Provincial Myelodysplastic Syndrome Treatment Guidelines

Approved at the Provincial Hematology Meeting on January 13, 2012

Clinical practice guidelines have been developed after multi-disciplinary consensus based on best available literature. As the name suggests, these are to be used as a guide only. These guidelines do not replace physician judgment which is based on multiple factors including, but not limited to, the clinical and social scenario, comorbidities, performance status, age, available resources and funding considerations. The Saskatchewan Cancer Agency disclaims all liability for the use of guidelines except as expressly permitted by the Agency. No portion of these guidelines may be copied, displayed for redistribution to third parties for commercial purposes or any non-permitted use without the prior written permission from the Agency.

Benefits and risk of the proposed should be discussed with patient. Participating in clinical trials is encouraged when available. Involvement of a multidisciplinary team is strongly recommended.

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 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.

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. While MDS is most commonly associated with increased bone marrow cellularity, myelofibrotic and hypoplastic variants are also reported. Classically, MDS has trilineage dysplasia, but occasionally dysplasia may be confined to 1 or 2 lines.

WHO classification of MDS (2008):

<u>Myelodysplastic Syndromes:</u>

a) Refractory cytopenia with unilineage dysplasia (RA,RN,RT)
b) Refractory anemia with ringed sidroblasts (RARS).
c) Refractory cytopenia with multilineage dysplasia (RCMD) ± RS

d) Refractory anemia with excess blasts (RAEB, 1 and 2).
e) 5q- Syndrome
f) MDS, unclassifiable

International Prognostic Scoring System (IPSS), Greenberg et al.

Scoring points	**0**	0.5	1.0	1.5	2.0
Bone marrow blasts(%)	<5	5–10	11–20		21–30
Cytogenetics	Good	Intermediate	Poor		
Cytopenias	0/1	2/3			

Cytogenetics: Good risk: Normal, -y, 5q-, 20q, Intermediate risk All others, Poor risk: Complex or chromosome 7 aberrations
Number of cytopenias: Hb < 10, ANC < 1,500, PLT < 100,000
Risk groups: Low: 0 - 0.5, Intermediate-1: 1.0 -1.5, Intermediate-2: 2.0 -2.5, High: > 2.5

WHO Based Prognostic Scoring System (WPSS):

Factors already included in the WHO subgroup or in the IPSS such as cytopenias, cytogenetic risk factors (the same subgroups as in the IPSS) and bone marrow blast counts were used. According to the data on the importance of transfusion dependency this feature replaced cytopenia. The WPSS discriminates five prognostic groups ranging from very low to very high risk with significant differences for overall and leukemia free survival.

WPSS (Adapted after Malcovati et al):

Scoring points	**0**	**1**	**2**	**3**
WHO subtype	RA, RARS	RCMD, RCMD-RS	RAEB-1	RAEB-2
Cytogenetics	Good	Intermediate	Poor	
Transfusion Requirement	No	Regular		

Cytogenetics: Good risk: Normal, -y, 5q-, 20q, Intermediate risk All others, Poor risk: Complex or chromosome 7 aberrations
Transfusion dependency: at least one transfusion every 8 weeks over a period of 4 months
Risk group :Very low: 0 , Low: 1, Intermediate: 2 , High: 3-4 , Very high: 5-6

Work Up:

Baseline Investigations:
The following should be performed in most patients with MDS at time of initial assessment:
- History and physical exam
- CBC, differential blood film with Retic count
- Liver and renal profile
- Vitamin B12, red cell folate, ferritin, iron saturation TSH Serum

- Serum EPO level
- Direct antiglobulin test (DAT)
- Bone marrow aspirate and biopsy with cytogenetics
- DR 15 testing should be ordered if patient being considered for immunosuppressive therapy
- JAK2 mutational testing in patients with myeloproliferative features e.g. thrombocytosis or leukocytosis
- PNH testing by flow cytometry
- 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:

Treatment is based on age, performance status and IPSS (Lower risk, including low and Intermediate 1 versus higher risk including Intermediate 2 and high IPSS patients or transfusion dependent patients who failed conventional measures)

Treatment objectives for lower risk patients are:
1. Improve blood cytopenia
2. Improve quality of life

Treatment objectives for higher risk patients are:
1. Delay disease progression
2. Prolong survival.

Treatment Options for Lower Risk MDS:

- ESAs (EPO and darbepoetin)
- Lenalidomide (del 5q)
- Immunosuppression
- Transfusion

1. Patients with Symptomatic Anemia:

- If serum epo is < 500 and/or transfusion requirement is less than 2 units/month, start treatment with ESAs even in 5 q- syndrome
- Dosing: Epo: 40-60,000 U once weekly X 8
  60-80,000 U weekly X 4 if no response
  Aranesp: 500 mcg sc q 3weeks X 2 months
  500 mcg sc q 2 weeks if no response
- Response defined by :
  1. Transfusion dependent patients:
     - Decrease frequency by 50 %
     - Freedom from transfusions

2. Transfusion–independent patients:
    - Increase Hb level (Maximum target is 120 g/L)
    - Alleviation of symptoms
- Therapeutic trial : 12 weeks
- Role of GCSF: Upfront in pts with RARS
  In addition to EPO in failed patients for 4 weeks trial
  Dose is 100 µmg sc 3 times/week

- In patients with 5 q- syndrome who failed EPO treatment, start Lenalidomide
- Dosing: 10 mg/day for 21 days q 28 days.
- Titrate the dose according to hematological toxicity.
- Monitoring: CBC weekly for the first 8 weeks and monthly thereafter
- RFT once monthly.

- Response defined by :
  1. Transfusion dependent patients:
     - Decrease frequency by 50 %
     - Freedom from transfusions
  2. Transfusion –independent patients:
     - Increase Hb level
     - Alleviation of symptoms
     - Therapeutic trial : 4 months

- Management of cytopenia:
  - ANC < 1X109 /L: DC or GCSF
  - ANC < 0.5X109 /L: DC and restart at a lower dose after one week if ANC > 0.75X109/L
  - Platelets < 30,000: DC and restart at a lower dose once > 50,000
- Patient who achieved CCR have More duration of response, less progression to AML and better OS
- Lenalidomide has limited efficacy in pts with other CG abnormalities

2. Treatment of neutropenia:

- Routine use of GCSG is not recommended
- Antibacterial prophylaxis is of questionable value, however treatment of febrile neutropenia is strongly recommended

3. Treatment of thrombocytopenia:

- TPO agonist is not recommended due to concerns of increased AML progression and increased marrow fibrosis

4. Use of Immunosuppressive therapy:

- Is generally indicated in lower risk MDS with hypocellualr marrow, young age , presence of HLA DR 15 patients
- Treatment is with combination ATG and cyclosporine

Treatment Options for Higher Risk MDS:

1. Stem Cell Transplantation:

- **Indications**:
  - Patients with higher risk MDS (Intermediate 2 and high risk IPSS) or lower risk transfusion dependent who failed other treatment measures
  - If the patient has less than 10 % blasts he can proceed directly to SCT, otherwise Debulking before transplant will be considered

- Patients up to the age of 60 years without co morbidities will receive myeloablative conditioning regimen prior to stem cell infusion, however patients between 60-65 years or patients with co morbidities will receive reduced intensity conditioning regimen

2. Azacitadine:

- **Indications**: As a frontline therapy for higher risk MDS including WHO defined AML (blasts 20-30%) who are ineligible or cannot proceed immediately to SCT

- Dosing: 75 mg/m^2/day for 7 days (5-2-2) q 28 days.

- Monitoring: CBC weekly for the first 2 cycles and adjust according to response.
- Response defined by:
  - Hematological improvement
  - Transfusion independence or reduced frequency.
  - Reduction in number of infections requiring Abs
- Azacitadine can be used in older patients not ready for SCT especially with unfavorable CG

- Hematological toxicity: No modification especially in the first 2 cycles.
- Therapeutic trial : 6 cycles (6 months)
- HI improvement is associated with improved survival.
- Patients > 75 y showed same OS advantage.
- Azacitadine improved survival in pts with 20-30 % blasts.

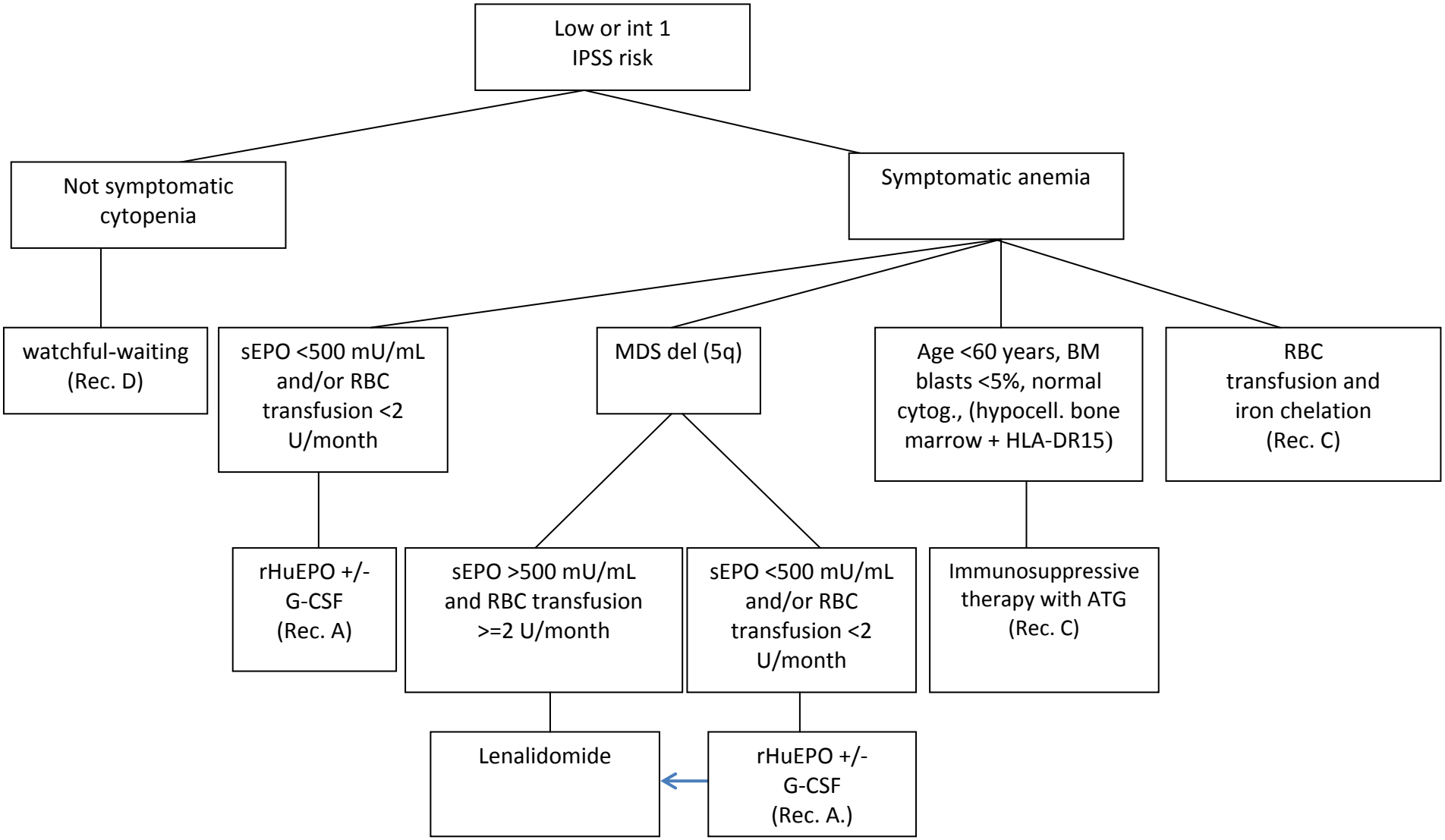
3. AML like induction chemotherapy (7+3) : can be used in higher risk MDS as a bridge to SCT especially in younger patients with available HLA matched donor.

Chelation Therapy in MDS:

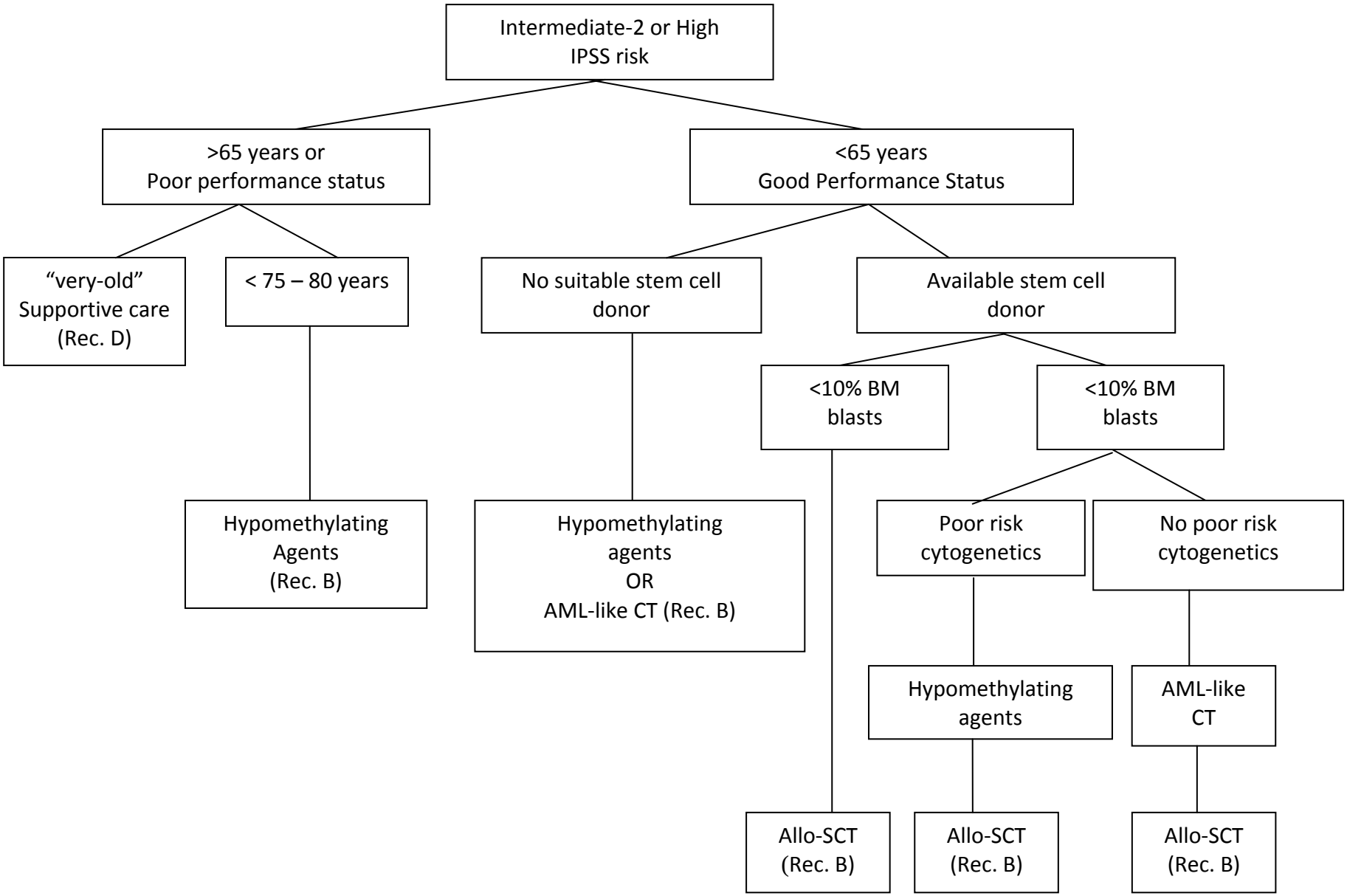
- Indications: Lower risk MDS or higher risk indicated for SCT with secondary iron over load as measured by serum ferritin concentration threshold greater than 1000 µg/ml

- Desferrioxamine (deferoxamine, Desferal)) administered by subcutaneous pump 30-40 mg/kg daily subcutaneously for 5 days via CADD pump .
- Deferasirox, Exjade at doses of 20 and 30 mg/Kg

Algorithm for treatment of lower risk MDS:
(Adapted by the European LeukemiaNet, 2010)



Algorithm for treatment of higher risk MDS:
(Adapted by the European LeukemiaNet, 2010)



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