has been shown to be effective in decreasing total body iron load, and variably effective at removing iron from body organs.

General principles of iron chelation include:

- Iron chelation should be considered in patients with a life expectancy of greater than 1 year, and either ferritin >1000, >20 units blood transfused or documented organ iron overload, especially if red cell transfusions are ongoing or iron stores are increasing due to ineffective erythropoiesis.
- Iron chelation is indicated in patients with increased iron stores who are planning HSCT.
- Transfusion dependent or iron overloaded patients should be encouraged to avoid iron-containing supplements and multivitamins.
- Chelation can be initiated with deferoxamine (20-50 mg/kg/day by subcutaneous or intravenous infusion over 8-12 hours or two times daily subcutaneous bolus injections 5 days/week) or deferasirox 20-30 mg/kg orally daily.
- Monitor for complications of iron overload and complications of drug therapy while administering iron chelation.

Psycho social support: The psychosocial situation of each patient should be monitored, and consultation made to social work, psychosocial services, home care or other supportive agencies as required.

Therapeutic Options for IPSS Low and Int-1 Myelodysplasia

Growth factors: The use of erythropoietin has been shown to increase the hemoglobin and reduce transfusion requirements in myelodysplasia; response has been reported in 18% of patients at 12 weeks and 45% at 26 weeks, with a complete response in 27%. Response rates are higher in patients with refractory anemia and refractory anemia with ringed sideroblasts compared to patients with refractory anemia with excess blasts. In addition, higher response rates are seen in transfusion-dependent patients, patients with good prognosis cytogenetics, and patients with erythropoietic levels <150 U/L. There appears to be a synergistic effect between erythropoietin and G-CSF as evidenced by a study analyzing the results of four trials using combination therapy; response rate (transfusion independence or increased Hb by 15g/L in patients never transfusion-dependent) was 50% in RARS, 39% in RA, and 31% in RAEB with no increase in survival or AML risk.

A decision model has been prospectively validated for combination erythropoietin and G-CSF, selecting patients on the basis of erythropoietin levels <500 and transfusion needs <2 U/month; patients were largely good or intermediate risk IPSS. The response rate was 61% in patients with 0 risk factors, and 14% in patients with 1 or 2 risk factors. Patients on growth factor therapy had an improvement in global quality of life and there may be an association with improved survival. In patients with Low or Int-1 IPSS myelodysplasia, erythropoietin levels <500 U and transfusion requirements of less than 2 U/month, combination erythropoietin (40,000-60,000 U subcutaneous 1-
3 times/week) or darbopoietin (150-300 µg/week subcutaneous or extended interval dosing) + G-CSF (3-5 µg/kg subcutaneous 3 times/week) therapy is recommended.

- Target Hb on growth factor support is no greater than 120g/L
- Alternative therapy is chronic transfusion

- Growth factor therapy should be maintained for at least 12 weeks and up to 26 weeks before lack of response is concluded.
- Patients on growth factors should have iron stores assessed to ensure they are iron replete prior to and throughout therapy.

**Immunomodulators:** Thalidomide and lenalidomide have immunomodulatory properties and have been shown to be effective in low risk MDS to decrease transfusion requirements. In a phase II dose-escalating trial, 59% of patients given thalidomide developed hematologic improvement, however only a minority of patients continued the drug up to 16 weeks because of side effects of neurotoxicity, fatigue and somnolence. Lenalidomide, a thalidomide derivative without the neurotoxicity of thalidomide, has been evaluated in Low and Int-1 IPSS risk transfusion-dependent MDS in patients without a 5q deletion; 26% became transfusion dependent after a median of 4.8 weeks, with a ≥ 50% reduction of transfusion requirements in a further 17% for a total 43% response rate (median duration 41 weeks). Grade 3-4 neutropenia was seen in 30% and thrombocytopenia in 25%.

Patients with isolated 5q- abnormality have a distinct syndrome associated with elderly female predominance, thrombocytosis, anemia, and a prolonged overall survival with a median of 69 months. Phase II data demonstrate that in MDS patients with Low and Int-1 del (5q) with or without other cytogenetic abnormalities, 67% (99/148) achieved transfusion independence for a median of 2.2 years, and of the 85 evaluable patients, 62 had a cytogenetic response (45% CR, 28% PR). Grade 3-4 neutropenia was seen in 55% and thrombocytopenia in 44%, with the majority of patients requiring dose reductions to 5mg/day or 5 mg/every other day after initial response. When the results of four prospective clinical trials of lenalidomide in del (5q) patients were analyzed, the median time to transfusion independence was 4.7 weeks, and median duration was 2.2 years. At ten years, the estimated survival for those with at least a partial cytogenetic response was 75% compared to 4% in those with no response, and risk of progression to AML was also lower at 15% compared to 67%.

**General principles:**

- Patients with Low or Int-1 IPSS scores and a del (5q) abnormality, with or without other cytogenetic abnormalities, and symptomatic anemia should be given first-line treatment with lenalidomide 10 mg/day for 21 days/month or 10 mg daily.

- Patients receiving lenalidomide should be monitored for the development of cytopenias with weekly CBCs for the first 8 weeks and dose reductions introduced as necessary.

- Dose adjustments should be made in patients with renal insufficiency.

- Lenalidomide is a treatment option for all patients with Low or Int-1 risk IPSS MDS who are red cell transfusion dependent regardless of del (5q) status, using a treatment regimen of 10 mg/day for 21 days/month or 10 mg daily dosing.

**Immune suppression:** In young patients with normal cytogenetics, marrow hypoplasia, early stage disease, and the presence of HLA-DR15 (DR2), immune-mediated suppression of hematopoietic stem cell function may be the underlying etiology of pancytopenia. Treatment with ATG ± cyclosporine or cyclosporine alone has been associated with achievement of transfusion independence in 32% and 15% of patients, respectively; 48% of HLA-DR15 positive patients responded compared to 17% of HLA-DR15
negative patients. A non-randomized study of 61 patients with variable marrow cellularity demonstrated transfusion independence in 34% of patients and improved overall survival in patients given ATG. The presence of a clone of PNH cells predicts response, as does a shorter duration of red cell dependence. Randomized placebo-controlled large studies of this therapy have not been performed.

In patients with Low and Int-1 IPSS MDS, especially in the presence of a hypocellular marrow, PNH clone, and/or HLA-DR15 (DR2) positivity, and a short duration of red cell transfusion dependence, consider a course of immunosuppression with ATG 40 mg/kg/day IV over 4-6 days ± cyclosporine starting at 5 mg/kg/day for a 6 month period.

**Therapeutic Options for Int-2 and High Risk Myelodysplasia**

**Demethylation agents:** Azacytidine is a pyrimidine nucleoside analog, which causes DNA demethylation and is cytotoxic to abnormal bone marrow hematopoietic cells. A phase III CALGB trial involved 191 patients randomized to 5-aza or supportive care, with crossover permitted after four months if disease was worsening. The response rate to azacytidine in this trial was 60% (7% complete, 16% partial, 37% hematologic improvement) compared to 5% response in the supportive care arm with median time to death or leukemic transformation of 21 months versus 13 months. In addition, improved quality of life was seen in patients on 5-aza.

Decitabine is another pyrimidine nucleoside analog which has been shown in a phase II multicentre trial to have a response rate of 25% in Int-1 disease, 48% in Int-2 disease, and 64% in high-risk IPSS score disease, with a median overall survival from time of treatment of 1.2 years. This compares to historical data showing expected survival of 0.3 to 0.5 years with supportive care. Major cytogenetic response was seen in 31% with abnormal cytogenetics and associated with longer survival. Several regimens have been used with intravenous or subcutaneous dosing. A matched comparison with a historical cohort given intensive chemotherapy for higher risk MDS showed a similar complete remission rate (46% versus 43%) but survival was better with decitabine compared to intensive chemotherapy because of decreased mortality with treatment (3% versus 13%, median survival 22 months versus 12 months).

**General principles:**
- In patients with Int-2 or High Risk IPSS MDS who are not candidates for intensive chemotherapy and HSCT, or Int-1 IPSS patients with significant cytopenias, therapy with azacytidine or decitabine should be considered.
- Azacytidine dose is 75 mg/m² per day subcutaneous for 7 consecutive days every 28 days, minimum 4 cycles before assessment. Treatment is continued for duration of clinical response.
- Decitabine dose is 20 mg/m² IV daily x 5 days every 28 days and is continued for the duration of response.

**Chemotherapy:** Chemotherapy is used in patients with excess blasts/transformation to acute leukemia from MDS. Chemotherapy is associated with inferior outcomes compared to those seen with de novo acute leukemia, and is generally a palliative therapy except in patients proceeding to HSCT.

Intensive chemotherapy for MDS with excess blasts may be useful in patients with rapidly increasing blast counts as a bridge to hematopoietic cell transplantation, although there is limited research available to support this, and randomized clinical trials are needed.
Hematopoietic Stem Cell Transplantation (HSCT)

HSCT is the only known curative treatment for myelodysplasia. HSCT is associated with increased treatment-related mortality, therefore the timing and appropriate patient population for transplant has been the subject of a recent decision analysis.\textsuperscript{38}

The recommendations of the Alberta Provincial Hematology Tumour Team with regards to HSCT include:

- Sibling typing should be initiated in transplant-eligible patients who are Int-1 IPSS score or higher.
- \textit{Low or Int-1 risk disease}: eligible patients with significant symptomatic cytopenias and/or evidence of transforming disease should be considered for allogeneic HSCT.
- \textit{Int-2 or high-risk disease}: allogeneic HSCT should be offered as first line therapy to eligible patients, especially those age <40 and/or with sibling donors.
- In patients with known myelodysplasia and increasing blasts, including those with blasts > 20%, induction chemotherapy is not necessary prior to allogeneic transplantation.
- In patients with a blast count $\geq 10\%$ TBI (200cGy x 2 doses) should be added to FLUBUP conditioning to reduce relapse risk.
- Options for relapsed disease include palliation, donor lymphocyte infusion (DLI) or second transplant.

\textbf{IWG Modified Criteria for Response}\textsuperscript{39}

\textbf{Complete remission}: Less than 5\% marrow blasts with resolution of dysplasia and hemoglobin level $\geq 110$ g/L in patients not receiving erythropoietin or transfusions, neutrophils $\geq 1.5 \times 10^9$/L, and platelets $\geq 100 \times 10^9$/L.

\textbf{Partial remission}: All of the above except that marrow blasts are decreased by $\geq 50\%$ compared with pre-treatment levels, or patients have a less-advanced MDS classification than prior to therapy.

\textbf{Hematologic improvement}: Specific improvement in cytopenias in one of the hematopoietic lineages at least 8 weeks duration, measured over 2 readings in one week, and independent of transfusion (no RBC transfusion for at least 1 week or platelet transfusion for 3 days prior to assessment):

- \textit{Erythroid (HI-E)}: in patients with pre-treatment Hb <110 g/L or RBC transfusion-independence, improvement of Hb by at least 15 g/L.
- \textit{Platelet (HI-P)}: in patients with pre-treatment platelets $<100 \times 10^9$/L or platelet transfusion-dependent; if platelets started out at $>20 \times 10^9$, an increase of $30 \times 10^9$ is required, and if platelets started $<20 \times 10^9$ an increase of $20 \times 10^9$ and by at least 100\% is required.
- \textit{Neutrophil (HI-N)}: in patients with pre-treatment neutrophil count $<1.0 \times 10^9$, an increase of at least 100\% in neutrophils and an absolute neutrophil increase of $>0.5 \times 10^9$ is required.

\textbf{Progression or relapse after hematologic improvement}: Hb reduction by $\geq 15$ g/L or transfusion dependence, or decrease in platelets or neutrophils by at least 50\% from the maximum response. Cytogenetic responses should be analyzed with at least 20 metaphases. A structural abnormality or additional chromosomes should be seen in at least two metaphases, and loss of a chromosome documented in at least three metaphases. FISH is acceptable to document changes in a chromosome abnormality.

- \textit{Major Cytogenetic Response}: Resolution of a previously documented chromosome abnormality.
- \textit{Minor Cytogenetic Response}: $\geq 50\%$ reduction in number of abnormal metaphases.
Chronic Myelomonocytic Leukemia (CMML)  

CMML has been considered a subtype of MDS under the FAB classification, and is now considered under a separate category of Myeloproliferative/Myelodysplastic diseases under the WHO classification. Diagnosis is based on a monocyte count greater than 1000/µL, lack of the Philadelphia chromosome, presence of dysplasia or cytogenetic abnormalities and blast count <20%. Additional considerations for CMML include:

- At diagnosis, all patients should have a full cytogenetic profile performed and FISH performed for t(5:12) where available.
- Patients with t(5:12) or other PDGFRβ mutations should be offered therapy with imatinib mesylate.

GLOSSARY OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>acute myeloid leukemia</td>
</tr>
<tr>
<td>ASA</td>
<td>acetylsalicylic acid</td>
</tr>
<tr>
<td>ATG</td>
<td>antithymocyte globulin</td>
</tr>
<tr>
<td>CALGB</td>
<td>Cancer and Leukemia Group B</td>
</tr>
<tr>
<td>CBC</td>
<td>complete blood count</td>
</tr>
<tr>
<td>CMML</td>
<td>chronic myelomonocytic leukemia</td>
</tr>
<tr>
<td>CMV</td>
<td>cytomegalovirus infection</td>
</tr>
<tr>
<td>CR</td>
<td>complete remission</td>
</tr>
<tr>
<td>DLI</td>
<td>donor lymphocyte infusion</td>
</tr>
<tr>
<td>FAB</td>
<td>French-American-British</td>
</tr>
<tr>
<td>FISH</td>
<td>fluorescence in-situ hybridization</td>
</tr>
<tr>
<td>FLUBUP</td>
<td>fludarabine + busulfan</td>
</tr>
<tr>
<td>G-CSF</td>
<td>granulocyte colony stimulating factor</td>
</tr>
<tr>
<td>HLA</td>
<td>human leukocyte antigen</td>
</tr>
<tr>
<td>HSCT</td>
<td>hematopoietic stem cell transplantation</td>
</tr>
<tr>
<td>Int-1 and Int-2</td>
<td>intermediate-1 and intermediate-2</td>
</tr>
<tr>
<td>IPSS</td>
<td>International Prognostic Scoring System</td>
</tr>
<tr>
<td>IV</td>
<td>intravenous</td>
</tr>
<tr>
<td>IWG</td>
<td>International Working Group</td>
</tr>
<tr>
<td>MDS</td>
<td>myelodysplastic syndromes</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>non-steroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>OS</td>
<td>overall survival</td>
</tr>
<tr>
<td>PDGFR</td>
<td>platelet-derived growth factor receptor gene</td>
</tr>
<tr>
<td>PNH</td>
<td>paroxysmal nocturnal hemoglobinuria</td>
</tr>
<tr>
<td>PR</td>
<td>partial remission</td>
</tr>
<tr>
<td>RA</td>
<td>refractory anemia</td>
</tr>
<tr>
<td>RAEB</td>
<td>refractory anemia with excess blasts</td>
</tr>
<tr>
<td>RAEB-T</td>
<td>refractory anemia with excess blasts – transformation</td>
</tr>
<tr>
<td>RARS</td>
<td>refractory anemia with ringed sideroblasts</td>
</tr>
<tr>
<td>RBC</td>
<td>red blood cells</td>
</tr>
<tr>
<td>RCMD</td>
<td>refractory cytopenia with multi-lineage dysplasia</td>
</tr>
<tr>
<td>TIBC</td>
<td>total iron binding capacity</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2014. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Hematology Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Hematology Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

REFERENCES


