

## Review Article



# Myelodysplastic Syndromes: A Challenging Disease for Patients and Physicians

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## Abstract

The biological mechanisms underlying the ineffective haematopoiesis and increased risk of leukaemic evolution in MDS is largely known. A careful clinical and cytogenetical assessment is required to correctly classify and risk stratify the patients. A curative approach with allogeneic stem cell transplantation should always be considered at the initial assessment. In low-risk patient receiving chronic RBC transfusions, symptomatic iron-overload is a reality and carries a significant mortality, and therefore, the iron status should be monitored and chelators used when indicated. The first line treatment of anaemia is erythroid growth factors. Lenalidomide is a highly potent therapy in low-risk MDS with del 5q, however, the treatment carries a high risk of rapidly developing neutropenia and thrombocytopenia. Several promising drugs are currently under investigation in low-risk MDS including thrombopoietin analogues and epigenetically active drugs.

## Introduction

The myelodysplastic syndromes (MDS) constitute a heterogeneous group of malignant bone marrow disorders characterized by ineffective haematopoiesis and increased risk of leukaemic evolution. MDS still remains a morphological and

clinical diagnosis and careful assessment is required for adequate risk evaluation and treatment selection.

**Table 1 : WHO 2008 Classification of MDS<sup>5</sup>**

S. No.	Disease	Blood Findings	Bone Marrow Findings
1.	Refractory cytopenias with Unilineage dysplasia (RCUD) Refractory anaemia (RA) Refractory neutropenia (RN) Refractory thrombocytopenia (RT)	Unicytopenia	Unilineage dysplasia; $\geq 10\%$ of the cells <5% blasts
2.	Refractory anaemia with ring sideroblasts (RARS)	Anaemia No blasts	Erythroid dysplasia only < 5% blasts $\geq 15\%$ ringed Sideroblasts
3.	Refractory cytopenias with multilineage dysplasia (RCMD)	Cytopenia (s) No blasts (<1%)	Dysplasia in $\geq 10\%$ of cells in two or more myeloid lineages <5% blasts
4.	Refractory anaemia with excess blasts – 1 (RAEB -1)	Cytopenias <5% blasts	5-9% blasts
5.	Refractory anaemia with excess blasts – (RAEB -2)	Cytopenias 5-19% blasts	Unilineage or multilineage dysplasia 10-19% blasts
6.	Myelodysplastic syndrome, unclassified (MDS-U)	Cytopenias No or rare blasts (<1%)	Unequivocal dysplasia in < 10% of cells in one or more myeloid cell lines < 5% blasts
7.	MDS associated with isolated Del (5q)	Anaemia No or rare blasts (<1%) Platelet count usually normal or increased	Normal to increased megakaryocytes with hypolobated nuclei <5% blasts Isolated del (5q) cytogenetic abnormality

## Epidemiology – A Disease of the Elderly

Incidence of MDS is around 4-5 per 1,00,000 yearly. MDS is one of the most common haematopoietic malignancies in people above 80 years.<sup>1</sup> Several weak risk factors have consistently been identified - smoking, exposure to organic solvents, ionizing radiation, male sex, and having a first degree relative affected by a haematopoietic malignancy. Exposure to certain cytotoxic drugs, or therapeutic radiation is associated with greatly increased risk of therapy-related MDS.<sup>2</sup>

## Diagnosis and Classification

Typical patient presents with unexplained anaemia, infections, bleedings. The bone marrow is usually hyper- or normocellular, although a minority are hypocellular. Bone marrow smears show uni – or multi- lineage dysplasia, defined as dysplastic features in at least 10% of the precursors of a particular lineage.<sup>3</sup> Compared to older FAB classification, the WHO categories (Table 1) have several important clinical implications. Patients with unilineage dysplasia have a favourable outcome compared to patients with multi-lineage dysplasia and they also respond better to erythropoietin. The presence of del 5q strongly correlates to the probability of response to lenalidomide.<sup>4,5</sup>

## Cytogenetic Features

Chromosomal aberrations are present in half of all de novo MDS.<sup>6</sup> Several cytogenetic abnormalities observed in MDS are also seen in AML, thus supporting a common origin. The abnormalities can be divided broadly in three groups i.e.

Favourable-Normal, 5q-, 20q-, -y and others.

Intermediate- +8, 12p- and others.

Unfavorable- -7/7q-

Of the various cytogenetic abnormalities, 5q deletion, monosomy 7 and complex abnormalities are of maximum clinical relevance. Complex abnormalities are defined by presence of minimum 3 independent abnormalities in one cell clone. Incidence of complex abnormalities is around 15%.<sup>7</sup>

## Prognosis

As MDS is a heterogeneous group of disorders with variable

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Received: 22.07.2009; Accepted: 29.11.2010

prognosis and survival of many years with minimum treatment at one end to few months only at other end with best possible way. A number of risk classification have been developed in the past to predict survival and to decide treatment; the most common is International prognostic scoring system (IPSS). It is based on percentage of bone marrow blasts, number of cytopenias and karyotype, defined four risk categories distinctly predicting survival and risk of AML evolution: Low, Intermediate-1 ( Int-1), Intermediate-2 ( Int-2) and High risk with median survival of 5.7, 3.5, 1.2, 0.4 years and respectively.<sup>8</sup>

WHO-classification based prognostic scoring system (WPSS) -Though IPSS has proved to be useful in clinical decision making system and currently the standard risk scoring system, it does not acknowledge prognostic implication of transfusion dependency or multilineage dysplasia (Table 2). Malcovati et al developed the WPSS based on WHO category, karyotype risk group and RBC transfusion requirement. The distinct benefit of the WPSS is its ability to identify patients within the low risk subgroups with poor prognosis, like those with multilineage dysplasia or transfusion need.<sup>9</sup>

## Pathogenesis

MDS is considered to be a clonal disorder of an early haematopoietic progenitor or stem cell<sup>10</sup>. Increased apoptosis in the haematopoietic progenitors resulting in peripheral cytopenias is a hallmark of MDS. A minority of MDS patients reside on the diagnostic border between MDS, aplastic anaemia and paroxysmal nocturnal haemoglobinuria. These MDS patients most often have a hypocellular bone marrow.<sup>11</sup> Immunosuppressive therapy can induce long lasting responses in this subcategory.

The other important studied pathogenetic mechanism is epigenetic alterations in promoter hypermethylation and histone deacetylation. Myelodysplastic syndrome is considered to require multiple hits and to date, no single genetic lesions has been shown to be sufficient for developing the disease.<sup>12</sup>

## Therapy-related MDS

Therapy related MDS together with therapy-related AML constitute a unique entity as the clinical out-come is equally poor. The strongest associated exposures are alkylating agents, topoisomerase II inhibitors and radiation.<sup>13</sup>

## The 5q – Syndrome

5q – syndrome, a unique subtype originates at the Haematopoietic stem cells level.<sup>10</sup> It is characterized by favorable prognosis, prolonged disease course and low rate of transformation to AML. Typical bone marrow findings are characteristics; dysmegakaryopoiesis, less than 5% blasts and decreased erythroid precursors.<sup>14</sup>

## Treatment

In lower risk MDS, where anemia is the main challenge, erythropoiesis stimulating agents(ESA) generally remain a first line modality. A wide range of therapeutic modalities like ESA, Immunomodulatory, Immunosuppressive, Hypomethylating agents and Allogenic bone marrow transplantation are now available.

## Transfusion Therapy

The majority of all MDS patients develop a RBC transfusion need. Anaemia per se is associated with severe impairment of quality of life and constitutes a risk factor for heart failure

related death. It is important to avoid significant anemia in view of better survival being seen in patients who have better control of anemia as against those who do not. A modern chronic transfusion therapy aims at maintaining a Hb level of 90 -100 g /l or higher depending on age, co-morbidities and the patient's preference. Around 20% of patients with MDS present with a significant thrombocytopenia and a proportion of these require platelet transfusions to prevent bleeding symptoms.<sup>15</sup>

## Iron Chelation

Transfusion related hemochromatosis affecting the heart and liver, is a reality in patients receiving chronic RBC transfusions.<sup>16</sup> The benefits of chelation in MDS are not well studied. International guidelines recommend iron chelation to transfusion dependent MDS with a reasonable expected survival and the S.ferritin level exceeding 1500 ng/ml.<sup>17</sup> The first line therapy is deferoxamine as s.c. or i.v. infusion.<sup>17</sup> Two oral chelators are currently available, deferiprone and deferasirox and both have activity in MDS.<sup>17</sup>

## Erythropoietic Growth Factors

Treatment with erythropoietic growth factors is an effective treatment of anaemia in MDS.<sup>17,18</sup> Recombinant human erythropoietin (EPO) is given as s.c. injections one to three times per week, in a weekly does of 30, 000 to 60, 000 units. The response rate correlates strongly to S-EPO level and degree of transfusion need.<sup>19</sup> Patient with refractory anaemia and ringed sideroblasts respond better to EPO and G-CSF than to EPO alone and should be given the combination up-front.<sup>20</sup>

## Adverse Effects of EPO

Erythroid growth factors carries an increased risk for thromboembolic events including deep vein thromboses, pulmonary emboli, strokes and myocardial infarctions. The baseline risk of thrombosis should therefore always be considered. Hypertension may also occur and should be monitored.<sup>21</sup>

## Lenalidomide

This non-teratogenic, immunomodulatory drug for MDS with del 5q got approval based on dramatic effects demonstrated in this subgroup; 67% major erythroid responses and 45% complete cytogenetic remissions. Frequent adverse events are grade III-IV neutropenia and thrombocytopenia. Lenalidomide also has a clinically significant activity in non-del 5q MDS, where 26% of low – risk patients become transfusion independent. It has revolutionized the treatment of MDS with 5q. Contrary to myeloma, where 25 mg is a common daily dose, only lower doses are generally tolerated in MDS, 10 mg/day for 21 days on and then 1 week off or even less.<sup>22</sup>

## Other Therapies in Low-risk MDS

Immunosuppressive treatment : Anti –thymocyte globulin or cyclosporine –A, has demonstrated highly variable response rates and duration of response. Limited evidence supports the use of CyA maintenance after ATG therapy, in analogy to the current standard of care in aplastic anaemia.<sup>11</sup>

## Hypomethylating Agents

The marrow complete response rates of the hypomethylating agent 5 –AZA cytidine (5-AZA) are generally <10 %; however, the erythroid response rate is around 50%. It demonstrated 9-month longer median survival for 5-AZA treated patient compared to those receiving conventional care regimens (24 vs. 15 months

**Table 2 : The International Prognostic Scoring System (IPSS) for MDS<sup>s</sup>**

Prognostic Variable	0 Points	0.5 Points	1.0 Points	1.5 Points
Number of Cytopenias <sup>a</sup>	0-1	1-2	-	-
Karyotype <sup>b</sup>	Good	Intermediate	Poor	-
Bone Marrow Blasts (%)	<5	5-10	-	11-20

  

Risk Group	Total Score	Median Survival (Years)	25% AML Evolution (Years)
Low	0	5.7	9.4
Intermediate	0.5-1.0	3.5	3.3
Intermediate-2	1.5-2.0	1.2	1.1
High	≥2.5	0.4	0.2

<sup>a</sup>Cytopenias defined as a hemoglobin-level below 100 gL<sup>-1</sup>, platelet counts below 100X10<sup>9</sup>L<sup>-1</sup>, and absolute neutrophil counts below 1.8X10<sup>9</sup>L<sup>-1</sup>. <sup>b</sup>Good: normal, -Y, del(5q), del(20q); Poor: complex (≥3 abnormalities) or chromosome 7 anomalies; Intermediate: all other abnormalities.

respectively) in high risk subsets of patients. Considering the low toxicity of 5-AZA and the observed improvement in survival, it is recommended as first-line therapy in patients with high-risk MDS that are not eligible for allogeneic stem cell transplantation. The recommended dose for the first cycle, regardless of baseline hematology laboratory valued is 75 mg/m<sup>2</sup> S.C. or I.V. daily for 7 days. The cycle should be repeated every 4 weeks. A minimum of 4 cycles are recommended. Treatment may be continued as long as the patient continues to benefit. Decitabine is another hypomethylating agent that has been evaluated in high-risk MDS with comparable response characteristics to those of 5-AZA.<sup>23</sup>

## Allogeneic Stem Cell Transplantation

It is currently the only curative approach to MDS, and all patients should be considered for a potential transplantation at the initial assessment. Most favorable outcome of transplant and the lowest transplant related mortality and the lowest risk of relapse is seen in low risk categories. However, many low-risk MDS patients can live a decent life for a number of years only with supportive care and this makes the timing of the transplant a delicate matter as it carries a considerable morbidity and mortality. Disease recurrence and non relapse mortality are the major causes of treatment failure in patients with advanced stage or high risk MDS treated with allogeneic transplantation. Dependent on the interval from diagnosis to transplant, patient age, the source of stem cells and conditioning regimen used non-relapse mortality is in range of 25-65%.<sup>24</sup>

## Acknowledgements

I acknowledge Mr. Pankaj Kumar Gupta, Clinical Research Co-ordinator from Department of Clinical Trials and Medical Oncology for his relentless efforts in preparing and designing manuscript of this article.

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