

Cancer Association of South Africa (CANSA)



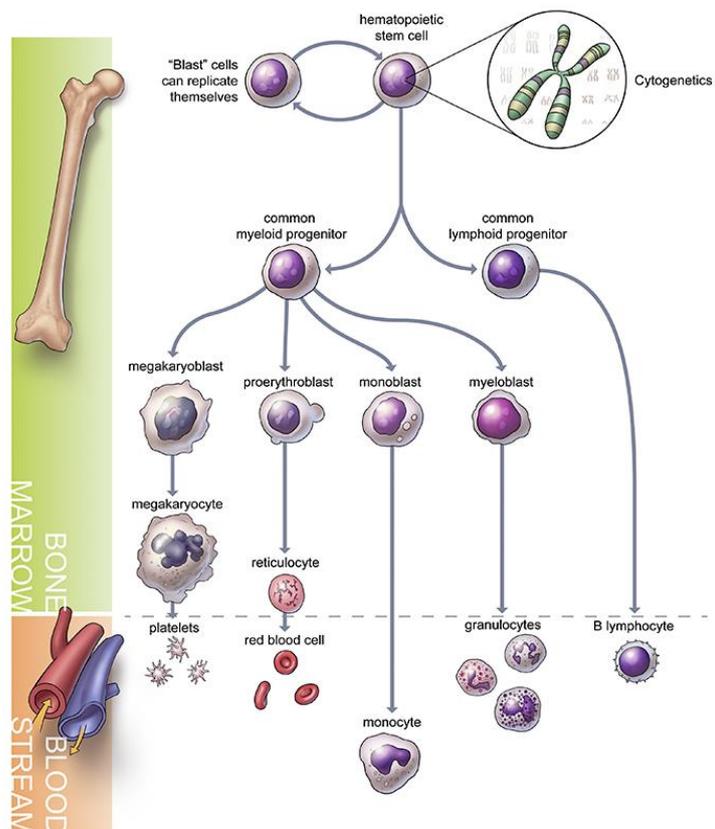
Fact Sheet on Myelodysplastic Syndromes

Introduction

Myelodysplastic syndromes (MDS) are a group of diseases that affect normal blood cell production in the bone marrow and is sometimes referred to as a pre-leukaemic disorder. In MDS the bone marrow produces abnormal, immature blood cells called *blast cells*. These cells fail to mature properly and are unable to work adequately. They often die before they leave the bone marrow, or shortly after reaching the bloodstream. Without enough normal cells being produced by the bone marrow (red cells, white cells and platelets) people with MDS can become fatigued, more susceptible to infections, and to bleeding and bruising more easily.

[Picture Credit: Haematopoiesis]

Aspect of Hematopoiesis Relevant to MDS



Visual Art: © 2013 The University of Texas MD Anderson Cancer Center

MDS is a collection of heterogeneous haematopoietic disorders. The disorders that belong to this group are characterised by either a hypo-cellular or hyper-cellular marrow with its maturation and morphology impaired. Simply put, they are conditions that have resulted due to ineffective production of blood cells.

There are five (5) different types of MDS and the disease can vary in its severity and the degree to which normal blood cell production is affected. About 30% of people with MDS will

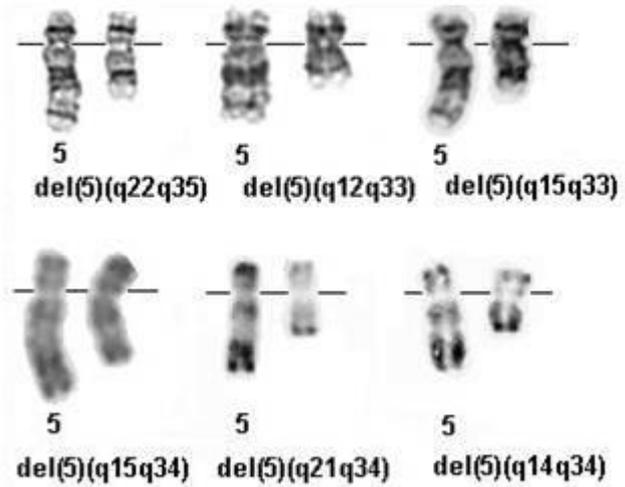
progress to a form of cancer called acute myeloid leukaemia (AML). MDS is sometimes referred to as a *pre-leukaemic* disorder.

According to the World Health Organization classification there are seven (7) types of MDS. They include:

- Refractory cytopaenia with unilineage dysplasia (RCUD) - About 5% to 10% of all MDS patients have RCUD. People with RCUD have low numbers of one type of blood cell, but normal numbers of the other 2 types. Examples of RCUD include refractory anaemia (RA), refractory neutropenia (RN), and refractory thrombocytopenia (RT). Refractory anaemia (RA) is the most common type of RCUD. People with RA have low numbers of red blood cells (anaemia) but have normal numbers of white blood cells and platelets. In the bone marrow of RA patients, only the cells that grow to become red blood cells look abnormal. In the bone marrow of RCUD patients, at least 10% of the early cells of the affected cell type look abnormal (show *dysplasia*), but the other types of cells in the bone marrow look normal. There is a normal number (less than 5%) of very early cells called *blasts* in the bone marrow and blasts are rare (or absent) in the blood. This type of MDS seldom, if ever, progresses to acute myeloid leukaemia. Patients with this type of MDS usually live a long time.
- Refractory anaemia with ringed sideroblasts (RARS) - About 10% to 15% of all people with MDS have this type. This condition is similar to refractory anaemia- the patient has low numbers of red blood cells but normal numbers of white blood cells and platelets. In the bone marrow, at least 10% of the early cells look abnormal. In RARS, though, 15% or more of the early red blood cells in the bone marrow contain circles of iron deposits (rings) around the nucleus (these cells are called *ringed sideroblasts*). This type rarely turns into leukaemia, and the outcome for people with this type is generally the same as for those with refractory anaemia.
- Refractory cytopaenia with multilineage dysplasia (RCMD) - About 40% of people with MDS have this type. In this condition, the counts of at least 2 types of blood cells are low. In the bone marrow, those same types of cells look abnormal under the microscope (dysplasia). Ringed sideroblasts may or may not be present. The number of blasts (very early cells) in the bone marrow is less than 5% and none of the blasts contain Auer rods (an abnormality seen in some leukaemia cells). Blasts are rare or absent in the blood. RCMD changes into leukaemia in about 10% of patients. Having this type of MDS will shorten a person's life. One estimate is that half of patients will die within 2 years of diagnosis.
- Refractory anaemia with excess blasts-1 (RAEB-1) - One or more cell types are low in the blood and look abnormal in the bone marrow. The number of blasts in the bone marrow is increased; but is still less than 10%. The blasts do not contain Auer rods. Blasts may be present in the blood, but they make up less than 5% of the white blood cells. The chance of RAEB-1 turning into acute myeloid leukaemia is about 25%. This type of MDS has a poor outlook and most patients die within 2 years.
- Refractory anaemia with excess blasts-2 (RAEB-2) - This type of MDS is similar to RAEB-1 except the bone marrow contains more blasts – between 10% and 20% of the bone marrow cells are blasts. The blood also contains more blasts: between 5 and 19% of the white blood cells in the blood are blasts. The blasts may contain Auer rods. Any one (or more) of the cell types can be low in the blood and look abnormal

in the bone marrow. The chance of RAEB-2 turning into acute myeloid leukaemia may be as high as 50%.

- Myelodysplastic syndrome, unclassified (MDS-U) - This type of MDS is uncommon. For a case to be considered MDS-U, the findings in the blood and bone marrow can't fit any other type of MDS. Numbers of any one of the cell types may be low in the blood but less than 10% of that type of cell looks abnormal in the bone marrow. The cells in the bone marrow have at least one certain chromosome abnormality that is only seen in MDS or leukaemia. The number of blasts in the bone marrow is less than 5%. Because this type is so rare, it has not been studied well enough to predict prognosis (outlook).
- Myelodysplastic syndrome associated with isolated del(5q) - In this type of MDS, the chromosomes of the bone marrow cells are normal except they show that a part of chromosome number 5 is missing. In the blood, the red cell counts are low, but the white blood cell counts are normal. Often the platelet count is increased. The number of blasts in the bone marrow is less than 5%. For unknown reasons, patients with this type of MDS have a very good prognosis (outlook). They often live a long-time and rarely go on to develop leukaemia.



[Picture Credit: Del(5q)]

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(Leukaemia Foundation; Mayo Clinic; Medicalook.Com; American Cancer Society).

Incidence of Myelodysplastic Syndrome (MDS) in South Africa

Because this is a pre-leukaemia condition, the National Cancer Registry (2011) does not provide any information about the incidence of this condition.

Causes of Myelodysplastic Syndrome (MDS)

The risks of MDS increase with age. Factors that raise your risk of these problems include:

Cancer therapy.- the use of certain chemotherapy drugs for cancer plays a role in many cases of later myelodysplastic syndrome. MDS may be more likely to occur after treatment for acute lymphocytic leukaemia in childhood, Hodgkin's lymphoma, or non-Hodgkin's lymphoma.

Cancer drugs linked to myelodysplastic syndrome include:

- Leukeran (chlorambucil)
- Cytoxan (cyclophosphamide)
- Adriamycin (doxorubicin)
- Etopophos (etoposide)
- Ifex (ifosfamide)

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- Mustargen (mechlorethamine)
- Alkeran (melphalan)
- Matulane (procarbazine)
- Vumon (teniposide)

Some inherited conditions raise people's risk of having myelodysplastic syndrome. These include:

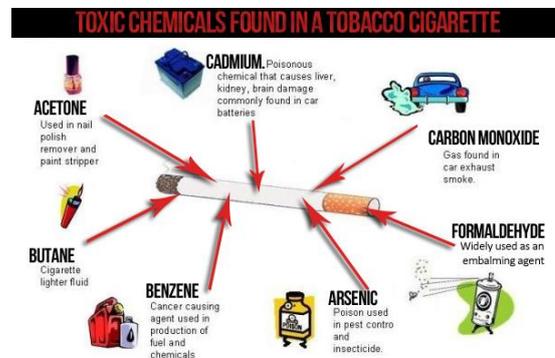
- Fanconi anaemia - in this condition, the bone marrow fails to make sufficient amounts of all three types of blood cells.
- Shwachman-Diamond syndrome - this keeps the bone marrow from making enough white blood cells.
- Severe congenital neutropenia.- this condition is marked by insufficient neutrophils, which are a type of white blood cell.

(WebMD).

Other causes of myelodysplastic syndromes

- Exposure to chemicals - one may be more likely to develop myelodysplastic syndrome following long-term workplace exposure to benzene and other chemicals used in the petroleum and rubber industries.
- Smoking also raises the risk of MDS.
- Radiation – gamma rays and X-rays.
- Pesticides
- Heavy metals – lead and mercury

(MDS Foundation; WebMD; American Cancer Society; Mayo Clinic).



[Picture Credit: Smoking]

Signs and Symptoms of Myelodysplastic Syndrome (MDS)

People with MDS may experience the following symptoms or signs. Sometimes, people with MDS do not show any of these symptoms. Or, these symptoms may be caused by a medical condition that is not MDS. If concerned about a symptom or sign on this list, please talk with a doctor.

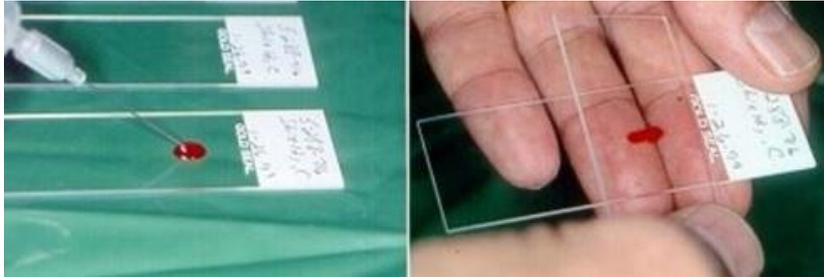
- Fatigue
- Weakness
- Unusual paleness (pallor) due to anaemia
- Easy bruising or bleeding
- Pinpoint-sized red spots just beneath the skin caused by bleeding (petechiae)
- Fever
- Bone pain
- Shortness of breath
- Frequent infections

(Cancer.Net; Mayo Clinic).

Diagnosis of Myelodysplastic Syndrome (MDS)

If signs and symptoms suggest a patient may have MDS, the doctors will look at cells from the blood and bone marrow to confirm this diagnosis.

Blood cell counts and blood cell examination - the complete blood count (CBC) is a test that measures the different cells in the blood, such as the red blood cells, the white blood cells, and the platelets. The CBC is often done with a *differential count* (or 'diff'), which is a count of the different types of white blood cells in the blood sample. In a blood *smear*, some of the blood is put on a slide to see how the cells look under the microscope.



[Picture Credit: Blood Smear]

Patients with MDS often have too few red blood cells. They may have shortages of white blood cells and blood platelets as well. Patients with RAEB

(refractory anaemia with excess blasts) may have a small number of myeloblasts in the blood. Blasts are very early cells that are produced by bone marrow stem cells and are normally only found in bone marrow. When blasts are present in the blood it is always abnormal and often signals a bone marrow problem. Blood cells from MDS patients may also have certain abnormalities in size, shape, or other features that can be seen under the microscope.

Blood abnormalities may suggest MDS, but the doctor cannot make an exact diagnosis without examining a sample of bone marrow cells.

Other blood tests - the doctor may also order tests to check for other possible causes of low blood counts, such as low levels of vitamin B12 and folate.

Bone marrow tests - bone marrow samples are obtained from a bone marrow aspiration and biopsy, tests that are usually done at the same time. The samples are usually taken from the back of the pelvic (hip) bone. These tests are used first for diagnosis and classification and may be repeated later to tell if the MDS is responding to therapy or is transforming into an acute leukaemia.

[Picture Credit: Bone Marrow Aspiration]

For a bone marrow *aspiration*, the patient lies on a table (either on his/her side or on the belly). After cleaning the area, the skin over the hip and the surface of the bone is numbed with local anaesthetic, which may cause a brief stinging or burning sensation. A thin, hollow needle is then inserted into the bone and a syringe is used to suck out a small amount of liquid bone marrow (about 5ml). Even with the anaesthetic, most patients still have some brief pain when the marrow is removed.



A bone marrow *biopsy* is usually done just after the aspiration. A small piece of bone and marrow is removed with a needle that is twisted as it is pushed down into the bone. The biopsy may also cause some brief pain. Once the biopsy is done, pressure will be applied to the site to help prevent bleeding.



A pathologist (a doctor specialising in the diagnosis of diseases using laboratory tests) examines the bone marrow samples under a microscope. A haematologist (a doctor specialising in medical treatment of diseases of the blood and blood-forming tissues) or an oncologist (a doctor specialising in medical treatment of cancer) usually reviews these as well.

The doctors will look at the size and shape of the cells and see whether the red cells contain iron particles or whether the other cells contain granules (microscopic packets of enzymes and other chemicals that help white blood cells fight infections). The percentage of marrow cells that are blasts is particularly important. Blasts are very early cells that are produced by bone marrow stem cells. Blasts eventually mature into normal blood cells. In MDS, the blasts do not mature properly, so there may be too many blasts and not enough mature cells. For a diagnosis of MDS, a patient must have less than 20% blasts in the bone marrow. A patient who has more than 20% blasts in the bone marrow is considered to have acute leukaemia.

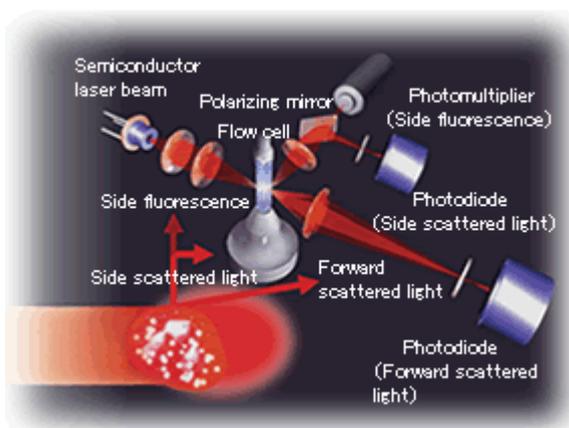
[Picture Credit: Microscopy]

Different types of tests that are done on the bone marrow help the doctor diagnose MDS:

Immunocytochemistry - cells from the bone marrow sample are treated with special antibodies that cause certain types of cells change colour. The colour change can be seen only under a microscope. This testing is helpful in distinguishing different types of MDS or leukaemia from one another and from other diseases.

[Picture Credit: Flow Cytometry]

Flow cytometry - this technique is sometimes used to examine the cells from bone marrow and blood samples. It is very helpful in diagnosing and classifying the type of MDS. It is also used in diagnosing leukaemia and lymphoma. A sample of cells is treated with special antibodies and passed in front of a laser beam. Each antibody sticks only to certain types of cells. If the sample contains those cells, the laser will cause them to give off light. The instrument detects the light, and a computer counts the cells. This test may not be needed for all patients.



Cytogenetics - this test looks at the chromosomes inside the cells. DNA in human cells is packed into chromosomes. Each cell should have 46 chromosomes (23 pairs). Abnormal chromosomes are common in MDS. Sometimes parts of chromosomes or even whole chromosomes are missing. MDS cells may also have extra copies of all or part of some chromosomes. Chromosome translocations (portions of chromosomes may trade places with each other) may also be seen.

Cytogenetic testing can take several weeks because the bone marrow cells need time to grow in laboratory dishes before their chromosomes can be viewed under the microscope. The results of cytogenetic testing are written in a shorthand form that describes which chromosome changes are present. For example:

- A minus sign (-) or the abbreviation 'del' is used to mean a deletion. For example, if a copy of chromosome 7 is missing, it can be written as -7 or del(7). Often, only a part of the chromosome is lost. There are 2 parts to a chromosome, called p and q. Thus the loss of the q part of chromosome 5 is written 5q- or del(5q).
- A plus sign is used when there is an extra copy of all or part of a chromosome. +8, for example, means that chromosome 8 has been duplicated, and too many copies of it are found within the cell.
- The letter 't' is used to indicate a translocation.



[Picture Credit: Cytogenetics]

Chromosome changes commonly seen in MDS include deletions in chromosomes 5 and 7 or an extra chromosome 8. Certain chromosome changes, such as del(5q) (a deletion of a part of chromosome 5), can predict a better outcome (as long as there are no other chromosome changes). Other changes, such as deletions of chromosome 7 or changes in 3 or more chromosomes, have a poorer outlook.

Molecular genetic studies - these tests are another way to find chromosome and gene abnormalities. An example of this is *fluorescent in situ hybridization* – more commonly called FISH. In FISH, specific gene sequences are tagged with a fluorescent dye. These may correspond to a certain area of a chromosome or even a certain translocation. An advantage of FISH is that it doesn't require actively dividing cells. This allows the testing to go a bit faster than cytogenetic testing. FISH is very good for finding translocations – it can even find some that may be too small to be seen with usual cytogenetic testing.



[Picture Credit: Molecular Genetics]

Polymerase chain reaction (PCR) is another molecular genetic test that can be used to look for specific gene abnormalities.

Molecular genetic studies are not needed to make a diagnosis in most cases of MDS, but they can be useful in determining a person's outlook (prognosis). (American Cancer Society).

Complications of Myelodysplastic Syndrome (MDS)

Complications include:

- Anaemia. Reduced numbers of red blood cells can cause anaemia, which can make one feel tired
- Recurrent infections. Having too few white blood cells increases the risk of serious infections
- Bleeding that will not stop. Lacking platelets in the blood to stop bleeding can lead to excessive bleeding that will not stop
- Increased risk of cancer. Some people with myelodysplastic syndromes may eventually develop leukaemia, a cancer of the blood cells

(Mayo Clinic).

Treatment of Myelodysplastic Syndrome (MDS)

The main types of treatment for MDS are:

- Supportive therapy
- Growth factors
- Chemotherapy (including hypomethylating drugs)
- Stem cell transplant
- A combination of the above is sometimes used

(American Cancer Society).

Medications used to increase the number of healthy blood cells the body produces include:

- Medications that increase the number of blood cells the body makes. Called growth factors, these medications are artificial versions of substances found naturally in one's bone marrow. Some growth factors, such as erythropoietin alfa (Epogen) or darbepoetin alfa (Aranesp), can reduce the need for blood transfusions by increasing red blood cells. Others may help prevent infections by increasing white blood cells in people with certain myelodysplastic syndromes
- Medications that stimulate blood cells to mature, rather than remain immature. Medications such as azacitidine (Vidaza) and decitabine (Dacogen) may improve the quality of life of people with certain myelodysplastic syndromes and help delay progression to acute myelogenous leukemia. But these drugs are not effective in all people, and some can cause further blood cell problems
- Medications that suppress the immune system. Medications used to suppress the immune system may be used in certain myelodysplastic syndromes
- Medication for people with a certain genetic abnormality. If the myelodysplastic syndrome is associated with a genetic abnormality called isolated del(5q), the doctor may recommend lenalidomide (Revlimid). Lenalidomide may reduce the need for blood transfusions in people with this abnormality

(Mayo Clinic).

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Bone Marrow Aspiration

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Flow Cytometry

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