Myelodysplasia

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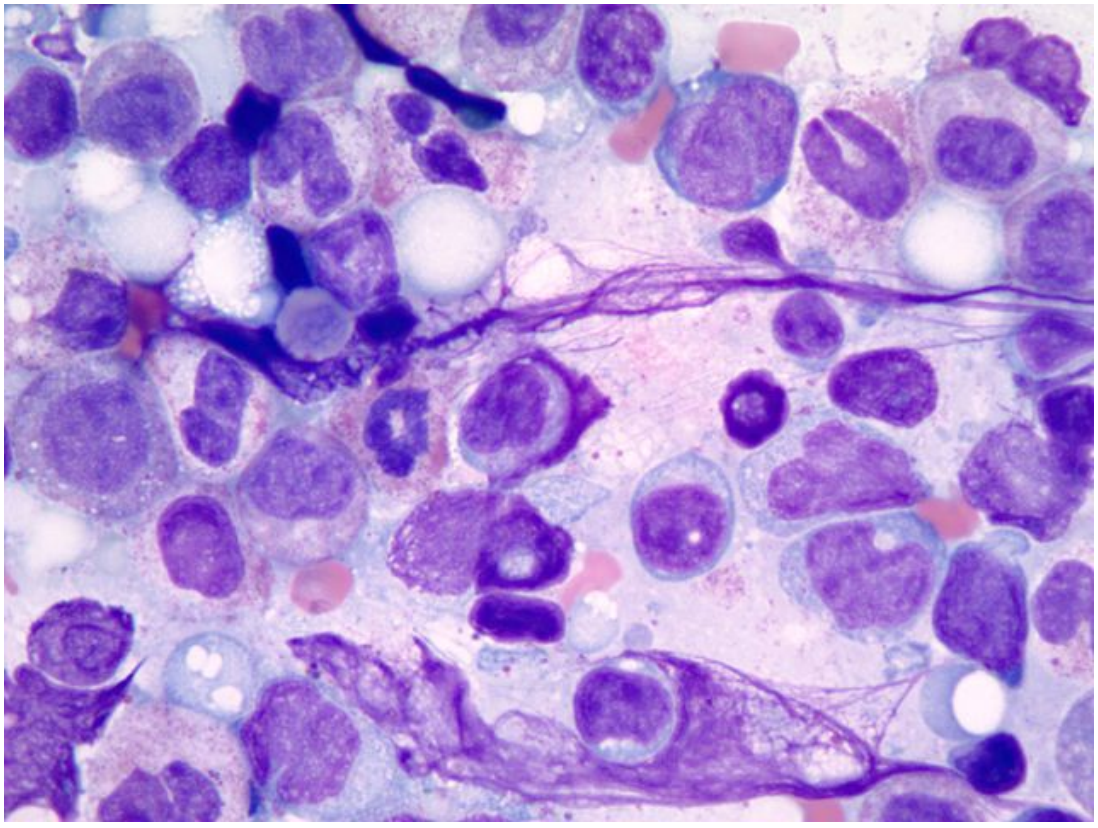
Myelodysplasias are a group of malignant myeloid stem cell disorders characterized by dysplasias and/or cytopenias and there is an increased risk of transformation into acute myelogenous leukemia. The pathogenesis of myelodysplasias is not completely understood but, like other neoplasms, it too involves oncogenic mutations that may arise spontaneously or as a result of environmental exposure. The diagnosis of myelodysplasia is done by finding changes in the peripheral blood smear and bone marrow aspirate. Management of myelodysplasias depends on the percentage of blast cells.



Definition of Myelodysplasia

Myelodysplasias are a **group of malignant myeloid stem cell disorders** characterized by dysplastic and ineffective bone marrow myeloid line cell production and an **increased risk of transformation to acute leukemia**. It usually presents in older patients, greater than 60 years of age. Myelodysplasia is also referred to as myelodysplastic syndrome (MDS) and starts by affecting hematopoiesis. One develops molecular mutation, morphologic abnormalities, cytogenetic abnormalities, as well as physiological abnormalities in the maturation and differentiation of hematopoietic cell lines.

It manifests as pancytopenia, thrombocytopenia, anemia, neutropenia and dysfunctional granulocytes, despite a hypercellular bone marrow. Most patients with myelodysplasia do not develop acute myelogenous leukemia because **complications of infection and bleeding lead to death before leukemia occurs**.

Classification of Myelodysplasia

World Health Organization classification of myelodysplasias

Cytogenetic abnormalities	Clinical presentation	Marrow blasts (%)	Disease
25	Anemia	<5	Refractory anemia
5—20	Anemia, greater or equal to 15% ringed sideroblasts in erythroid precursors	<5	Refractory anemia with sideroblasts
100	Anemia, normal platelets	<5	Myelodysplasias with isolated del (5q) (5q syndrome)
50	Bicytopenia or pancytopenia	<5	Refractory cytopenia with multi-lineage dysplasia
30—50	Cytopenias with or without peripheral blood blasts (<5%)	5—9	Refractory anemia with excess blasts -1
50—70	Cytopenias, peripheral blood blasts present	10—19	Refractory anemia with excess blasts -2
50	Neutropenia or thrombocytopenia	<5	Myelodysplastic syndrome, unclassified

Pathogenesis of Myelodysplasia

The pathogenesis of myelodysplasias is **not completely understood** but, like other neoplasms, it too **involves oncogenic mutations** that may arise spontaneously, or after exposure to certain forms of chemotherapy like alkylating agents, viral infections, environmental toxins like benzene, topoisomerase II inhibitors, people heavily treated with bone marrow transplants (autologous) pesticides, tobacco, heavy metals and radiations. The mutation affects the production of healthy blood cells.

Clinical features of Myelodysplasia

The majority of patients are asymptomatic and are brought to the doctor's attention when cytopenias are detected on a routine complete blood count. Some patients present with symptoms of the abnormalities, like:

- Fatigue from anemia,
- Petechiae,
- Purpura,
- Bleeding or bruising from thrombocytopenia or
- Fever from bacterial infection due to neutropenia.

Anemia is the most common cytopenia found in myelodysplasia and presents as fatigue, exercise intolerance, chest pain or vertigo. Cognitive impairment or altered sensorium can also result from anemia.

Systemic symptoms including weight loss are uncommon, and mostly present in the late stages of disease.

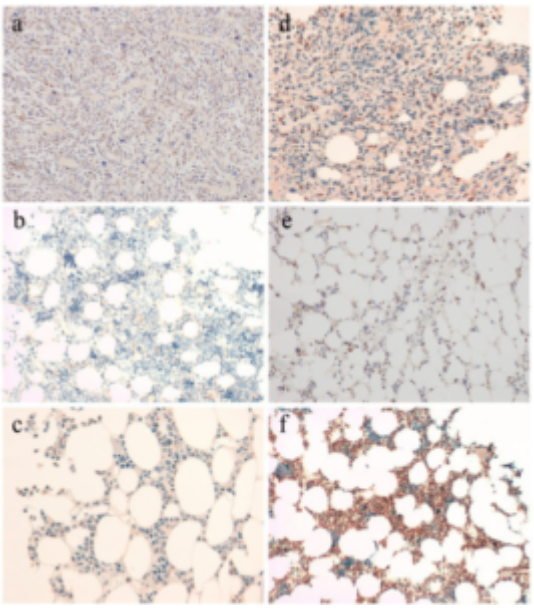


Image: “Pictures of immunohistochemistry assays (200× magnification) performed with anti-FOXP1 antibody showing different levels of protein expression in the bone marrow biopsies of investigated cases. (a) patient under study (level 3); (b) normal BM (level 0); (c) MDS case no. 558/10 with del(5q) as a sole cytogenetic abnormality (level 1); (d) MDS case no. 7737 with del(5q) and trisomy 21 (level 2); (e) MDS case no. 2374 with del(5q) and monosomy 7 (level 3); (f) AML case no. 635/12 with normal karyotype (level 4).” by L’Abbate A, Lo Cunsolo C, Macrì E, Iuzzolino P, Mecucci C, Doglioni C, Coco M, Muscarella LA, Salati S, Tagliafico E, Minoia C, De Tullio G, Guarini A, Testoni N, Agostinelli C, Storlazzi CT. License: CC BY 2.0

Decreased neutrophils and abnormal granulocytes lead to infection, with **bacterial infections being the most common and the skin being the most common site**, while fungal, viral, and mycobacterial infections are rare and mostly occur when there is concurrent administration of immunosuppressive drugs.

Abnormalities of the adaptive immune system can also be found in myelodysplasias, although, in most cases, there is no dysplasia of the lymphoid lineage. Decreased lymphocytes are largely due to a reduced number of CD4+ T cells. Antibody production is also affected with hypogammaglobulinemia, polyclonal hypergammaglobulinemia and monoclonal gammopathy found in many patients.

Autoimmune diseases, although not very common, complicate the course of myelodysplasias. The most common autoimmune diseases are:

- Chronic rheumatic heart disease,
- Rheumatoid arthritis,
- Pernicious anemia,
- Psoriasis,
- Polymyalgia rheumatica.

Others may also occur:

- Sweet syndrome
- Pericarditis

- Pleural effusions
- Skin ulcerations
- Iritis
- Myositis
- Peripheral neuropathy
- Pure red cell aplasia

Acquired alpha thalassemia is found in 8% of patients with myelodysplasias. It results in microcytosis, hypochromia and hemoglobin H containing red blood cells. It is due to an acquired somatic mutation of the ATRX gene.

Skin lesions like Sweet Syndrome or myeloid sarcoma of the skin are uncommon in patients with myelodysplasias, but, if present, indicate conversion of myelodysplasia to acute leukemia. In fact, **the presence of myeloid sarcoma of the skin, also called granulocytic sarcoma, maybe the first sign of progression to acute leukemia**.

Investigations of Myelodysplasia

To make the right diagnosis, MDS has to be distinguished from cytopenia and stem cell disorders. This requires the collection of all information on lifestyle, occupation, past treatments, and complete physical examination.

Complete blood count

Anemia with an increased MCV, nucleated red blood cells and a small number of blast cells, <20%. The greater the percentage of blast cells, the more severe the disease.

Bone marrow

Shows hypercellularity. Topography and fibrosis should be checked too.

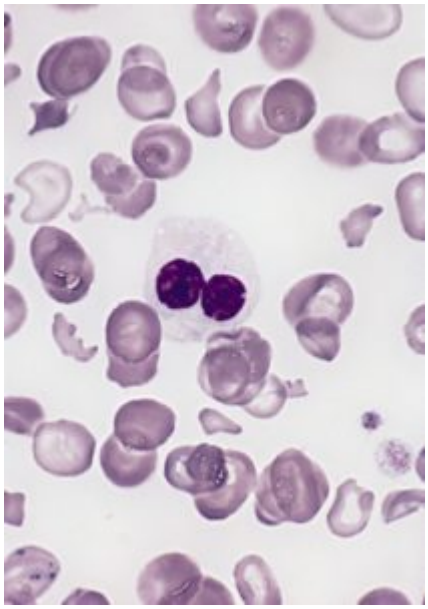


Image: “Hypogranular neutrophil with a pseudo-Pelger-Huet nucleus in MDS” by The Armed Forces Institute of Pathology (AFIP). License: Public Domain

Presence of ringed sideroblasts

Ringed sideroblasts are erythroblasts with iron-loaded mitochondria. They can be seen

with a Prussian blue stain.

Pelger-Huet cells

These are hyposegmented neutrophils. They are the most distinct abnormality found in myelodysplasias.

Chromosome 5q deletion

It is the most characteristic abnormality seen in myelodysplasias. Patients with 5q deletion have a better prognosis than those without it, and such patients have an excellent response to lenalidomide. This deletion leads to a loss of genetic information and supportive care is suggested as medication may lead to neutropenic infections.

Differential diagnosis of Myelodysplasia

Myelodysplasia should be differentiated from other conditions that may also present with cytopenias and/or dysplasia.

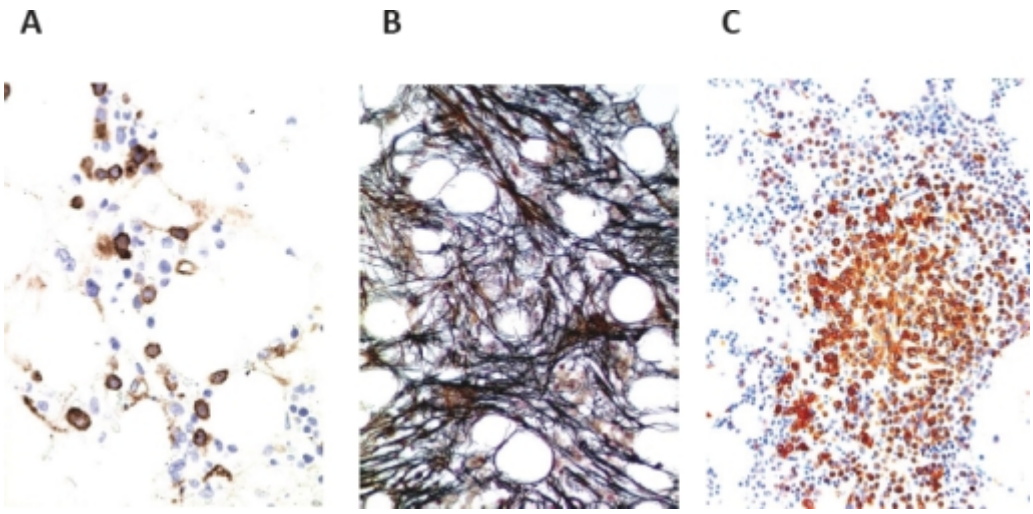


Image: “Diagnostic potential of histomorphological features in MDS and delineation of MDS subtypes. A: Immunohistochemistry reveals an increase in CD34+ precursor cells in a patient with hypoplastic MDS. Note focal clustering of CD34+ precursor (blast) cells in the bone marrow section. B: The fibrotic form of MDS (MDS-F) as evidenced by Gömöri’s silver stain (grade III). C: MDS associated with systemic mastocytosis (SM-MDS) as evidenced by staining the bone marrow section for mast cell tryptase. Note the compact infiltrate of spindle-shaped tryptase-positive mast cells in this patient. ” by Valent P, Orazi A, Büsche G, Schmitt-Gräff A, George TI, Sotlar K, Streubel B, Beham-Schmid C, Cerny-Reiterer S, Krieger O, van de Loosdrecht A, Kern W, Ogata K, Wimazal F, Várkonyi J, Sperr WR, Werner M, Kreipe H, Horny HP . License: CC BY 2.5

Idiopathic cytopenia of undetermined significance

The term ‘idiopathic cytopenia of undetermined significance’ describes the cases of persistent cytopenia without evident dysplasia, without cytogenetic abnormalities found in myelodysplasia and without a related hematologic or non-hematologic disorder. Its presence may not necessarily lead to MDS, but can also lead to other conditions such as myeloproliferative neoplasm; thus, its presence cannot be used to arrive at a conclusive diagnosis.

Clonal hematopoiesis of indeterminant potential

The term ‘clonal hematopoiesis of indeterminant potential’ describes the cases in which **blood cells possess somatic mutations** which are also found in hematologic malignancies but there is **an absence of other diagnostic criteria** for hematologic malignancy.

Persons with ‘clonal hematopoiesis of indeterminant potential’ may have normal cell counts, cytopenias that are unrelated to myelodysplasias or cytopenias that are related to myelodysplasia but do not meet the criteria for it.

Another related term, ‘clonal cytopenia of undetermined significance’, describes the cases that have clinically evident, but idiopathic cytopenias, plus a mutation that does not meet the criteria for myelodysplasia or another hematologic malignancy. More common are the clonal cytopenias than MDS. They have a comparable blood count as well as allele frequencies.

Acute myeloid leukemia

Acute myeloid leukemia can be **differentiated from myelodysplasias by the following criteria:**

1. The presence of myeloid sarcoma or any of the following genetic mutations, regardless of blast cell count, is suggestive of acute myeloid leukemia.
2. At least 20% blast cells in the bone marrow or peripheral blood is suggestive of acute myeloid leukemia.
    a. AML with t (8;21) (q22;q22); RUNX1-RUNX1T1 (previously AML1-ETO).
    b. AML with inv (16) (p13.1q22) or t (16;16) (p13.1;q22); CBFB-MYH11.
    c. APL with t (15;17) (q24.1;q21.1); PML-RARA.
    d. It may not be possible to differentiate myelodysplasia from early evolving acute myeloid leukemia by checking the blast cell count and can **only be made reliably after at least 30 days of observation**.
    e. As a general rule, the **percentage of blast cells should continue to rise in evolving acute myeloid leukemia and remain relatively stable in myelodysplasias**.

Its predisposing factors include Fanconi anemia, bloom syndrome, neurofibromatosis and Down syndrome.

Myelodysplasia and myeloproliferative syndromes

Myelodysplasia and myeloproliferative syndromes are syndromes in which **features of both myelodysplasias and myeloproliferative disorders co-exist**.

Myeloproliferative features include evident thrombocytosis, for example, a platelet count of at least 450 x 109 per liter, accompanied by megakaryocytic proliferation and leukocytosis (white blood cell count of at least 13 x 109 per liter), with or without splenomegaly.

Myelodysplasia and myeloproliferative syndromes include:

1. Chronic myelomonocytic leukemia

Chronic myelomonocytic leukemia is characterized by the **excessive multiplication of mutated monocytes** and sometimes mutated neutrophils, accompanied by anemia and

thrombocytopenia.

In chronic myelomonocytic leukemia, the blood monocyte count is greater than 1,000 per microliter while, in myelodysplasias, borderline or sometimes relative elevations in the monocyte count are present.

Proliferative features, such as **splenomegaly and leukocytosis, may be present in chronic myelomonocytic leukemia but are not found in myelodysplasias**. Furthermore, dysplastic features are more subtle in chronic myelomonocytic leukemia as compared to myelodysplasias and are often found in less than 10% of mononuclear cells counted. Risk factors include old age, male gender, use of anti-cancer drugs, environment and radiation.

2. Atypical chronic myeloid leukemia (BCR-ABL1 negative)

Atypical chronic myeloid leukemia is characterized by the **excessive multiplication of mutated neutrophils** accompanied by dysgranulopoiesis.

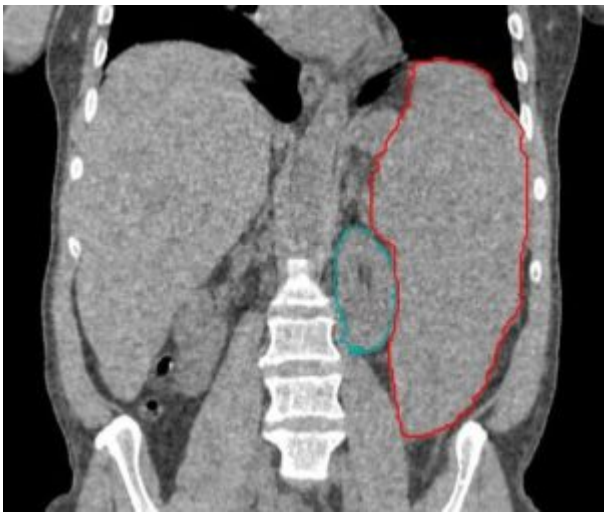


Image: “Enlarged spleen due to myelodysplastic syndrome; CT scan coronal section. Spleen in red, left kidney in green.” by Tdvorak. License: CC BY-SA 3.0CC BY-SA 3.0

3. Juvenile myelomonocytic leukemia

Juvenile myelomonocytic leukemia is a rare disorder affecting infants and children. It is characterized by **hepatomegaly, splenomegaly, and lymphadenopathy**, with or without dysgranulopoiesis.

4. Myelodysplasia and myeloproliferative syndrome with ring sideroblasts and thrombocytosis

In some cases, patients will have **clinical and morphologic characteristics of myelodysplasias with ring sideroblasts, but will also have thrombocytosis and megakaryocytosis**. Such cases are termed as ‘myelodysplasia and myeloproliferative syndrome with ring sideroblasts and thrombocytosis’.

The diagnosis of myelodysplasia and myeloproliferative syndrome with ring sideroblasts and thrombocytosis requires all of the following:

- **Anemia due to erythroid lineage dysplasia** with or without multi-lineage dysplasia, at least 15% ring sideroblasts, less than 1% blast cells in the peripheral blood and less than 5% blast cells in the bone marrow.

- **Persistent thrombocytosis** with a platelet count of at least 450,000 per microliter.
- **Presence of an SF3B1 mutation** or in the absence of SF3B1 mutation, no recent evidence of cytotoxic or growth factor therapy that could have given rise to features of myelodysplasia and myeloproliferative syndrome.
- **No BCR-ABL1 or PCM1-JAK2 fusion gene**; no rearrangement of PDGFRA, PDGFRB or FGFR1; no (3;3) (q21;q26), inv(3) (q21;q26), or del(5q).
- **No previous history** of myeloproliferative neoplasms, myelodysplasia (except for myelodysplasias with ring sideroblasts) or some other type of myelodysplasia and myeloproliferative syndrome.

5. Unclassifiable myelodysplasia and myeloproliferative syndromes

Aplastic anemia

Aplastic anemia is when there are **decreased or absent pluripotent stem cells**. Peripheral pancytopenia, marrow hypoplasia normocytic anemia.

Although most myelodysplasias have normal or increased bone marrow cellularity, a minority of cases have a lower bone marrow cellularity as compared to the patient's age. Such myelodysplasia is called hypoplastic myelodysplasia. Hypoplastic myelodysplasia is usually therapy-induced.

To differentiate hypoplastic myelodysplasia from aplastic anemia, the bone marrow cells should be checked. Cells in myelodysplasia have abnormal karyotype and morphology.

Primary myelofibrosis

Although myelodysplasia can present with mild to moderate fibrosis of bone marrow, severe fibrosis can be seen in a small number of cases which makes it very **difficult to differentiate it from primary myelofibrosis**. Primary myelofibrosis has the symptoms, such as hepatosplenomegaly, leukoerythroblastosis, anemia, and extramedullary, as well as myelofibrosis.

Myelodysplasia with severe bone marrow fibrosis is **often associated with pancytopenia, dysplasia of all three myeloid lineages and atypical megakaryocyte proliferation**.

In most cases, primary myelofibrosis can be differentiated from myelodysplasia by the presence of splenomegaly in primary myelofibrosis.

In some cases, the genotype needs to be seen. Mutations in JAK2, CALR or MPL gene suggest primary myelofibrosis.

Human Immunodeficiency Virus (HIV)

The most common finding in patients affected by HIV are **dysplasias of bone marrow cells**. These are thought to result from medications, opportunistic infections or the direct effect of the virus on progenitor cells.

Other findings may include:

- Cytopenias,
- Hypercellularity,

- Megaloblastic hematopoiesis,
- Fibrosis of bone marrow,
- Increased bone marrow iron stores,
- Lymphocyte aggregates or
- Granulomas.

Therefore, it is important to rule out the HIV infection in a patient with unexplained cytopenias and/or dysplasia.

Poor nutritional status

Many patients with myelodysplasias have macrocytics, low reticulocytes, and pancytopenia.

These findings may also be present in megaloblastic anemias, copper deficiency or zinc excess.

Therefore, **these need to be differentiated**. For example, hyposegmented neutrophils (Pelger-Huet cells) are present in myelodysplasia, while hypersegmented neutrophils with macrocytes are present in megaloblastic anemia.

Medications

Some medicines **can cause macrocytosis, hyposegmented neutrophils, neutropenia, thrombocytopenia and dysplasias** in all three myeloid lineages of the bone marrow.

These features are **reversible** on the reduction or discontinuation of these medicines, usually within a few weeks.

These medicines include granulocyte colony-stimulating factor, valproic acid, mycophenolate mofetil, ganciclovir, alemtuzumab, methotrexate, and cyclophosphamide.

Inherited and acquired sideroblastic anemias

Sideroblastic anemias are **anemias resulting from abnormal heme synthesis and abnormal mitochondrial function**. Ring sideroblasts that are erythroblasts with iron-loaded mitochondria are a characteristic feature of sideroblastic anemia.

Ring sideroblasts may also be found in myelodysplasias (or ‘myelodysplasia and myeloproliferative syndrome with ring sideroblasts and thrombocytosis’) and it is important to differentiate it from sideroblastic anemias.

For acquired sideroblastic anemia, **one should rule out its causes like copper deficiency, medicines or alcohol abuse**.

For X-linked sideroblastic anemia, **either ALAS2 gene mutation should be checked or persistent sideroblasts after a three month trial of vitamin B6 can point to a diagnosis**. An acquired mutation in SF3B1 or JAK2 gene confirms myelodysplasia and rules out inherited sideroblastic anemia.

Management of Myelodysplasia

The management approach is determined by age, personal goals, and co-morbidities, as well as expectations. Younger patients are generally allowed to take up high-risk

treatment options.

Patients with <5% blast cells in the bone marrow

They are usually **managed conservatively with red blood cell and platelet transfusions** and antibiotics for infections as needed. Haemopoietic growth factors, like erythropoietin and G-CSF, may be useful in some patients.

Patients with >5% blast cells in the bone marrow

They have a less favorable prognosis and a number of treatment options.

Supportive care

Only suitable for elderly patients with other medical problems.

Gentle chemotherapy

(Low-dose or single-agent like azacytidine) may be useful in patients with high white blood cell counts.

Cytotoxic chemotherapy

Patients with high levels of myeloblasts, as well as those with acute leukemia that has progressed, use this therapy where combined anthracycline and cytarabine yield up to 40% response rate.

Intensive chemotherapy

Can be tried for patients below the age of 60 with acute myeloblastic leukemia, but the remission rate is less, and prolonged pancytopenia may occur because of decreased regeneration since there is a defect in pluripotent stem cells.

Lenalidomide (a thalidomide analogue)

Has been proven to be remarkably successful in the treatment of early-stage myelodysplasia with a chromosome 5q deletion.

Bone marrow transplantation

Offers the hope of a cure in the small proportion of myelodysplasia patients who are under the age of 50 and who have an HLA-identical sibling or an unrelated HLA-matched donor.

Complications of Myelodysplasia

Myelodysplasias are associated with common complications, such as:

- Anemia
- Recurrent infections bleeding
- Petechie, purpura
- Bruises
- Acute myelogenous leukemia

References

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Notes