

# Literature-based followup recommendations

## PART 4: Myelodysplastic and myeloproliferative syndromes and management of iron overload in multiply-transfused oncology patients

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**ABSTRACT**

Many smaller Canadian cancer centres or those employing hematologists to manage malignant hematology as a community service often follow patients with myelodysplastic or myeloproliferative syndromes. Similarly, most cancer programs will have a number of patients dependent on regular transfusion support who also require management for potential iron overload. There are few randomized studies in these con-

ditions and best practice is, by necessity, literature-based. This article reviews practical aspects of followup of these syndromes, as well as management of iron overload in the multiply-transfused oncology patient.

**Key words:** myelodysplastic disorders, myeloproliferative syndromes, hematology, transfusion, myelofibrosis, thrombocythemia, polycythemia, iron chelation, iron overload.

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The 3 preceding parts of this series reviewed the literature-based followup recommendations for solid tumours and common hematologic malignancies. In Canada, many smaller cancer centres or those employing hematologists to manage malignant hematology will provide followup care to patients with myelodysplastic or myeloproliferative syndromes. Most cancer programs have patients dependent on regular transfusion support who require management for potential iron overload. Best practice is, by necessity, literature-based because there are few randomized clinical trials addressing these conditions.

## THE MYELOYDYSPLASTIC SYNDROMES

The myelodysplastic syndromes (MDS) represent a heterogeneous group of clonal stem cell disorders characterized by inefficient hematopoiesis, peripheral blood cytopenias and risk of progression to acute myeloid leukemia (AML).<sup>1-3</sup> The 2008 World Health Organization (WHO) classification of MDS is the current standard and is based on dysplastic cell lineages, percent marrow blasts, the presence of ring sideroblasts and cytogenetic abnormalities.<sup>2</sup> Good prognostic features includes partial deletion of chromosome 5q (5q- syndrome) or deletion of the Y chromosome, while complex karyotype abnormalities or deletions experience poorer outcomes.<sup>1-3</sup> Primary MDS must be distinguished from secondary MDS occurring post antineoplastic or immunosuppressive therapy (therapy-related MDS or t-MDS), which carries a uniformly

**TABLE 1. International Prognosis Scoring System (IPSS) in Myelodysplastic Syndrome<sup>3</sup>**

Prognosis variables	Risk scores*				
	0	0.5	1.0	1.5	2.0
Bone marrow blast (%)	<5	5-10	-	11-20	21-30
Karyotype	Good	Intermediate	Poor	-	-
Cytopenias	0/1	2/3	-	-	-

\*Risk groups according to IPSS scores: Low = 0; Intermediate-1 = 0.5-1.0; Intermediate-2 = 1.5-2.0; High = 2.5-3.5 Adapted from Greenberg P et al. Blood 1997;89:2079-88.

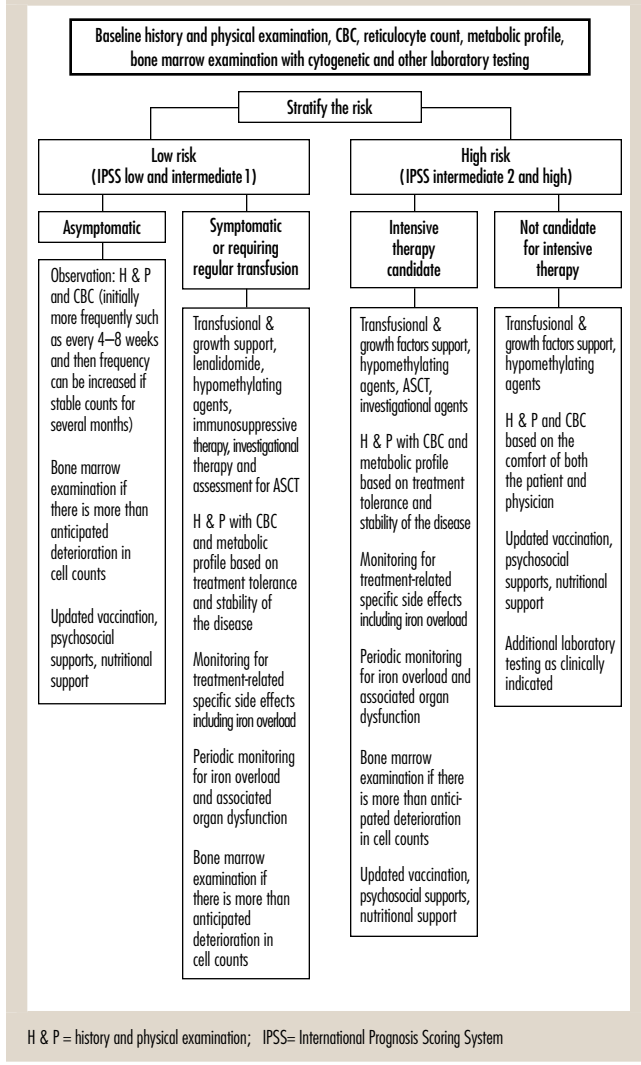
poor prognosis with typical survival of 6 to 9 months.

The International Prognostic Scoring System (IPSS) is based on bone marrow blast percentage, karyotype and number of cytopenias<sup>3</sup> (Table 1). Risk quantification is often simplified by grouping low and intermediate-1 risk in a low-risk category, whereas intermediate-2 and high risk are lumped together as higher-risk disease. Median survival for

high-risk disease without therapy is only approximately 12 months. Survival in lower-risk disease varies from several months to more than a decade.<sup>1,3</sup>

Despite the variable risk of transformation to AML, the majority of deaths are due to bone marrow failure resulting in infection, transfusion-dependent anemia with iron overload or hemorrhage. Treatment options include supportive care, low-intensity therapy and high-intensity therapy including stem cell transplant, currently the only curative option<sup>4,5</sup> (Figure 1). To date, because there is no evidence that treating asymptomatic patients improves long-term survival, treatment goals are supportive and centre on symptom control and quality of life. Transfusion support, infection management and judicious use of growth factors all play a therapeutic role.<sup>6</sup> For patients requiring active therapy, lenalidomide results in a cytogenetic response in 50% of patients with 5q- syndrome. Lenalidomide also significantly reduces transfusion requirements in this population.<sup>4,5</sup> For patients with an intermediate-2 or high-risk IPSS score with good performance status, treatment options are commonly the DNA-hypomethylating agents, among which 5-azacytidine has shown an overall survival benefit.<sup>5</sup>

**FIGURE 1. MDS followup based on risk score and treatment<sup>4,5</sup>**



## FOLLOWUP PRE OR POST THERAPY

Baseline studies include hematology profile, reticulocyte count, serum vitamin B<sub>12</sub> and folate, erythropoietin (EPO) level, serum ferritin, serum copper level, serology for human immunodeficiency syndrome (HIV) infection, and bone marrow examination including cytogenetics and human leukocyte antigen (HLA) typing in transplant candidates.

Conduct history and physical examination with hematology profile at regular intervals, based on risk profile and anticipated disease progression. For the stable asymptomatic patient, 3-4 month visit intervals may be gradually lengthened.

Erythroid-stimulating agents (ESAs) are commonly used for significant anemia unless the serum EPO is >500 U/L. Periodic hematology profile monitoring is required to assess response, usually observed within the 12-week trial period.

The transfusion trigger varies with age and comorbidity but is usually <80 g/L. Regular transfusion necessitates periodic serum ferritin monitoring for iron overload and associated organ dysfunction.

Repeat bone marrow aspirate with cytogenetics as required to rule out evolution or acute leukemic transformation.

Annual influenza vaccine with pneumococcal immunization is recommended every 5-6 years, and diphtheria and pertussis every 10 years.

## THE MYELOPROLIFERATIVE SYNDROMES

The myeloproliferative diseases (MPD) include chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET) and idiopathic myelofibrosis (MF).<sup>7,9</sup> CML is characterized by a specific chromosome abnormality, the Philadelphia chromosome (Ph; followup was described in Part 3 of this series).<sup>10</sup> There has been a growing recognition that the other 3 conditions probably represent a con-

tinuum rather than separate clinical entities.<sup>7</sup> This concept was reinforced by the discovery of the Janus kinase 2 (JAK2) mutation in 2005 and the subsequent realization that it was present in more than 95% of patients with PV and approximately 50-60% of cases of ET and MF. There is also evidence that the severity of the disease process is related to overall JAK2 allele burden, with JAK2-positive ET patients having

**TABLE 2. Revised WHO criteria for the myeloproliferative diseases<sup>9</sup>**

<b>Poly-cythemia vera</b>	<b>Major criteria</b> 1. Hemoglobin >185 g/L in men, >165 g/L in women, or hematocrit >52 in men and >48 in women, or other evidence of increased red cell volume 2. Presence of JAK2617V>F or other functionally similar mutation	<b>Minor criteria</b> 1. Bone marrow biopsy showing hypercellularity with trilineage growth and panmyelosis 2. Serum erythropoietin level below the reference range for normal 3. Endogenous erythroid colony formation in vitro
	Diagnosis requires the presence of both major criteria and 1 minor criterion or the first major criterion together with 2 minor criteria.	
<b>Essential thrombocythemia</b>	1. Sustained platelet count > 450 x 10 <sup>9</sup> /L 2. Bone marrow biopsy showing mainly megakaryocytic proliferation with increased enlarged, mature megakaryocytes; no significant erythroid or granulocytic increase or left-shift 3. Not satisfying WHO criteria for PV, MF, CML (no BCR-ABL), MDS or other myeloid neoplasm 4. Presence of JAK2617V>F or other clonal marker or, if absent, no evidence for reactive thrombocytosis	
	Diagnosis requires meeting all 4 criteria.	
<b>Idiopathic myelofibrosis</b>	<b>Major criteria</b> 1. Bone marrow with megakaryocyte proliferation and atypia, usually accompanied by either reticulin or collagen fibrosis 2. Not satisfying WHO criteria for PV, CML (no BCR-ABL), MDS or other myeloid neoplasm 3. Demonstration of JAK2617V>F or other clonal marker or, if absent, no evidence of secondary marrow fibrosis	<b>Minor criteria</b> 1. Leukoerythroblastosis on blood film 2. Increased serum lactate dehydrogenase (LDH) 3. Anemia 4. Palpable splenomegaly
	Diagnosis requires meeting all 3 major criteria and 2 minor criteria.	

WHO=World Health Organization; PV=polycythemia vera; MF=idiopathic myelofibrosis; CML=chronic myelogenous leukemia; MDS=myelodysplastic syndrome; JAK2617V>F=Janus kinase 2 mutation  
Adapted from the Nordic MPD Study Group Guidelines for the diagnosis and treatment of patients with polycythemia vera, essential thrombocythemia and primary myelofibrosis.

a higher thrombotic rate similar to that of PV vs wild-type ET cases, and patients with PV and MF more likely to be homozygous.<sup>7-9</sup>

While future therapeutic attention will increasingly focus on genetic profiling, the updated World Health Organization (WHO) diagnostic criteria are still helpful in confirming the diagnosis for each entity (Table 2). Bone marrow morphology examination remains essential for a confirmation of the diagnosis of both ET and MF. Similarly, it is important to ensure that the diagnosis of MF is only applied to patients with evidence of characteristic clinical features such as anemia, splenomegaly, constitutional symptoms or a leukocytoblastic blood film.<sup>9,11</sup>

In terms of followup and treatment considerations for ET and PV, thrombosis remains the principal mortality risk, secondary only to progression to MF or AML. Thrombosis rates range from 2.5%/patient-year in younger asymptomatic PV patients to 5%/patient-year in those >65 years or with prior history of thrombosis. For patients with ET, the corresponding figures are 1.9% in the low-risk and 3% in the high-risk patient groups.<sup>7-9,12</sup>

Arterial thrombosis, such as pulmonary embolus, accounts for 60-70% of events. With venous thrombosis,

**TABLE 3. Therapeutic recommendations in essential thrombocythemia and polycythemia vera patients**

<b>All patients regardless of risk or platelet count</b>
<ul style="list-style-type: none"> <li>Assess and manage cardiovascular risk factors</li> <li>Low-dose aspirin therapy unless otherwise contraindicated</li> <li>All PV patients: phlebotomize q3-4 weeks to maintain target Hct 45</li> </ul>
<b>High-risk patients or platelet count &gt;1500 x 10<sup>9</sup>/L</b>
<ul style="list-style-type: none"> <li>Age &gt;60: hydroxyurea therapy</li> <li>Age &lt;60: hydroxyurea therapy or consider possibility of pegylated interferon</li> </ul>

PV=polycythemia vera; Hct=hematocrit  
NB: Some consider patients with platelet counts >1500 x 10<sup>9</sup>/L similar to the high-risk group, even in the absence of age >60 years or prior thrombotic history.

**TABLE 4. Lille and IPSS 2009 prognostic scoring systems for primary myelofibrosis<sup>11</sup>**

		<b>Lille 1996</b> (at diagnosis of MF)	<b>IPSS 2009</b> (at diagnosis of MF)
<b>FACTORS</b>	Anemia (Hb <100 g/L)	X	X
	Leukocytes (<4 or >30 x 10 <sup>9</sup> /L)	X	X (>25 x 10 <sup>9</sup> /L)
	Blasts in peripheral blood		X
	Constitutional symptoms		X
	Age >65 years		X
<b>CATEGORIES</b>	Low	0 factors Median survival 93 months	0 factors Median survival 135 months
	Intermediate-1	1 factor Median survival 26 months	1 factor Median survival 95 months
	Intermediate-2		2 factors Median survival 48 months
	High	2 factors Median survival 13 months	3 or more factors Median survival 27 months

MF = myelofibrosis; Hb = hemoglobin  
Adapted from Mesa RA. *Hematology Am Soc Hematol Educ Program* 2010;115-121.

lower-extremity and intra-abdominal locations (hepatic portal and mesenteric) are common. Involvement of the microcirculatory system is typical for ET, manifesting as erythromelalgia, transient ischemic attacks and transient visual or hearing defects.<sup>9,11-12</sup> While erythromelalgia clearly appears to be secondary to abnormal platelet number or function, the pathogenesis of thrombosis in MPD in general is undoubtedly multifactorial. Red cell mass and viscosity, platelet function and leukocyte-vascular endothelial interactions all contribute.<sup>7-9,12</sup> Several studies have confirmed that a lowering of the platelet count in isolation has no influence on the subsequent incidence of thrombosis.<sup>7-9</sup>

The rates for hemorrhage at diagnosis vary from 1.7-20% in PV and 3.6-37% for ET. The majority of hemorrhagic events are minor, involving the skin, mucous membranes or gastrointestinal tract. Reducing the number of platelets lessens

the hemorrhagic tendency in ET, presumably by normalizing the von Willebrand multiple profile.<sup>12</sup>

Various identified risk factors have led to a risk-stratified approach for thrombosis prevention in both ET and PV.<sup>7,9</sup> Major attention is paid to age >60 years and a history of prior thrombosis in order to separate high- and low-risk groups (Table 3). An intermediate-risk group in ET, defined by age <60 years and cardiovascular risk factors, is less well characterized. Obviously, all cardiovascular risk factors such as dyslipidemia, smoking and hypertension should be uniformly treated. Similarly, many clinicians would also classify any otherwise low-risk patients with an extreme thrombocytosis (count >1500x10<sup>9</sup>/L) with the high-risk group, as candidates for cytoreductive therapy.<sup>7,9</sup>

The optimum effective dose of aspirin remains unclear but 81mg–100 mg/day is usually recommended. In ET, some studies have indicated that daily doses as low as 50 mg may be equally effective for the platelet-dependent vascular complications.<sup>9</sup> Hydroxyurea is usually given at a starting dose of 15–20 mg/kg/day, with the maintenance dose adjusted to keep the platelet count and hematocrit satisfactory without causing other clinically significant cytopenias.<sup>9,13</sup> Anagrelide is no longer frequently used because of an increased rate of both myelofibrotic transformation and arterial thrombosis as compared to hydroxyurea-based therapy.<sup>9,13</sup> Patients taking hydroxyurea may experience an overall incidence of AML of approximately 3–4%. However, this remains similar to the natural history of untreated patients.<sup>7,9</sup> Pegylated interferon may be considered as a cytoreductive option for younger or pregnant patients since it is both non-leukemogenic and non-mutagenic and does not cross the placenta.<sup>14</sup> Similarly, the use of busulfan or <sup>32</sup>p may be considered for those aged >75 years, where leukemic risk may now be considered acceptable.<sup>9,13</sup>

MF remains the MPD with the greatest morbidity and

shortest life expectancy.<sup>11,15</sup> A retrospective international prognostic scoring system (IPSS 2009) developed by the International Working Group for Myelofibrosis Research and Treatment,<sup>16</sup> has superseded the Lille classification.<sup>17</sup> This system allows for a quantifiable prediction of prognosis and survival<sup>11</sup> (Table 4).

MF treatment and followup remain largely supportive except for those 20% of patients who are <55 years of age with high-risk or intermediate-2 disease, where allogeneic stem cell transplantation is an option. The long-term survival of transplantation is approximately 50–60%.<sup>9,15</sup> Erythropoietin and danazol may be utilized to treat anemia, and hydroxyurea or splenic radiation may help with symptomatic splenomegaly.<sup>11,15</sup> JAK2 inhibitors have recently become available and significantly reduce constitutional symptoms and splenomegaly. Unfortunately, their usefulness appears to be blunted by an accompanying significant incidence of cytopenias and GI symptomatology. There has also been a lack of clear benefit in relation to the use of JAK2 inhibitors and complete remissions, survival or prevention of thrombosis in MF, PV and ET.<sup>7,15</sup>

## GENERAL FOLLOWUP GUIDELINES IN MPD

For patients taking antiplatelet agents: obtain monthly hematology profile; follow up every 3 months with physical examination and ongoing assessment of risk factors, with appropriate adjustment of therapeutic plan.

For patients taking hydroxyurea: obtain hematology profile twice a week for 2 months, then monthly; follow up every 3 months with physical examination and ongoing assessment of risk factors, with appropriate adjustment of therapeutic plan.

For patients with MF: as above plus regular periodic assessments including physical examination and updated risk assessment, with careful attention to progressive splenomegaly, constitutional symptoms, leukoerythroblastosis or presence of blast cells.

## IRON OVERLOAD IN MULTIPLY-TRANSFUSED ONCOLOGY PATIENTS

There is no physiologic mechanism for excretion of excess iron because total body iron is in a delicate daily balance of 1–2 mg dietary absorption with equivalent loss due to bleeding and sloughed intestinal epithelium. Iron overload results when total body iron exceeds the capacity of the proteins ferritin and transferrin for transport and storage.<sup>18</sup> Under these circumstances, free iron distributed in plasma and within cells generates highly toxic free radicals leading to lipid peroxidation, mitochondrial damage, DNA mutations and dysfunctional cellular signalling pathways. These changes in turn produce the end-organ damage associated with iron overload, affecting the heart, liver, endocrine organs and bone marrow.<sup>18,19</sup>

Each unit of packed red blood cells contains approximately 250 mg of iron, so iron overload is typically present after transfusion of only 15–20 units. A second important mechanism contributing to overload is the cytokine-mediated upregulation of intestinal iron absorption seen with ineffective marrow erythropoiesis. This is particularly prominent in the refractory anemia with ringed sideroblasts (RARS) subtype

of MDS, frequently resulting in an iron overload already present prior to transfusion dependency.<sup>19,20</sup>

Despite any argument that life expectancy in MDS may be too short to be adversely affected by iron toxicity, large registry studies have successfully linked iron exposure (both rate of transfusion and serum ferritin measurements) to reduced survival in lower-risk MDS.<sup>18,19</sup> American Medicare data have demonstrated higher cardiac disease and diabetes rates in the transfusion-dependent MDS subset.<sup>18,19</sup> Further, 2 cohort studies and a single matched-pair analysis have shown that transfusion-dependent MDS patients treated with iron chelation therapy (ICT) experience superior survival.<sup>19,20</sup> Finally, analyses of transplant outcome data reveal that pretransplant serum-ferritin status represents an important independent predictor of posttransplant outcome.<sup>18</sup> In MDS, there is also some evidence that iron overload may predispose to more rapid disease evolution and leukemic transformation.<sup>21</sup>

Thus, pending the forthcoming results of the TELESTO (Myelodysplastic Syndromes [MDS] Event Free Survival With Iron Chelation Therapy) multinational randomized


**TABLE 5. Managing common side effects of deferasirox therapy<sup>17</sup>**

Adverse event	Typical incidence (%)	Possible management strategy
Mild-to-moderate gastrointestinal disturbances	15-20 for diarrhea	<ul style="list-style-type: none"> <li>• Generally resolve without discontinuation of treatment.</li> <li>• Diarrhea is often related to lactase deficiency. Avoid dairy products.</li> <li>• Diphenoxylate-atropine and other antidiarrheal agents as necessary.</li> <li>• Consider reducing deferasirox dose to 10 mg/kg till diarrhea resolves, then escalate dose by 5 mg/kg/week until full target dose is reached.</li> </ul>
Mild-to-moderate rash	10	<ul style="list-style-type: none"> <li>• Continue treatment without dose adjustment as rash often spontaneously resolves.</li> </ul>
Severe rash	5-10	<ul style="list-style-type: none"> <li>• Topical steroid or antihistamines can be utilized.</li> <li>• If treatment interruption required, reintroduce deferasirox at lower dose; after resolution, gradually escalate dose.</li> <li>• In severe cases, reintroduction may require oral steroids.</li> </ul>
Serum creatinine increases (not attributable to other causes)	15-20	<ul style="list-style-type: none"> <li>• With progressive creatinine rise (&gt;33%) above baseline x 2, reduce treatment dose by 10 mg/kg per day.</li> <li>• Ensure no concomitant nephrotoxic drug therapy.</li> <li>• Stop therapy for progressive creatinine rise above normal.</li> <li>• Once creatinine levels have normalized, reintroduce at lower dose of 10 mg/kg per day (depending on clinical circumstances) and gradually escalate.</li> </ul>
Serum transaminase increases (not attributable to other causes)	1-4	<ul style="list-style-type: none"> <li>• With persistent, progressive or unexplained increases, interrupt treatment.</li> <li>• Once cause is found or levels normalize, consider cautious reintroduction at lower dose, followed by gradual escalation.</li> </ul>

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**FOLLOWUP OF THE MULTIPLY-TRANSFUSED PATIENT**

Ensure that a mechanism is in place for monitoring the number of transfusions as well as liver function and serum ferritin associated with each transfusion. Monitoring should take place every 1-2 months and is usually best coordinated with staff from the local blood bank.

Patients on deferasirox require monthly monitoring for liver function, serum creatinine, urinalysis, serum ferritin and transferrin saturation. Baseline audiometry and ophthalmic testing are recommended with annual followup. 

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controlled trial, current consensus is to offer iron chelation therapy to transfusion-dependent MDS patients with proven iron overload. According to the 2008 Canadian guideline, eligibility criteria include patients with low- or intermediate-1 risk MDS, a serum ferritin >1000 µg/L and life expectancy >1 year, as well as to all transplant-eligible patients, regardless of risk factors.<sup>22</sup> In Canada, 2 iron-chelating agents are licensed. Desferrioxamine is administered by continuous parenteral infusion over 12-15 hours daily, 5-7 days per week. In addition to the associated inconvenience and cost, other adverse effects include retinal and ototoxicity.<sup>18,22</sup> The newer oral agent deferasirox has shown effectiveness in reducing total body iron stores in a variety of chronic anemias including MDS, although data confirming survival advantage are currently lacking.<sup>19,20</sup> Other adverse effects include rash, diarrhea, elevated serum creatinine and rare hepatotoxicity. However, side effects can usually be managed with proper dosing modifications (Table 5).

Deferasirox is typically started at 20-30 mg/kg/day with appropriate dosage changes made every 1-3 months. Approximately 75% of patients are controlled at 20 mg/kg/day.<sup>20</sup>