

Understanding Anemia and Fatigue

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Introduction

You may be wondering why you feel so tired and cannot do many of the things you want to do, or used to do. You may also be wondering if there is anything you can do to feel better, be more productive, and regain your energy. Your healthcare team may have told you that you have **anemia**, which may explain, in part, why you feel so tired and lack the energy necessary to perform your daily activities. Anemia and fatigue can be caused by **multiple myeloma** itself or by the treatment for the disease. You have been given this booklet to learn more about fatigue and anemia and how they relate to multiple myeloma and its treatment. In this booklet, you will also learn about what you can do and which medications are available to help you better manage your fatigue and anemia and enable you to feel better and participate in more activities. After reading this booklet, you should know the following:

- What fatigue and anemia are and how they relate to multiple myeloma;
- When anemia and fatigue should be treated;
- How anemia and fatigue are treated;
- The possible side effects of treatment of anemia and fatigue;
- If treatment for anemia interferes with your treatment for multiple myeloma;
- What else you can do to feel less tired.

A short overview of multiple myeloma will be presented first, so that you can see how fatigue and anemia are related to the disease and its treatment, and better understand why it is so important that they be managed properly.

This booklet is meant to provide you with general information only. It is not meant to replace the advice of your doctor, nurse, or other healthcare practitioner. Your healthcare team can answer questions related to your specific treatment plan. All words that appear in **bold type** are defined in a glossary at the end of this booklet.

What Is Multiple Myeloma?

Multiple myeloma (also known as “myeloma” and “**plasma cell neoplasm**”) is a malignancy of the **immunoglobulin**-producing plasma cells found in the **bone marrow**. It is a **hematologic malignancy** that resembles leukemia. However, the malignant plasma cells, or myeloma cells, rarely enter the blood stream as they do in a true leukemia. Instead, the myeloma cells accumulate in the bone marrow, causing the following:

- Disruption of normal bone marrow function, most commonly causing anemia (a low level of **red blood cells** in the blood-stream), although reduction in **white blood cell** and **platelet** counts can also occur;
- Damage to bone surrounding accumulated myeloma cells;

- Release of an abnormal **protein, monoclonal protein (M-protein)**, into the blood-stream;
- Suppression of normal immune function; observed as reduced levels of normal immunoglobulins and increased susceptibility to infection.

Myeloma cells can also grow in the form of localized tumors or **plasmacytomas**. Plasmacytomas may be single or multiple, and either medullary (confined within bone marrow and bone) or extramedullary (outside of the bone). When there are multiple plasmacytomas inside or outside bone, this condition is also called multiple myeloma.

When confronted with a diagnosis of multiple myeloma, your doctor must determine the stage of the disease. Disease staging will help determine what parts of the body have been affected and to what extent. This will allow the doctor to determine the best treatment option.



The Stages of Multiple Myeloma

<p>Stage I (low cell mass) <i>All of the following:</i></p> <ul style="list-style-type: none"> • Hemoglobin value >10 g/dL • Serum calcium value normal or <10.5 mg/dL • Bone X-ray, normal bone structure (scale 0) or solitary bone plasmacytoma only • Low M-component production rates IgG value <5.0 g/dL IgA value <3.0 g/dL • Urine light chain M-component on electrophoresis <4 g/24h 	600 billion myeloma cells*
<p>Stage II (intermediate cell mass) <i>Fitting neither stage I nor stage III</i></p>	600 to 1,200 billion myeloma cells*
<p>Stage III (high cell mass) <i>One or more of the following:</i></p> <ul style="list-style-type: none"> • Hemoglobin value <8.5 g/dL • Serum calcium value >12 mg/dL • Advanced lytic bone lesions (scale 3) • High M-component production rates IgG value >7.0 g/dL IgA value >5.0 g/dL • Urine light chain M-component on electrophoresis >12 g/24h 	>1,200 billion myeloma cells*
<p>Subclassification (either A or B)</p> <ul style="list-style-type: none"> • A: relatively normal renal function (serum creatinine value) <2.0 mg/dL • B: abnormal renal function (serum creatinine value) >2.0 mg/dL <p><i>Examples:</i> Stage IA (low cell mass with normal renal function) Stage IIIB (high cell mass with abnormal renal function)</p>	

*myeloma cells in the whole body

A prognostic factor system called the International Staging System (ISS) was introduced in 2005. It is based upon the levels of two blood proteins: beta-2 microglobulin (β 2M) and albumin; the levels of these proteins predict overall outcome with myeloma treatment.

STAGE	CRITERIA
Stage 1	Serum β 2 microglobulin <3.5 mg/L Serum albumin \geq 3.5 g/dL
Stage 2	Serum β 2 microglobulin < 3.5 mg/L and serum albumin < 3.5 g/dL or Serum β 2 microglobulin 3.5 - 5.5 mg/L
Stage 3	Serum β 2 microglobulin >5.5 mg/L

Multiple myeloma is a serious malignancy, but it is treatable. Many patients experience a series of responses, relapses, and remissions. New treatments can extend the survival of many patients diagnosed with multiple myeloma.

Following diagnosis, several options are available for initial or frontline therapy. For patients who may be candidates for high-dose therapy with stem cell transplant, various induction regimens can be considered, including thalidomide with dexamethasone, VELCADE® (bortezomib) with dexamethasone, Revlimid® with dexamethasone, dexamethasone alone, other dexamethasone-containing combinations, or combinations containing other **adrenal cortical steroids**. The combination of the **alkylating agent** melphalan plus prednisone,

a simple oral therapy, is an option for patients not considering high-dose melphalan with autologous stem cell transplant, as are combinations of melphalan plus prednisone with the novel agents VELCADE®, thalidomide, or Revlimid®. At the time of relapse, the novel agents are frequently required to achieve further response. Revlimid® and VELCADE® are important agents available for use in this setting.

What Is Fatigue?

In healthy people, fatigue is typically characterized by extreme exhaustion or feelings of tiredness that interfere to some extent with normal everyday activities. It usually occurs after excessive stimulation or prolonged exertion of some kind and is temporary. Rest and refraining from strenuous activity can help restore energy and make a person feel better. Fatigue that is related to cancer, however, is different and more severe than normal fatigue and tends to last longer. Simply resting does not alleviate the fatigue. This type of fatigue has been defined by the National Comprehensive Cancer Network as “a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.” In patients with multiple myeloma, fatigue often is a symptom that anemia is present.

What Is Anemia?

Anemia is an abnormally low level of red blood cells (RBCs) in your body. RBCs contain hemoglobin. Hemoglobin is a protein found in RBCs that contains iron and transports much-needed oxygen from the lungs to tissues and organs throughout the body. If the number of RBCs is low, however, then the hemoglobin count is low, and the body does not receive the amount of oxygen that it needs to function properly. Anemia can have multiple causes: it may be caused by some underlying disease that interferes with normal RBC production and functioning, or it may be the result of the negative effects of chemotherapy on RBC production.

What Causes Fatigue and Anemia in Patients with Multiple Myeloma?

Fatigue: You're Not Alone

Fatigue associated with multiple myeloma usually is caused by underlying anemia. This type of fatigue severely affects patients' quality of life and everyday functioning. The continued interference with normal functioning is what sets cancer-related fatigue apart from normal fatigue. Fatigue is very common in patients with multiple myeloma and is estimated to affect 90%–100% of patients with the disease. Patients need to understand that fatigue is a symptom of their disease and is not necessarily a sign that their condition is getting worse. Even though cancer-related

fatigue is very common in patients with multiple myeloma, the exact physiologic mechanisms that cause the fatigue are not known. It is known, however, that it is related to the patient's anemia, and there are ways to manage it and help you cope.

Anemia: The Case of Missing RBCs

Anemia occurs in patients with multiple myeloma because plasma cells in bone marrow grow faster than normal, increase in number, and produce tumors in the marrow. These tumors interfere with the blood-producing activities of bone marrow, leading to a shortage of red blood cells (RBCs). This shortage is known as anemia.

There are a number of causes of anemia in patients with multiple myeloma. The disease itself suppresses the body's ability to make enough RBCs, resulting in low RBC counts. Unfortunately, the chemotherapy that kills the cancer cells in patients with multiple

myeloma also destroys normal RBCs, thus also increasing the chances of developing anemia. Anemia is very common in patients with multiple myeloma. In fact, at least 60%–70% of patients with multiple myeloma have anemia at the time they are diagnosed with the disease.

How are Fatigue and Anemia Diagnosed?

Fatigue: Give Them Something to Talk About

It can be difficult to diagnose fatigue associated with multiple myeloma for a number of reasons. There are no laboratory tests that can be used to diagnose fatigue; hence, information about fatigue provided by patients is very important. Your healthcare team will need to evaluate your situation and try to identify the source of your fatigue and ways to manage it most effectively. Patients need to openly discuss their feelings of fatigue with members of their healthcare team. Do not think that your fatigue is not important enough to mention at your appointments. Although fatigue is an expected symptom with multiple myeloma, you do not have to accept it. There are things that you and your healthcare team can do that will help you feel better. Make notes for yourself when you feel fatigued or when anything in particular makes you feel better or worse. Keep track of how limiting your fatigue is by noting to what extent it interferes with your daily activities. Your healthcare team will be asking questions about your fatigue and any input you



can provide will be very helpful. In addition to their screening, they need your feedback so that they can determine the severity of your fatigue and develop strategies to help you manage it. Based on your feedback, your healthcare team will rate your fatigue on a scale of 0 to 10 (with 0=no fatigue and 10=worst fatigue imaginable) and then classify your fatigue as one of the following:

- Mild (0 to 3)
- Moderate (4 to 6)
- Severe (7 to 10).

Examples of things that you should be looking at and want to report to your healthcare team include (but are not limited to) the following:

- Time when fatigue is most noticeable
- Medications that you are taking
- Emotional stress, anxiety, or depression
- Presence and location of physical pain
- Existence of other conditions or illnesses
- Sleep disturbances
- Dietary changes
- Changes in weight
- Changes in activity or daily routine
- Changes in health.

If there are any changes or other factors that you think could be adding to your fatigue, do not hesitate to bring them to the attention of your healthcare team. There are factors that may not be obvious that could be making your fatigue

worse. Many factors that contribute to fatigue are treatable. There are things that can be done to alleviate your fatigue, and your healthcare team can work with you and your family and caregiver(s) to develop a plan for you.

Anemia

If your doctor suspects you have anemia, he or she performs tests for it and determines its severity. You will be asked questions about your health in general. Remember to report any of the following symptoms:

- Shortness of breath
- Lack of energy and motivation
- Rapid heartbeat
- Swelling in the legs, especially in the ankles
- Dizziness
- Headache
- Chills
- Change in appetite
- Decreased libido.

A physical examination will be performed. After the examination, your healthcare team will ask you questions in an attempt to identify and uncover the source of your fatigue. It is wise to have a family member or caregiver with you at your appointment. He or she may be able to add to the information you provide.

A simple blood test is used to determine what your hemoglobin level is. Hemoglobin levels

are used to measure the number of RBCs in the body. Low hemoglobin levels indicate anemia. Severity of anemia is determined by hemoglobin level, measured in units designated as grams of RBCs per deciliter (g/dL). Normal hemoglobin levels are 14 to 18 g/dL for men and 12 to 16 g/dL for women. The National Cancer Institute (NCI) has developed the following scale that determines the degree of severity of anemia through relative levels of hemoglobin.

Grade	Severity	Hemoglobin Level (g/dL)
0	None	Normal value
1	Mild	10 to normal value
2	Moderate	8 to 10
3	Severe	6.5 to 7.9
4	Life-threatening	Less than 6.5

When Should Anemia and Fatigue Be Treated?

It is important that you discuss your symptoms and how you are feeling with members of your healthcare team. Do not hesitate to mention that you feel tired or aren't feeling particularly well. Let them know how much your fatigue is disrupting your everyday activities. Fatigue typically is a sign of some underlying problem; it needs to be treated as soon as possible. Left unmanaged, fatigue can have a dramatic effect on your daily life and on your health. Your healthcare team

will start treating your anemia as soon as it is diagnosed. They will want to begin restoring your RBC count as soon as possible. Your health and response to other treatments depend upon holding these levels to as near-normal as possible. In some instances, in attempts to increase RBCs before anemia fully develops, treatment may be started in patients identified as being at high risk for developing anemia.

What Treatments Are Available for Fatigue and Anemia?

There are a number of treatments and things you can do for fatigue and anemia that will improve your health and make you feel better. Treatment of your anemia and fatigue will be based on the severity of each. All patients are not candidates for all treatments. Your healthcare team will determine which treatment regimen is best suited to and safest for you.

FATIGUE

Your healthcare team will determine if there are contributing factors to your fatigue. Depending on their findings, they may do the following:

- Adjust your medications
- Change or modification of your dietary intake
- Improve your fluid and electrolyte (sodium, potassium, calcium, and magnesium) intake

- Treat the underlying cause(s) as is appropriate
- Create strategies for coping and managing your fatigue.

ANEMIA

For a number of years, the primary treatment option for anemia has been blood transfusion. Transfusions replace and replenish the RBCs that you have lost and are recommended when immediate correction of the anemia is desired. Although transfusions have an immediate effect that is beneficial for patients, the increase in hemoglobin levels may not be very large and may last only up to a few weeks, so repeated transfusions may be necessary.

Another option for anemia that needs to be treated but that does not have to be corrected immediately involves treatment with a class of medications known as erythropoiesis-stimulating agents, or ESAs (epoetin alfa, epoetin beta, and darbepoetin alfa). These agents stimulate **erythropoiesis**, which is another name for the formation of new RBCs, and are used to treat anemia caused by a variety of conditions. These drugs have been used to treat anemia associated with cancer since the early 1990s. They are biologically equivalent to erythropoietin, a hormone made in the kidney that is found naturally in your body. This hormone stimulates your bone marrow to produce RBCs. Administering erythropoietic agents thus signals your body to make RBCs, which

helps to restore normal levels. You should be aware that it may take several weeks for these medications to take effect, so you may not feel better right away. Treatment with erythropoietic agents can also reduce the number of transfusions patients need. Thus, treatment with this class of drugs may be initiated to increase hemoglobin levels, reduce or eliminate the need for blood transfusions, and make patients who have been suffering from anemia feel better. In some patients, an erythropoietic agent and transfusion may be given together. You may also be given iron supplements to restore your iron levels to as near normal as possible. Iron is needed to produce RBCs, and iron supplements are often given during erythropoietic treatment.

In light of recent reports of shortened overall survival and/or increased risk of tumor progression or recurrence, as well as the risk of serious cardio- and thrombovascular events in some clinical trials for patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers where the patients were treated with ESAs, the use of ESAs in cancer patients has been re-evaluated by the Food and Drug Administration (FDA). The FDA has concluded that ESAs should be administered to cancer patients only in the context of myelosuppressive chemotherapy (drug therapy that causes a drop in the number of blood cells made in the bone marrow).

A program called the APPRISE (Assisting Providers and cancer Patients with Risk

Information for the Safe use of ESAs) Oncology Program has been established for patients with cancer receiving an ESA [Aranesp® (darbepoetin alfa), Epogen® (epoetin alfa), or Procrit® (epoetin alfa)].

The ESA APPRISE Oncology Program is part of a Risk Evaluation and Mitigation Strategy (REMS) and is designed for healthcare providers treating patients with an ESA for their cancer. The Food and Drug Administration has determined that a REMS is necessary for ESAs to ensure that the benefits of these drugs outweigh the risks. Your physician is required to provide documentation that he or she has counseled and educated you about the risks of ESAs prior to ESA administration.

How Are These Treatments Administered?

TRANSFUSIONS

Blood transfusions are administered as intravenous infusions in a hospital or other healthcare facility. A trained healthcare professional will give the transfusion. It is recom-



mended that a caregiver or family member drive you to and from the transfusion center. The entire process can take a few hours.

ERYTHROPOIETIC AGENTS

Erythropoietic agents are administered as subcutaneous injections by a healthcare professional. The amount of medication, frequency of injections, and schedule of your injections will be determined by your healthcare team.

IRON SUPPLEMENTS

Iron supplements are available in oral and intravenous formulations. However, oral products are used most often. Intravenous products are helpful in patients who, for various reasons, cannot use the oral forms.

What Are Some of the Possible Side Effects of Treatment?

POSSIBLE SIDE EFFECTS WITH TRANSFUSIONS

There are a number of possible side effects that can occur after receiving a blood transfusion. Some patients may have a mild fever or develop a rash or hives. These reactions are temporary and usually not severe. In very rare instances, patients may experience serious incompatibility reactions. These reactions will be managed immediately by the healthcare team. Strict screening processes are used to prevent the spread of viral infections transmitted in blood during infusions. Such transmissions were more of a concern in earlier years when screening was not so common or stringent.

POSSIBLE SIDE EFFECTS WITH ERYTHROPOIETIC AGENTS

Erythropoietic agents generally are well tolerated by patients. The most commonly reported side effects experienced by patients treated with these drugs are:

- Fever
- Diarrhea
- Nausea
- Vomiting
- Swelling at the injection site
- Fatigue.

Allergic reactions tend to be rare; when they do occur, they tend to be mild in nature. Remember that not all patients treated with erythropoietic agents experience any or all of the reactions that have been reported by other patients. Similarly, patients do not experience side effects to the same degree. However, at the first sign of any reaction, patients should contact a member of their healthcare team immediately.

Will Treatment for Fatigue and Anemia Interfere with Treatment for Multiple Myeloma?

Treatments chosen by healthcare teams to manage your fatigue and anemia will not interfere with treatments for multiple myeloma. Treatments approved to treat anemia and fatigue can be done safely and in conjunction with treatment for multiple myeloma.

What Else Can Be Done to Help Patients with Anemia and Fatigue Feel Better?

Along with transfusions, medications, and other adjustments, there are also a number of other things you can do to manage and cope with your fatigue and anemia, including the following:

- Exercise (walking, cycling, swimming)
- Developing coping strategies (distractions)
- Modification of activities (naps, re-establishment of priorities, use of labor-saving devices)
- Counseling.

Patient education can help you understand anemia and fatigue. Ask members of your healthcare team if they have any information that they can pass on to you or if they can direct you to other sources of information. Your healthcare team can also work with you to develop a general strategy for managing your fatigue. Involve your family and caregivers. They can be great support. Do not be ashamed or afraid to talk about your fatigue and the impact it has on your life.

For more information on multiple myeloma and treatment options, contact the IMF.

About the IMF

*“One person can make a difference,
Two can make a miracle.”*

Brian D. Novis
IMF Founder

Myeloma is a little-known, complex, and often misdiagnosed bone marrow cancer that attacks and destroys bone. Myeloma affects approximately 75,000 to 100,000 people in the United States, with approximately 20,000 new cases diagnosed each year. Although there is presently no known cure for myeloma, doctors have many approaches to help myeloma patients live better and longer.

The International Myeloma Foundation (IMF) was founded in 1990 by Brian and Susie Novis shortly after Brian’s myeloma diagnosis at the age of 33. It was Brian’s dream that future patients would have easy access to medical information and emotional support throughout their battle with myeloma. He established the IMF with the 3 goals of treatment, education, and research. He sought to provide a broad spectrum of services for patients, their families, friends, and health care providers. Although Brian died 4 years after his initial diagnosis, his dream didn’t. Today, the IMF reaches out to an international membership of more than 195,000. The IMF was the first organization dedicated solely to myeloma, and today it remains the largest.

The IMF provides programs and services to aid in the research, diagnosis, treatment, and management of myeloma. The IMF ensures that no one must brave the myeloma battle alone.

We care for patients today, while working toward tomorrow’s cure.

How Can the IMF Help?

PATIENT EDUCATION

INFORMATION PACKAGE

Our free IMF InfoPack provides comprehensive information about myeloma, treatment options, disease management, and IMF services. It includes our acclaimed *Patient Handbook*.

INTERNET ACCESS

Log on to myeloma.org for 24-hour access to information about myeloma, the IMF, education, and support programs.

ONLINE MYELOMA FORUM

Join the IMF Internet Discussion Group at www.myeloma.org/listserve.html to share your thoughts and experiences.

MYELOMA MINUTE

Subscribe to this free weekly email newsletter for up-to-the-minute information about myeloma.

PATIENT & FAMILY SEMINARS

Meet with leading experts in myeloma treatment to learn more about recent advances in therapy and research.

MYELOMA MATRIX

On our website and in print, this document is a comprehensive guide to drugs in development for myeloma.

MYELOMA TODAY NEWSLETTER

Our quarterly newsletter is available free of charge by subscription.

SUPPORT

MYELOMA HOTLINE: 800-452-CURE (2873)

Toll-free throughout the United States and Canada, the IMF Hotline is staffed by trained information specialists and is in frequent interaction with members of our Scientific Advisory Board.

SUPPORT GROUPS

A worldwide network of more than 100 myeloma support groups holds regular meetings for members of the myeloma community. The IMF conducts annual retreats for myeloma support group leaders.

RESEARCH

BANK ON A CURE®

This DNA bank will provide genetic data for research in new drug development.

INTERNATIONAL MYELOMA WORKING GROUP (IMWG)

IMF's International Myeloma Working Group consists of 145 leading myeloma researchers from around the world who collaborate on a broad range of myeloma research projects. With a goal to improve myeloma treatment options and diagnostic systems, their work focuses on protocols to provide a more durable remission for myeloma patients while improving quality of life, addressing the needs of both myeloma patients and the physicians who treat them.

THE INTERNATIONAL STAGING SYSTEM (ISS)

This updated staging system for myeloma will enhance physicians' ability to select the most appropriate treatment for each patient.

RESEARCH GRANTS

Leading the world in collaborative research and achieving extraordinary results, the IMF Grant Program supports both junior and senior researchers working on a broad spectrum of projects. The IMF has attracted many young investigators into the field of myeloma who remain in the field and actively pursue a cure for the disease.

Glossary

Adrenal cortical steroid: Any of the steroidal hormones produced by the adrenal cortex or their synthetic equivalents. Also known as adrenocorticoids, glucocorticosteroid, or corticosteroid.

Alkylating agent: An agent that prevents the growth and division of new cancer cells by inhibiting their ability to replicate DNA.

Anemia: A low level of red blood cells in the bloodstream.

Antibody: A protein produced by some of the body's white blood cells that helps fight infection.

Bone marrow: A soft spongy tissue found in most large bones that produces red and white blood cells and platelets.

Cell: The smallest unit of life. Millions of microscopic cells comprise each body organ.

Cytokine: A growth factor produced by T-cells that stimulates the growth of T-cells and B-cells.

Erythropoiesis: The formation of new red blood cells.

Hematologic malignancy: A cancer of the blood or bone marrow.

Immunoglobulin: An antibody.

Lytic (lysis): Dissolution or destruction of cells.

Monoclonal protein (M protein): An abnormal protein produced by myeloma cells that accumulates in and damages bone and bone marrow. A high level of M protein indicates that myeloma cells are present in large numbers.

Multiple myeloma: A cancer arising from the plasma cells in the bone marrow. The plasma cells in patients with multiple myeloma form abnormal antibodies, possibly damaging the bone, bone marrow, and other organs.

Plasma cell: A type of white blood cell that produces antibodies.

Plasmacytoma: A tumor made up of cancerous plasma cells.

Platelet: An element in the blood that helps with clotting, which in turn helps repair damaged blood vessels.

Proteins: A group of compounds that are the main components of a cell.

Red blood cell (RBC): A blood cell that carries oxygen from the lungs throughout the body.

White blood cell: A cell made by the bone marrow that helps fight infection and/or disease.