

## Update On Myelodysplastic Syndrome

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**Myelodysplastic Syndrome (MDS)** is a bone marrow stem cell disorder, most commonly occurring in patients over 60 years old, characterized by cytopenias, bone marrow morphologic changes and cytogenetic abnormalities. Risks of MDS include infection, anemia, bleeding and transformation to **Acute Myelogenous Leukemia (AML)**. Older adults, at higher risk, present a treatment challenge due to atypical presentation, multiple co-morbidities, and increased risk of adverse effects from treatment.

### RISK FACTORS

There is a predominance of MDS in males and Caucasians. Prior treatment with chemotherapy and radiation predisposes towards MDS. Other exposures that can increase risk include tobacco, pesticides, benzenes, and heavy metals, such as mercury and lead. There is less evidence of a genetic predisposition for MDS.

### SIGNS AND SYMPTOMS

The presenting symptoms are typically related to resultant cytopenias. Symptoms can include fatigue, pallor, shortness of breath, easy bruising or bleeding, manifesting as petechiae, nose or gum bleeding. Sometimes, the cytopenias of MDS can exacerbate preexisting medical conditions, especially in older patients, in whom multiple co-morbidities are likely. For example, anemia can lead to congestive heart failure exacerbations. In addition, patients can present with frequent, unexplained infections or fevers. Not uncommonly, patients may present without symptoms and incidentally discovered cytopenias on routine lab work. As in many conditions, older

patients tend to present atypically, resulting often in late detection.

### DIAGNOSIS

A bone marrow aspirate and biopsy are required for the diagnosis of MDS, which typically shows hypercellularity and uni-lineage or multi-lineage dysplasia. The combination of peripheral cytopenias despite a hypercellular bone marrow is the hallmark of MDS, and is a consequence of a dysfunctional bone marrow with an excessive rate of bone marrow cell apoptosis.

Bone marrow cytogenetic abnormalities are seen in 40-70% of patients with MDS and are helpful not only in characterizing and prognosticating MDS, but also in the determination of treatment options.<sup>1</sup>

### CLASSIFICATION

MDS can be primary or secondary. In primary MDS, there is no specific cause. In 50% of these patients, chromosomal abnormalities can be found, typically in the form of deletions. In secondary MDS, there is usually an inciting event, such as previous exposure to chemotherapy. Chromosomal abnormalities are seen in 80% of these patients. These abnormalities are most commonly numerical (ie: hypoploidy) or structural. Secondary MDS typically carries a worse prognosis.

The **World Health Organization (WHO)** Classification of MDS is summarized in Table 1. The classification system primarily uses percentages of bone marrow blasts, number of ringed sideroblasts, and number of dysplastic lineages to differentiate the subtypes of MDS.<sup>2</sup>

Refractory anemia	Erythroid dysplasia only, <5% bone marrow blasts with no peripheral blasts, <15% ringed sideroblasts
Refractory anemia with ringed sideroblasts	Erythroid dysplasia only, <5% bone marrow blasts with no or rare peripheral blasts, >15% ringed sideroblasts
Refractory anemia with excess blasts	Uni-lineage or multi-lineage dysplasia, 5-19% of bone marrow cells are blasts
MDS-Unclassified	Cytopenias, unilineage dysplasia in granulocytes or megakaryocytes, <5% bone marrow blasts with no or rare peripheral blasts
Refractory cytopenia with multilineage dysplasia	Bi- or pancytopenia in blood, dysplasia in >10% of cells in two or more of myeloid cells lines, < 5% bone marrow blasts with no or rare peripheral blasts
MDS with del(5q)	Anemia, platelets usually normal to increased, normal to increased megakaryocytes with hypolobulated nuclei. Isolated 5q deletion seen in cytogenetics.

Table 1.

## PROGNOSIS

The most widely accepted prognostic tool is the International Prognostic Scoring System, which takes into account bone marrow blast percentage, specific cytogenetic categories (good risk, intermediate risk and poor risk), and number of cytopenias to develop four risk groups. Overall survival ranges from 5.7 years in patients in the most favorable risk group (less than 5% blasts, good risk cytogenetic, and  $\leq 1$  cytopenic lineage), 3.5 years and 1.2 years in the intermediate risk groups and 0.4 years in patients in the least favorable risk group (typically greater than 10 % blasts, poor or intermediate risk cytogenetics with cytopenias).<sup>4</sup>

## TREATMENT

Historically, supportive care has been the mainstay of treatment, and almost all patients will need supportive care periodically during their disease course. Patients who develop infections can be treated with antibiotics. Thrombocytopenia may require intermittent platelet transfusions. Patients with anemia are treated with transfusion support or supplementation with Erythropoietin (Epo). Patients who are red blood cell transfusion dependent are at risk for iron overload and its complications, such as heart failure and liver dysfunction, and may require chelation therapy.<sup>5</sup>

Erythropoietin (Epo) has been used in patients with symptomatic anemia. It is most effective when given at high doses (40,000 Units weekly). Although the time for response could be up to 26 weeks, roughly 20 to 55% of patients will respond to Epo treatment, allowing for complete elimination or a decreased need for blood transfusions. Interestingly, when Epo is used in combination with growth factors, such as GM-CSF or G-CSF, effects on hemoglobin values are synergistic.

Two new classes of agents have been incorporated into the treatment for patients with MDS. First are the DNA methyltransferase inhibitors.<sup>6</sup> It is thought that DNA methylation plays a role in the pathogenesis of MDS. DNA methylation typically serves to deactivate genes. Tumor suppressor genes are found to be more frequently methylated in MDS compared to normal hematopoiesis. This leads to a predominance of oncogenes which may result in the phenotype of MDS. Two drugs, azacitidine and decitabine, both of which are analogs of the pyrimidine nucleoside cytidine, are DNA-hypomethylating agents. Because they decrease the amount of DNA methylation, there is an increase in the expression of these tumor suppressor genes. Cytopenias in 24-39% of patients treated with these agents improved. These agents may be especially useful in preventing the transition of MDS to AML which is hallmarked by a further increase in DNA methylation.

The second class of drugs with demonstrated efficacy in MDS is immunomodulatory. Although various theories exist, the exact mechanism of action in MDS is unknown. Lenalidomide is the immunomodulatory agent which has had the most success in improving hemoglobin count in patients with MDS.<sup>7</sup> This thalidomide analogue lacks the neurological toxicities of thalidomide, such as neuropathy and somnolence, and has been shown to be especially effective in patients with deletion of chromosome 5q, with about two-thirds of patients becoming transfusion independent. In patients with non-

5q deletion MDS, 49% of patients experience some hematologic improvement with lenalidomide.

Additionally, chemotherapy is used; however, the use is limited because patients with MDS are older and more susceptible to the side effects of chemotherapy. In patients who can tolerate it, the two situations in which chemotherapy may be used are in patients who have advanced MDS (refractory anemia with excess blasts) and in patients who have progressed to AML.

The treatment that offers the greatest chance of cure for patients with MDS is allogeneic stem cell transplantation.<sup>8</sup> This aggressive strategy has a high rate of morbidity and mortality in older patients and therefore can be offered to only patients who can tolerate it. Elderly patients often have other comorbid medical conditions that preclude this option.

**Reduced intensity transplantation (RIC)** uses lower doses of chemotherapy during transplantation and carries with it lesser morbidity. Therefore, it can be offered to a larger number of older patients. However, there is still significant toxicity to RIC and it is reserved for patients with high-risk MDS who have adequate organ function, or those who have transformed to AML.<sup>9</sup>

However, for all the treatments mentioned, it is important to assess the older adult as a whole, and not entirely based upon medical co-morbidity. Functional status and level of cognitive, social and physical functioning are as important as age and medical condition when determining "prognosis" and ability to tolerate treatments. Older adults should not be automatically discounted from more aggressive treatments due to age alone.

## CONCLUSION

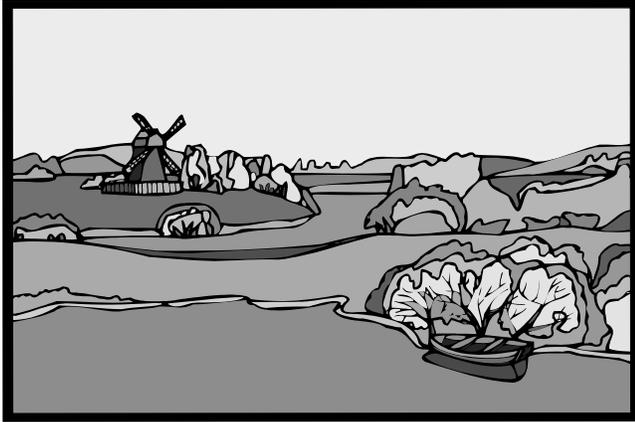
MDS is a heterogeneous stem cell disorder that leads to significant morbidity and mortality. It commonly occurs in the older adult population. Newer treatments aimed at improving cytopenias are available; however, a majority of patients do not respond to therapy and are at risk for death from cytopenias or transformation to AML.

Elderly patients are seldom able to tolerate more aggressive treatments such as allogeneic bone marrow transplantation and thus are a population that has the most to benefit from improved treatments options and further research. However, consider functional status when determining prognosis and ability to tolerate treatment.

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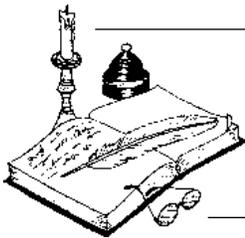
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## Physician's Lexicon

### Epochs, Eras and Eons

Each of the formal scientific disciplines, including medicine, possesses its own vocabulary. Some terminologies are shared as when medicine and the law overlap in the forensic sciences. Perhaps the least likely of the physical sciences to share scientific nomenclature with medicine is geology; yet even here there is some common ground in paleopathology and the Darwinian timelines.

Geologists whose timelines are more profoundly rooted than physicians' think in terms of millions – if not billions – of years. Thus they divide the 4.35 billion years of this globe's existence into eons, eras, periods and epochs. And the names that they have chosen for the Periods generally reflect geographic place-names rather than personages of classical mythology. Thus, for example, the Cambrian Period is named after the Latin name for Wales [*Cambria*]; the Ordovician Period is named after a Celtic tribe of ancient Wales

named the Ordovices; the Silurian Period is named after the Silures, the Brithonic people of ancient Wales; the Permian Period is named after the east Russian province of Perm; the Devonian Period is named after Devon, an English county; the Cretaceous Period is named after a Latin word, *creta*, meaning chalk; and the Jurassic Period is named after the Jura mountains in France and Switzerland.

There are a number of Greco-Roman prefixes appended to the geologic epochs that also crop up in medical nomenclature. These include the many prefixes attached to the Greek root *-cene*, meaning recent. These include: *paleo-* [Greek, meaning ancient], *proto-* [Greek, meaning first], *pleio-* [Greek, meaning more than or greater], *eo-* [Greek, meaning dawn], *oligo-* [Greek, meaning few or small], *pleisto-* [Greek, meaning the most of that which is new], and *holo-* [Greek, meaning entire or complete as in the Holocene Epoch and repre-

senting the geologic interval from 11,700 years ago to the present.] Medical terms employing these prefixes include paleoencephalon, pleiotropy, pleochromocytoma, pleocytosis, oligodendroglioma, holocrania and holozoic.

The eons are given the following names: Hadean [about 4 billion years ago] representing the early formation of the solar system, named after the Greek word, Hades, the lower, or invisible, world. The Archaean [about 3 billion years ago], named for the Greek word meaning ancient or primitive; Proterozoic [about 2.8 billion years ago] from the Greek, meaning former or anterior, while the *-zoic* root is Greek, meaning living; and the Phanerozoic Eon [about 542 million years ago to the present] is from the Greek, meaning visible or manifest.

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