What Does My Bone Marrow Do?
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Vidaza™ (azacitidine)

Dacogen® (decitabine)

Revlimid® (lenalidomide)

Growth Factors

For More Information on MDS
Bone marrow is a nutrient-rich spongy tissue located mainly in the hollow portions of long flat bones like the sternum and the bones of the hips. There are two types of bone marrow: red marrow and yellow marrow. Yellow marrow has a much higher amount of fat cells than red marrow. Both types of marrow contain blood vessels.

Stem Cells
The bone marrow works like a ‘factory’ that produces all of the cells that are found in the bone marrow and in the peripheral blood stream. This factory is dependent on the function of the pluripotent stem cells. Pluripotent refers to the ability of a cell to become many different types of cells.

Did You Know?
At birth, all bone marrow is red. As we age, more and more of the marrow converts to yellow bone marrow. In adults, about half of the bone marrow is red and half is yellow.
Long Bone
Spongy Bone
Compact Bone
Red Marrow
Spongy Bone
The bone marrow has two types of stem cells, *mesenchymal* and *hematopoietic*. This process of development of different blood cells from these pluripotent stem cells is known as hematopoiesis. Pluripotent hematopoietic cells can become any type of cell in the blood system. Under the influence of tissue and hormonal factors these cells develop into specific blood cell lines. When these cells differentiate or mature they become the cells that we can recognize in the blood stream.

*Mesenchymal* is embryonic tissue from which the connective tissue, blood vessels and lymphatic vessels are formed.

*Hematopoietic* is the formation and development of blood cells in the bone marrow.
These include the erythroid or red blood cells (RBCs). RBCs are responsible for carrying oxygen from the lungs to all parts of the body. White blood cells (WBCs) include lymphocytes, the cornerstone of the immune system and myeloid cells which include granulocytes: neutrophils, monocytes, eosinophils, and basophils. WBCs fight infection by attacking and destroying bacteria or viruses and granulocytes are involved in a variety of immune processes. Platelets are fragments of the cytoplasm of megakaryocytes, another bone marrow cell.

Did You Know?
Platelet cells (platelets) control bleeding by forming blood clots when your body is injured.
The majority of RBCs, platelets, and most of the WBCs are formed in the red marrow while only a few of them are formed in the yellow marrow. Everyone needs a continuous production cycle of blood cells from our bone marrow throughout our lives since each blood cell has a set life expectancy. Healthy bone marrow produces as many cells as your body needs. Red cell production is increased when the body needs additional oxygen, platelets increase when bleeding occurs, and white cells increase when infection threatens.

**Importance of the Circulatory System**

The circulatory system touches every organ and system in your body. Red cells flow in the blood circulation to transport oxygen. Every cell needs access to the circulatory system in order to function since oxygen is essential for proper cell function.

**Hemoglobin**

Hemoglobin (Hgb) is a protein that is found within red blood cells. This protein is what makes ‘red cells’ red. Hemoglobin’s job is to pick up oxygen in the lungs, carry it in the RBCs, and then release oxygen to the tissues that need it like the heart, muscles, and brain. Hemoglobin also removes CO₂ or carbon dioxide and carries this waste product back to the lungs where it is exhaled.

**Did You Know?**

Red blood cells live an average of 120 days and platelets live 8 – 10 days. Some white blood cells are very short lived and live only hours, while others can live for many years.
Iron

Iron is an important nutrient in the body. It combines with protein to make the hemoglobin in red blood cells and is essential in the production of red blood cells (erythropoiesis). The body stores iron in the liver, spleen, and bone marrow. The storage form of iron is known as ferritin and ferritin can be measured through a blood test. Most of the iron needed each day for making hemoglobin comes from the recycling of old red blood cells.

Red Blood Cells

The production of red blood cells is called erythropoiesis. It takes about 7 days for a committed stem cell to mature into a fully functional red blood cell. Red blood cells have a limited life span of approximately 120 days and must be continuously replaced by the body.

Erythropoiesis is stimulated by a lack of oxygen (hypoxia) in the body. This lack of oxygen tells the kidneys to produce a hormone, erythropoietin (EPO). EPO then stimulates the bone marrow to produce RBCs. Erythropoietin does this by entering the blood stream and traveling throughout the body. All the body’s cells are exposed to erythropoietin, but only red bone marrow cells respond to this hormone. As these new red cells are produced they move into the blood stream and increase the oxygen-carrying ability of the blood. When the tissues of the body sense that oxygen levels are enough, they tell the kidneys to slow

Did You Know?

The body has no active way to excrete unwanted iron, so little iron is lost from the body naturally.
Red Blood Cell

Hemoglobin

Oxygen
the secretion of erythropoietin. This ‘feedback’ within your body ensures that the number of RBCs remains fairly constant and that enough oxygen is always available to meet the needs of your body.

As RBCs age, they become less active and become more fragile. The aging red cells are removed or eaten up by white blood cells (Macrophages) in a process known as phagocytosis and the contents of these cells are released into the blood. The iron from the hemoglobin of the destroyed cells is carried by the blood stream to either the bone marrow for production of new RBCs or to the liver or other tissues for storage.

Normally, a little less than 1% of the body’s total RBCs are replaced every day. The number of red blood cells produced each day, in the healthy person, is about 200 billion cells.

Macrophage is derived from the Ancient Greek: ‘macro’ meaning big and ‘phage’ meaning eat.
**White Blood Cells**

The bone marrow produces many types of white blood cells, which are necessary for a healthy immune system. These cells both prevent and fight infections. There are five main types of white blood cell, or leukocytes:

* **Lymphocytes**  
  Lymphocytes are produced in bone marrow. They make natural antibodies to fight infection caused by viruses that enter your body through your nose, mouth, or cuts. They do this by recognizing foreign substances that enter the body and then sending a signal to other cells to attack those substances. The number of lymphocytes increases in response to these invasions. There are two major types; B- and T-lymphocytes.

* **Monocytes**  
  Monocytes are also produced in the bone marrow. Mature monocytes have a life expectancy in the blood of only 3-8 hours, but when they move into the tissues, they mature into larger cells called macrophages. Macrophages can survive in the tissues for long periods of time where they engulf and destroy bacteria, some fungi, dead cells, and other material foreign to the body.

* **Granulocytes**  
  Granulocyte is the family or collective name given to three types of white blood cells: neutrophils, eosinophils and basophils. The development of a granulocyte
may take two weeks, but this time is shortened when there is an increased threat like a bacterial infection. The marrow also stores a large reserve of mature granulocytes. For every granulocyte circulating within the blood, there may be 50 to 100 cells waiting in the marrow to be released into the blood stream. As a result, half the granulocytes in the blood stream can be available to actively fight an infection in your body within 7 hours of recognizing that an infection exists! Once a granulocyte has left the blood it does not return. It may survive in the tissues for as long as 4 or 5 days depending on the conditions it finds, but it only survives for a few hours in the circulation.

*Neutrophils*

Neutrophils are the most common granulocyte. They can attack and destroy bacteria and viruses.

*Eosinophils*

Eosinophils are involved in the fight against many types of parasitic infections and against the larvae of parasitic worms and other organisms. They are also involved in some allergic reactions.

*Basophils*

Basophils are the least common of the white blood cells and respond to various allergens that cause the release of histamines and other substances. These substances cause irritation and inflammation in the affected tissues. Your body recognizes the irritation/inflammation and widens (dilates) the blood vessels allowing fluid to leave the circulatory system and enter the tissue in an effort to dilute the irritant. This reaction is seen in hay fever, some forms of asthma, hives, and in its most serious form, anaphylactic shock.
Platelets

Platelets are produced in bone marrow by a process known as thrombopoiesis. Platelets are critical to blood coagulation and the formation of clots to stop bleeding.

Sudden blood loss triggers platelet activity at the site of an injury or wound. Here the platelets clump together and combine with other substances to form fibrin. Fibrin has a thread-like structure and forms an external scab or clot. Platelet deficiency causes you to bruise and bleed more easily. Blood may not clot well at an open wound, and there may be a greater risk for internal bleeding if the platelet count is very low.

Did You Know?

Healthy bone marrow normally manufactures between 150,000 and 450,000 platelets per microliter of blood, an amount of blood that fits on the head of a pin.
How Does MDS Affect My Bone Marrow?

In people with Myelodysplastic Syndromes (MDS) the bone marrow cannot produce enough healthy blood cells. It may affect only one of the cell lines or it may affect all three cell lines produced in the bone marrow. RBCs, WBCs, and platelets may not mature and all or some of them may not be released into the blood stream but accumulate in the bone marrow. These cells may have a shortened life span, resulting in fewer than normal mature blood cells in circulation. The cells may actually die in the bone marrow before they mature. This results in a higher than normal number of immature cells or blasts in the bone marrow and fewer than normal mature blood cells in the circulation. Low blood cell counts in any of these three cell lines (red cells, white cells, or platelets) are the hallmark feature of MDS. Low blood counts are responsible for some of the problems that MDS patients experience such as infection, anemia, easy bruising, or an increased chance of bleeding.

In addition to the lower number of blood cells in the circulation, the cells may be dysplastic. The formal definition of dysplasia is an abnormal shape and appearance (morphology) of a cell. The prefix myel- is from the Greek and it means marrow. So myelodysplasia simply means that the mature blood cells found in the bone marrow or circulating in the blood ‘look funny’. Dysplastic cells cannot function properly. In addition to the dysplasia, 50% of patients have an increase in very immature cells called “blasts”.
Effect on Red Blood Cells
Low Red Cell Count (Anemia)

The bone marrow normally produces mature red blood cells and the hemoglobin in these cells carry oxygen to the tissues in your body. The percentage of red blood cells in the total blood volume is called the hematocrit. In healthy women the hematocrit is 36% to 46% while in healthy men the hematocrit is 40% to 52%. When the hematocrit falls below the normal range there are an insufficient number of healthy, mature red blood cells to effectively supply oxygen to all tissues of the body. This condition of below-normal numbers of red blood cells, low hemoglobin levels and low oxygen is called anemia, which can be relatively mild (hematocrit of 30% to 35%), moderate (25% to 30%), or severe (less than 25%). Anemia can also result from the inefficient transport of oxygen by dysplastic (mature but misshapen) red blood cells.
Effect on White Blood Cells
Low White Cell Count (Neutropenia)
The bone marrow normally makes between 4,000 and 10,000 white blood cells per microliter of blood; in African-Americans the range is lower, between 3,200 and 9,000 white cells per microliter.

Some MDS patients develop neutropenia or a low white cell count. MDS patients with neutropenia usually have too few neutrophils. With fewer numbers of neutrophils, the risk of contracting bacterial infections such as pneumonia and urinary tract infections increases. Fever may accompany these infections. Sometimes infections occur despite adequate numbers of neutrophils because the WBCs are not able to function as well as they do in a person without MDS.

Effect on Platelets
Low Platelet Cell Count (Thrombocytopenia)
MDS can also cause a low platelet count, or thrombocytopenia. People with abnormal or low platelet counts may suffer from bruising or bleeding even after minor bumps, scrapes, or cuts.

Severe thrombocytopenia, which is uncommon, is defined as a platelet count below 20,000 and is associated with more serious bleeding problems.
At the present, three drugs have been approved by the U.S. Food & Drug Administration (FDA) for the treatment of MDS: Vidaza™ (azacitidine), Dacogen™ (decitabine), and Revlimid® (lenolidamide). Vidaza has been approved for authorized use as a prescription medicine by the European drug regulatory agency (European Agency for the Evaluation of Medicinal Products, or EMEA). The other two drugs are still under review in Europe but may be prescribed to patients in some countries through country-specific approvals or special programs.

**Vidaza™ (azacitidine)**
Vidaza was the first drug approved specifically to treat MDS. Vidaza may be appropriate for any MDS subtype. It is administered by subcutaneous (under the skin) injection or intravenously (into the vein). In Europe it is only approved for subcutaneous injections.

**Dacogen® (decitabine)**
Dacogen is approved in the U.S. for use in all MDS subtypes. Dacogen is administered intravenously.
How Do These Drugs Work?
Both Vidaza and Dacogen work by preventing a cellular process called methylation that silences the genes involved in controlling the development of cancer. In MDS, the genes have excessive methylation (Fig. 1) and these drugs may be able to alter the methylation pattern (Fig. 2) so the MDS cells cannot continue to grow. The stem cells in the bone marrow begin to function normally and to make healthier, functioning RBCs, WBCs, and platelets. Initially, treatment with Vidaza or Dacogen often causes a further decrease in the white blood cell and platelet count; however, by the 4th or 5th cycle of treatment this effect should begin to reverse itself and the levels of platelets and white blood cells increase. Low WBCs and/or platelets can be managed with platelet transfusions and medications to boost counts or help prevent infection. In some cases patients may be taken off the medication for a period of time, allowing their blood counts to recover. Treatment may be restarted at a reduced dose.
Revlimid® (lenalidomide)

Revlimid is approved in the United States for MDS patients who need red blood cell transfusions and have a special chromosome abnormality, called 5q minus (5q-). Revlimid is taken orally and is available in capsule form. Revlimid works by stimulating the immune system and it also inhibits new blood vessel growth (anti-angiogenesis).

Starting treatment with Revlimid may be associated with significant thrombocytopenia and neutropenia. If this occurs, the treatment is usually stopped so that the blood counts can increase. When the blood counts are at a safe level, the treatment is restarted, but usually with a lower dosage of the drug. Normally, the blood counts do not decrease with the reduced dose.

Growth Factors

In addition, it is common practice to administer an erythroid stimulating agent (ESA) for low risk MDS patients with a low endogenous (produced within the patient’s body) erythropoietin level (<500) and a minimal transfusion burden. On occasion, another growth factor (G-CSF) may be given in small doses to improve the efficacy of the ESA.
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