Understanding The Immune System in Myeloma

A publication of the **International Myeloma Foundation**

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Improving Lives **Finding the Cure**®

INTERNATIONAL MYELOMA FOUNDATION

Founded in 1990, the International Myeloma Foundation (IMF) is the first and largest organization focusing specifically on multiple myeloma. The IMF's reach extends to more than 525,000 members in 140 countries worldwide. The IMF is dedicated to improving the quality of life of myeloma patients while working toward prevention and a cure through our four founding principles: Research, Education, Support, and Advocacy.

RESEARCH The signature project of the IMF's Research division is the Black Swan Research Initiative®, a groundbreaking and collaborative effort to develop the first definitive cure for myeloma. Each year, the IMF also awards Brian D. Novis Grants, which promote research for better myeloma treatments, management, and practices in the field. In addition, more than 200 leading myeloma researchers comprise the IMF's International Myeloma Working Group (IMWG), a research body that has developed myeloma guidelines that are followed around the world. Finally, the IMF's Nurse Leadership Board (NLB), comprised of nurses from leading myeloma treatment centers, develops recommendations for the nursing care of myeloma patients.

EDUCATION The IMF Patient & Family Seminars and Regional Community Workshops are held around the world to provide up-to-date information presented by leading myeloma specialists and researchers directly to patients and their families. The IMF's library of more than 100 publications, for patients and caregivers as well as for healthcare professionals, is updated annually and available free of charge. Publications are available in more than 20 languages.

SUPPORT The IMF's InfoLine is staffed by information specialists who answer myeloma-related questions and provide support via phone and email to thousands of families each year. In addition, the IMF sustains a network of more than 150 myeloma support groups and offers training for the hundreds of dedicated patients, caregivers, and nurses who volunteer to lead these groups in their communities.

ADVOCACY The IMF's Advocacy team has educated and empowered thousands of individuals who make a positive impact each year on issues critical to the myeloma community. Working in the US at both federal and state levels, we lead coalitions to advocate for parity in insurance coverage. We also represent the myeloma community's interests before the US Congress and agencies such as the National Institutes of Health, the Food and Drug Administration, the Centers for Medicare and Medicaid Services, and the Veterans Administration. Outside the US, the IMF's Global Myeloma Action Network (GMAN) works to help patients gain access to treatment.

Learn more about the ways the IMF is helping to improve the quality of life of myeloma patients while working toward prevention and a cure.
Contact us at 818.487.7455 or 800.452.CURE, or visit myeloma.org.

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Table of contents

What you will learn from this booklet

The IMF's *Understanding* series of booklets is designed to acquaint you with treatments and supportive care measures for **multiple myeloma** (which we refer to simply as "myeloma"). Words in **bold+blue** type are explained in the "Terms and definitions" section at the end of this booklet, as well as in a more complete compendium of myeloma-related vocabulary, the IMF's *Glossary of Myeloma Terms and Definitions*, located at glossary.myeloma.org.

Myeloma is a **cancer** that is not known to most patients at the time of diagnosis. To be empowered to play an active role in your own medical care and to make good decisions with your doctor, it is vital for you to learn as much as possible about myeloma and its treatments. The information in this booklet will help you in discussions with your healthcare team. The more information you have about resources that are available to you, the better and more fruitful those discussions will be.

Understanding the Immune System in Myeloma will help you understand immune system basics. The immune system is extremely complex. It involves multiple mechanisms that work together to protect and defend the human body from external threats such as bacteria, viruses, and toxins, and from internal threats such as cancer.

Immune system basics

The immune system can be likened to a fine Swiss watch, with many tiny moving parts working together seamlessly. A change or malfunction in even one of those tiny parts can affect all the others.

Innate and adaptive responses

The immune system has two major components. The innate response, a first line of defense, is made up of cellular **proteins** and killer cells. The adaptive response is based on immune system cells' ability to recognize and attach to specific antigens on the surface of infected cells and tumor cells.

The immune system is made up of various types of white blood cells (WBC). All blood cells derive from blood-cell making ("hematopoietic") stem cells in the **bone marrow**. These stem cells can make white blood cells (leukocytes), red blood cells (erythrocytes), or platelets (thrombocytes), depending upon the body's needs. White blood cells circulate in the bloodstream and in the lymphatic system.

Types of white blood cells

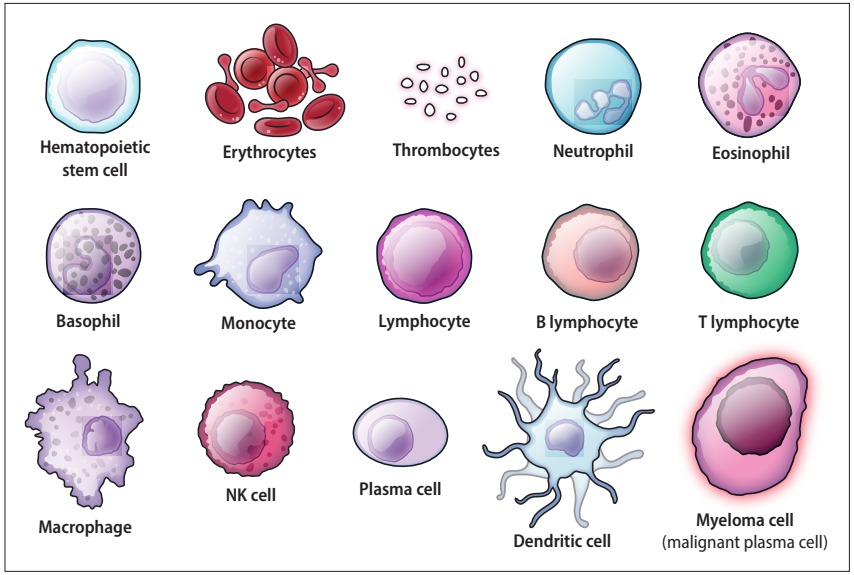
If you have seen a copy of your laboratory report for your complete blood count (CBC), you will know that there are several types of WBC: neutrophils, eosinophils, basophils, monocytes, and lymphocytes. Each type of WBC has a different function in the immune system.

- Neutrophils, which constitute about 60% of WBC, target bacteria and fungi.
- Eosinophils target larger parasites and modulate allergic responses.
- Basophils release histamine for inflammatory responses.
- Monocytes migrate from the bloodstream to other tissues and become invader-devouring macrophages.
- Lymphocytes (B cells, T cells, and natural killer [NK] cells), which constitute approximately 30% of WBC, are responsible for the adaptive immune response, which enables immune system cells to attach to specific **antigens** on the cell surfaces of infectious organisms and other foreign substances.

B lymphocytes

B cells (B lymphocytes) originate and mature in the bone marrow. When activated by a specific antigen, some of the B cells in the bone marrow mature into **plasma cells**, which make **antibodies** to that antigen. Other

Figure 1. **Immune system cells that play a role in myeloma**



B cells multiply and become memory B cells that remain in the body and carry long-term memory of, and protection from, the antigen. Memory cells give us immunity to infectious agents after we have had a disease or have been immunized against one.

Myeloma is a cancer of the plasma cells in the bone marrow. Normally, plasma cells secrete antibodies into the blood stream and lymphatic system, where they attach to and disable invading organisms ("**pathogens**") before the invaders infiltrate other cells in the body. In myeloma, however, the plasma cells are unable to secrete functioning antibodies, resulting in impaired immune function.

T lymphocytes

T cells (T lymphocytes) originate in the bone marrow but mature in the thymus, a gland beneath the breastbone (sternum). Like antibodies, T cells recognize specific antigens and bind to them in order to surround and disable pathogens. They also can become memory cells that provide long-lasting immunity. There are three types of T cells: helper T cells (T_h), regulatory T cells (T reg or T_{reg}), and cytotoxic (cell-killing) T cells (T_c). T cells are reduced in number and function in patients with myeloma, contributing to the immune suppression that is characteristic of the disease.

- Helper T cells secrete chemical messengers called **cytokines**, which, among other things, stimulate the differentiation of B cells into plasma cells, thereby prompting antibody production.
- Regulatory T cells control immune reactions. Cancer patients generally have an increased and functional supply of these cells, suggesting that T_{reg} cells may have something to do with suppression of the immune response that is seen in myeloma patients. Conversely, they also contribute to the restored immune function seen in patients who have deep and prolonged **responses** to therapy.
- Cytotoxic T cells, which are activated by various cytokines, bind to specific antigens on infected cells and cancer cells and kill them.

Natural Killer (NK) cells are lymphocytes that can recognize and kill cells that have been infected with viruses or transformed by tumors. Unlike cytotoxic T cells, NK cells can do this without recognition of specific antigens. They are responsible for tumor surveillance and are able to induce strong responses against tumors through the release of cytokines. Like many other immune system cells, NK cells are reduced both in number and in function in patients with active myeloma.

Dendritic cells

Dendritic cells activate helper T cells and stimulate them to release cytokines. They are called "professional antigen-presenting cells" (APC), since they are able to bring antigens from pathogens to other immune system cells for recognition and destruction.

Macrophages

Macrophages begin life as monocytes, which enter damaged tissue through blood vessels and then undergo a series of changes to become macrophages. Macrophages are present in all tissues. Their function is to engulf and digest anything – including cancer cells – that does not have the types of proteins on its surface that are specific to the surface of healthy body cells. There are two types of macrophages. Depending on the body's needs, one type can increase inflammation, while the other type decreases it.

How does myeloma evolve and grow?

In a normal immune response, an antigen triggers B cells, which in turn develop into plasma cells that "home" from the circulating blood to the bone marrow. From there the plasma cells secrete antibodies specifically targeted to attack the triggering antigen. When myeloma develops, the plasma cells are damaged in specific ways, and they secrete proteins that are not functional as antibodies. These non-functional antibodies are called "monoclonal protein," which is a marker of the amount and activity of myeloma cells.

Myeloma evolves from a single clone in its earliest stages to many clones during the course of the disease and treatments. As more and more treatments successfully eliminate dominant clones, smaller sub-clones that are resistant to treatment survive and become dominant.

How does myeloma affect the immune system?

Remember the analogy of the fine Swiss watch? When even a tiny part of the system is affected, the whole mechanism can suffer. Because myeloma is a disease of an immune system cell (the plasma cell), its growth affects the whole immune system. Myeloma suppresses the immune response as a whole, reducing the number of normal antibodies and affecting all the cells that would patrol for and attack abnormal cells. Regulatory T cells, NK cells, and macrophages can no longer perform their functions. In a perversion of the normal safeguards, some of the cytokines that are secreted to trigger an immune response in fact stimulate the growth of myeloma cells.

Thus normal **immunoglobulins** (antibodies) are reduced in number, suppressive regulatory T cells become over-reactive, there is a lack of specific cytotoxic T cells, helper T cells are blocked, and NK cells are both reduced in number and blocked. Treating myeloma successfully allows the immune system to function well again by restoring the number and function of immune system cells.

Immune therapy (immunotherapy)

"Immuno-oncology," the treatment of cancer with therapies that trigger cells in the immune system, is a vital and growing field of research. **Immunotherapies** have already been approved for myeloma, and several more are being tested in **clinical trials**. Among these are monoclonal antibodies, antibody-drug conjugates (ADCs), chimeric antigen receptor T cells (CAR T cells), bispecific T-cell engagers (BiTEs®), checkpoint (PD-1/PD-L1) inhibitors, vaccine therapies, and virotherapies.

In addition to these new experimental therapies, one of the older (yet still experimental) therapies for myeloma, allogeneic ("allo") **transplant**, is an immune therapy. It takes immune system cells from a donor and infuses them into a myeloma patient whose immune system has first been wiped out, or "ablated," by chemotherapy. The donated cells provoke an immune response against the recipient's myeloma cells: The donor's immune system cells recognize the recipient's myeloma cells as foreign pathogens and attack them. However, the problem is that they also attack tissues and organs in the recipient's body as if they were foreign invaders, causing graft-versus-host disease (GVHD), a major complication of allo transplant. The new immune therapies borrow their basic idea from allo transplant – using the immune system to attack myeloma cells – and refine this idea in creative and novel ways.

Monoclonal antibodies

The first monoclonal antibodies for the treatment of myeloma, Darzalex® (daratumumab) and Empliciti® (elotuzumab), were approved in November 2015. For detailed information about these therapies, please read two IMF publications, *Understanding Darzalex® (daratumumab) Injection* and *Understanding Empliciti® (elotuzumab)*.

- Daratumumab, the first monoclonal antibody approved for myeloma, targets a specific single protein on the surface of myeloma cells, CD38. ("CD" is usually defined as "cluster of differentiation.") Two other anti-CD38 monoclonal antibodies are in clinical trials for myeloma: isatuximab (SAR650984) and MOR-03087 (formerly MOR-202).
- Researchers believe that the anti-CD38 monoclonal antibodies attach to the myeloma cells and then signal and attract macrophages and NK cells to attack and kill myeloma cells. Other immune system cells called complement proteins, which boost the power of antibodies, bind to the monoclonal antibodies and punch holes in the myeloma cells. The anti-CD38 antibodies also cause myeloma cells to undergo self-destruction, known as "**apoptosis**."
- Empliciti, the first monoclonal antibody tested in myeloma, was approved in combination with Revlimid® (lenalidomide), itself an immune modulator, and the steroid dexamethasone. Empliciti targets the cell surface receptor SLAMF7 and does not directly attack the myeloma cells. Rather, it attaches to NK cells and stimulates them to attach to and attack myeloma cells via the SLAMF7 receptor. Elotuzumab "revs up" the immune response by activating NK cells.

Figure 2. **Six ways anti-CD38 monoclonal antibodies attack myeloma**

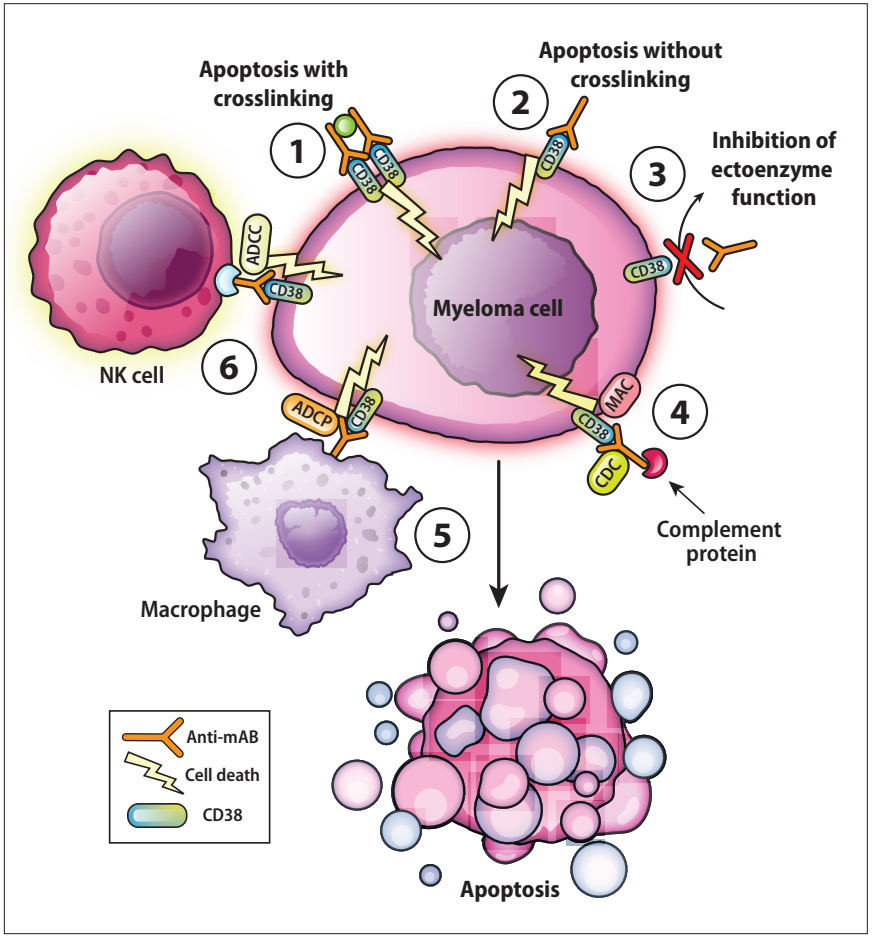
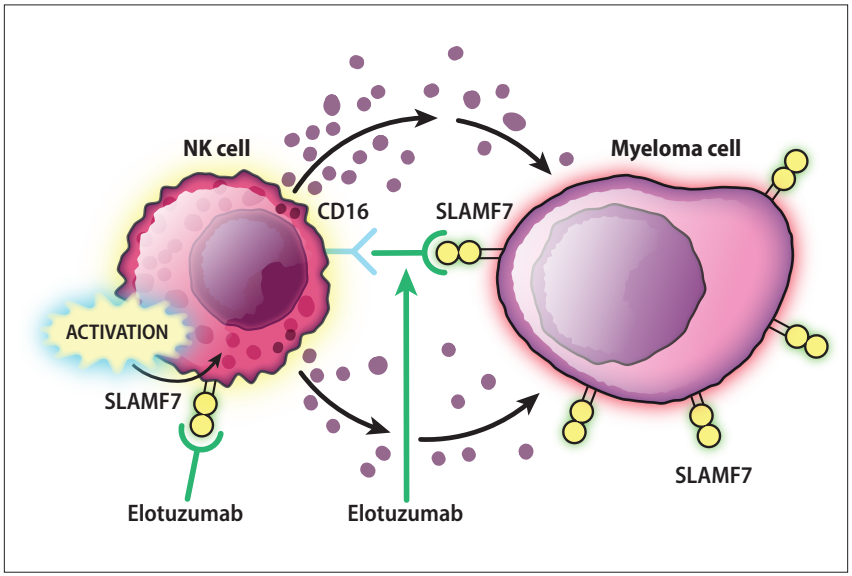


Figure 3. **Using your NK (Natural Killer) cells to attack myeloma with elotuzumab (anti-SLAMF7)**



Antibody-drug conjugates (ADCs)

Another promising approach being studied in clinical trials is the antibody-drug conjugate. ADCs work by binding to a receptor on the surface of myeloma cells (such as B-cell maturation antigen [BCMA], CD46, or CD74) and then releasing a cytotoxic agent that is rapidly internalized by the myeloma cells. ADCs in clinical trials for relapsed/refractory myeloma include GSK2857916 (belantamab mafodotin), STRO-001, and FOR46.

Bispecific T-cell Engager (BiTE®)

A new class of antibody called a "BiTE" or a "DuoBody®" has emerged, binding at the same time to a cell surface protein marker on T cells (CD3) and to the BCMA on the surface of myeloma cells. This double ("bi-specific") binding brings T cells to the myeloma cells, inducing T-cell activation and cytokine release. The result is destruction of myeloma cells and proliferation of cytotoxic T cells, which release toxic chemicals and/or prompt cancer cells to self-destruct.

BiTEs perform the same function as CAR T cells, but BiTEs do not need to be engineered from patients' T cells because they are manufactured in a lab and are available "off-the-shelf", thus saving the 3–4 weeks required to modify and expand the T cells for re-infusion.

While BiTE therapy has been approved for the treatment of another hematologic cancer, it is new to myeloma. BiTE drugs currently in early clinical trials for patients with myeloma include AMG 420, AMG 701, EM801, and JNJ-64007957.

CAR T cells

One of the most robust lines of research in hematologic cancers is an immunotherapy technique called CAR T-cell therapy. In this approach, a patient's T cells are collected from the blood and genetically engineered to express receptors specifically directed toward antigens on the patient's tumor cells, then infused back into the patient to launch an immune attack.

One such therapy has already been approved by the US Food and Drug Administration (FDA) for the treatment of pediatric acute lymphoblastic leukemia. Many CAR T-cell drug candidates in myeloma, including bb2121 (which has been given a "breakthrough therapy" designation by the FDA), use CAR T cells directed to BCMA. Newer CAR T-cell approaches are exploring the use of two binding sites on myeloma cells as well as other modifications of the early technology. With more than 200 active CAR T-cell clinical trials in the US and China, researchers hope to identify the patients best suited for this therapy, increase the durability of responses, and better understand and manage the immune-mediated side effects of CAR T cells.

Checkpoint inhibitors

Certain proteins help keep immune responses in check so that the body is not overwhelmed. When one such protein, PD-1 (programmed cell death protein 1 receptor of lymphocytes) binds to another protein called PD-L1, it helps keep T cells from killing other cells. Cancer cells, including myeloma cells, use the binding of PD-1 to PD-L1 to evade immune attack. Checkpoint inhibitors that block PD-1 allow the immune system to mount a robust T-cell attack against the cancer. The checkpoint inhibitors Keytruda® (generic name pembrolizumab) and Opdivo® (nivolumab) are PD-1 inhibitors that have been approved by the FDA for treatment of other cancers and are in clinical trials for myeloma. We have learned that simply blocking PD-1 is not effective in myeloma, and that combining a checkpoint inhibitor with the immune modulators Revlimid® (lenalidomide) or Pomalyst® (pomalidomide) is not safe. Current clinical trials with checkpoint inhibitors in myeloma use various combination therapy approaches in an attempt to find a modality that is both safe and effective.

Vaccine therapies

The basic premise behind this research is that vaccines tailored to a patient's myeloma cells can be used to activate plasma cells (which make antibodies) and cytotoxic T cells. Sometimes, additional substances ("adjuvants") are added to vaccines to enhance the immune response to the antigen.

Many vaccine clinical trials are looking at vaccine therapy as maintenance therapy to prolong response after stem cell transplant or other therapy has already put the patient in remission. Another new approach is to use DKK1 vaccine therapy to prevent progression to active disease in people with **monoclonal gammopathy of undetermined significance (MGUS)**, a non-cancerous precursor to myeloma, or in those with stable or **smoldering multiple myeloma (SMM)**.

Oncolytic virotherapy

Oncolytic (cancer-destroying) viruses are engineered to directly target and kill cells within the tumor, leaving non-cancerous cells unharmed. One such approach currently being tested as part of a combination therapy is Reolysin® (pelareorep), which uses a virus that has been modified to replicate only in cancer cells, causing their death and releasing virus particles that infect nearby tumor cells. Patients who have no or very few anti-measles antibodies (those who never had the disease or lost their immunity during high-dose therapy and stem cell transplant) may participate in a clinical trial using an engineered measles virotherapy combined with cyclophosphamide.

Combination therapies

It is important to note that many of the drugs already approved for myeloma have immune effects: **immunomodulatory drugs** enhance the ability of NK cells to kill myeloma cells; **proteasome inhibitors** increase dendritic cell-activated T-cell cytotoxicity. Using multiple immune system components, rather than a single target or pathway, seems to be the most effective way to attack myeloma.

The impact of successful treatment on the immune system

Excellent, deep response to therapy can bring with it robust recovery of the immune system. Immunophenotypic studies of long-term survivors – those who have lived 10 years or more without treatment – demonstrate a unique immune signature among these potentially cured patients. The immunosuppressive regulatory T cells diminish, while levels of NK cells, helper T cells, normal B cells, plasma cells, macrophages, and dendritic cells return to normal. The level of the cytokine interleukin 17 (IL-17) is higher than normal in these patients.

Next steps

Perhaps the most promising feature of the new immunotherapies is that, because they target antigens on the outside of the cancer cell, they are effective despite the high-risk mutations that may be present inside the cancer cell's nucleus. Immunotherapy appears to be largely independent of such high-risk genetic features as deletion of the short arm of **chromosome** 17 (del 17p, or 17p–), where an important tumor suppressor gene is located, or translocation of genetic material between chromosomes 4 and 14 [t(4;14)].

As monoclonal antibodies, CAR T cells, ADCs, BiTEs, and other immunotherapies join the arsenal of agents against myeloma, the next challenge will be learning how to combine and sequence these treatments. Will immunotherapies be best used early in the treatment course in combination with other types of therapies to try to reach a cure, or will some of them be better used as **consolidation** or **maintenance** therapy to achieve and/or enhance **minimal residual disease**-negative status? Researchers must address these and many other questions as immuno-oncology takes its place in the standard of care for myeloma.

In closing

While a diagnosis of cancer is something you cannot control, gaining knowledge that will improve your interaction with your doctors and nurses is something you can control, and it will have a significant impact on how well you do throughout the disease course.

This booklet is not meant to replace the advice of your doctors and nurses who are best able to answer questions about your specific healthcare management plan. The IMF intends only to provide you with information that will guide you in discussions with your healthcare team. To help ensure effective treatment with good quality of life, you must play an active role in your own medical care.

We encourage you to visit myeloma.org for more information about myeloma and to contact the IMF InfoLine with your myeloma-related questions and concerns. The IMF InfoLine consistently provides callers with the most up-to-date and accurate information about myeloma in a caring and compassionate manner. IMF InfoLine specialists can be reached at InfoLine@myeloma.org or 818.487.7455 or 800.452.CURE.

Terms and definitions

Antibody: A protein produced by white blood cells called plasma cells in response to an antigen that enters the body. The medical term for antibody is "immunoglobulin."

Antigen: Any foreign substance (such as bacteria, a virus, toxin, or tumor) that causes the immune system to produce natural antibodies.

Apoptosis: A normal cellular process leading to the death of a cell.

Bone marrow: The soft, spongy tissue in the center of bones that produces white blood cells, red blood cells, and platelets. This is the tissue within which abnormal plasma cells build up when myeloma is growing.

Cancer: A term for diseases in which malignant cells divide without control. Cancer cells can invade nearby tissues and spread through the bloodstream and lymphatic system to other parts of the body.

Chromosome: A strand of DNA and proteins in the nucleus of a cell. Chromosomes contain genes and function in the transmission of genetic information. Normally, human cells contain 46 chromosomes (23 pairs).

Clinical trial: A research study of new treatment that involves patients. Each study is designed to find better ways to prevent, detect, diagnose, or treat cancer and to answer scientific questions.

- ***Control group*** – The arm of a randomized clinical trial that receives the standard treatment or placebo (no treatment).
- ***Experimental group*** – The arm of a randomized trial that gets the new treatment.
- ***Randomized clinical trial*** – A research study in which subjects are randomly assigned to receive a particular treatment or not.
- ***Arm*** – One of the treatment groups of a randomized trial. The majority of randomized trials have two, but some have more.
- ***End point*** – The goal of the trial; what a clinical trial is trying to measure or find out. Typical end points include measurements of toxicity, response rate, and survival.
- ***Double blind*** – Aspect of a randomized trial in which neither the participant nor the investigator knows the arm of the trial to which the patient is assigned. The purpose is to eliminate any bias in the reporting of results.
- ***Phase I trial*** – A trial designed to determine the maximum-tolerated dose (MTD) of a new drug or a new combination of drugs. It is usually the first human testing of a new treatment, although in phase I trials of combination therapies, the individual elements may already have been well tested. Patients in phase I trials generally have advanced cancer that is refractory to all standard treatment. In a typical phase I trial, successive groups ("cohorts") of 3 to 6 patients are given the treatment. All patients in a cohort get the same dose. The first cohort typically gets a very low dose, and the dose is raised in each subsequent cohort until a set number of patients experience dose-limiting toxicity (DLT). The dose level used for the previous cohort is then taken to be the MTD. This dose is then used in a phase II trial.
- ***Phase II trial*** – A trial designed to determine the response rate of a new therapy that has already been tested in phase I trials. Typically, 14 to 50 patients with one type of cancer are treated to see how many have a response. Patients are usually required to have advanced cancer that is refractory to any standard treatment. In addition, patients must have measurable disease. If results from a phase II trial are promising enough, the treatment may then be tested in a phase III trial. If the results are obviously much better than the standard treatment, then it may not be necessary to do a phase III trial, and the treatment may be approved based on phase II trial results.
- ***Phase III trial*** – A trial designed to compare two or more treatments for a given type and stage of cancer. The end point of a phase III trial is usually survival or disease-free survival. Phase III trials are usually randomized, so patients don't choose which treatment they receive. A typical phase III trial has 50 to thousands of patients. Some phase III trials compare a new treatment that has had good results in phase II trials with an older, well known, standard treatment. Other phase III trials compare treatments that are already in common use. Some treatments in phase III trials may be available outside the clinical trial setting.
- ***Phase IV trial*** – Even after a drug has been approved by the United States Food and Drug Administration (FDA) for use in a particular indication, there may be need for additional studies. Phase IV clinical trials may be required by regulatory authorities or may be undertaken by the sponsoring company for a variety of reasons. For example, safety surveillance is designed to detect any rare or long-term side effects over a larger patient population and longer time period than was possible during the phase I–III clinical trials.

Consolidation therapy: Treatment given for a short duration (i.e., 2 to 4 cycles), usually with the same regimen used for induction therapy, following high-dose therapy with autologous stem cell rescue.

Cytokine: Cytokines are proteins secreted by cells which can stimulate or inhibit growth/activity in other cells. Cytokines are produced locally (for myeloma, in the bone marrow) and circulate in the bloodstream. Cytokines are normally released in response to infection.

Immunoglobulin (Ig): A protein produced by plasma cells; an essential part of the body's immune system. Immunoglobulins attach to foreign

substances (antigens) and assist in destroying them. The classes (also called isotypes) of immunoglobulins are IgG, IgA, IgD, IgE, and IgM. The non-medical word for immunoglobulin is "antibody."

Immunomodulatory drug: An agent that affects, enhances, or suppresses the immune system. Sometimes called an IMiD® compound.

Immunotherapy: Treatment that enhances the body's natural defenses to fight cancer. Also called biological therapy.

Maintenance therapy: Drugs given to patients in remission to delay or prevent a relapse.

Minimal residual disease (MRD): The presence of residual tumor cells after treatment has been completed and complete remission (CR) has been attained. Even patients who have attained a stringent complete response (sCR) may have MRD. Very sensitive new testing methods are now able to detect 1 myeloma cell among 1,000,000 sampled cells in blood or bone marrow.

Monoclonal gammopathy of undetermined significance (MGUS): A category of plasma cell disorder characterized by comparatively low levels of monoclonal protein in the blood and/or urine. Bone marrow plasma cell levels are low (< 10%). Myeloma-related symptoms (i.e., anemia, renal failure, hypercalcemia, and lytic lesions) are absent.

Multiple myeloma: A cancer of the bone marrow plasma cells, white blood cells that make antibodies. The cancerous plasma cells are called myeloma cells.

Natural killer (NK) cell: A lymphocyte (type of white blood cell) that is a component of the innate immune system. NK cells are responsible for tumor surveillance and are able to induce strong responses against tumors through the release of cytokines.

Pathogen: An infectious agent such as a virus, bacterium, prion, fungus, viroid, or parasite that causes disease in its host.

Plasma cells: Special white blood cells that produce antibodies (immunoglobulins). Myeloma is a cancer of the plasma cells. Malignant plasma cells are called myeloma cells. In myeloma, malignant plasma cells produce abnormal antibodies that lack the ability to fight infection. These abnormal antibodies are the monoclonal protein, or M-protein, that functions as a tumor marker for myeloma. The presence of malignant plasma cells in the bone marrow can lead to organ and tissue damage (anemia, kidney damage, bone disease, and nerve damage).

Proteasome inhibitor: Any drug that interferes with the normal function of the proteasome, an enzyme complex responsible for breaking down and recycling unwanted proteins in both normal cells and cancer cells.

Proteins: Substances composed of amino acids. Proteins are an essential part of all living organisms, especially as structural components of body tissues such as muscle, hair, collagen, etc., as well as enzymes and antibodies.

Response or remission: Complete or partial disappearance of the signs and symptoms of cancer. Remission and response are interchangeable terms.

- ***Stringent complete response (sCR)*** – sCR is CR (as defined below) plus normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence.
- ***Complete response (CR)*** – For myeloma, CR is negative immunofixation on serum (blood) and urine, and disappearance of any soft tissue plasmacytomas, and ≤ 5% plasma cells in bone marrow. CR is not the same as a cure.
- ***Very good partial response (VGPR)*** – VGPR is less than CR. VGPR is serum M-protein and urine M-protein detectable by immunofixation but not on electrophoresis, or 90% or greater reduction in serum M-protein, plus urine M-protein less than 100 mg per 24 hours.
- ***Partial response (PR)*** – PR is a level of response in which there is at least a 50% reduction in M-protein, and reduction in 24-hour urinary M-protein by at least 90% (or to less than 200 mg per 24 hours).

Smoldering multiple myeloma (SMM): SMM is a higher level of disease than MGUS, but is still not active myeloma with CRAB features indicating organ damage. Patients with standard-risk SMM do not require treatment, but should be observed at regular intervals by a hematologist-oncologist. Patients with high-risk SMM may choose to participate in a clinical trial.

Toxins: Poisons produced by certain animals, plants, or bacteria.

Transplant (transplantation): There are several different types of transplantation.

- ***Peripheral blood stem cell (PBSC) transplant*** – Doctors remove healthy blood-making stem cells from a patient's circulating blood (not from the bone marrow), which are then frozen and stored. The patient receives high-dose chemotherapy to destroy the cancer cells, but healthy blood cells are also destroyed. The frozen stem cells are then defrosted and returned to the patient, where they can produce new blood cells to replace cells destroyed by the treatment.
- ***Autologous transplant*** – A procedure in which stem cells are removed from a patient's blood and then are given back to the patient following intensive treatment.
- ***Bone marrow transplant*** – This term refers to the process of collecting stem cells from the bone marrow and infusing them into a patient. This term is used less frequently today in myeloma as stem cells are now collected from the peripheral (circulating) blood.

- ***Allogeneic (allograft) transplant*** – The infusion of bone marrow or stem cells from one individual (donor) to another (recipient). A patient receives bone marrow or stem cells from a compatible, though not genetically identical, donor. An HLA blood test is done to determine if a patient has a potential donor match. A donor may be a family member or may be obtained through a donor registry such as the National Marrow Donor Program (NMDP). Rarely, donor cells may be obtained from an umbilical cord blood bank. The donor's immune system cells recognize the recipient's myeloma cells as foreign, and attack them. Unfortunately, the donated cells also attack other tissues in the recipient's body, causing graft-versus-host disease (GVHD), which may be fatal.
- ***Reduced-intensity conditioning (RIC) allo transplant*** – A newer and, for myeloma, safer technique than an allogeneic transplant. RIC is a non-myeloablative, reduced-intensity "mini-allo" transplant performed within 180 days after a standard autologous transplant.
- ***Tandem transplant*** – A term used to indicate two autologous transplants done in succession. Tandem transplants are usually planned with 3-month to 6-month intervals between transplants. Tandem transplantation has become less common in the US in the era of effective novel therapies.
- ***Matched unrelated donor (MUD) transplant*** – Refers to a stem cell transplantation procedure in which the patient and the stem cells are genetically matched but are not from family members. This procedure is not recommended for myeloma patients because it carries an unacceptably high mortality rate from graft-versus-host disease (GVHD).
- ***Syngeneic transplant*** – The infusion of bone marrow or stem cells from one identical twin into another.
- ***Umbilical cord blood transplant*** – Stem cells obtained from the umbilical cords of newborns. These are frozen and stored in cord blood banks. Because multiple cords are needed to provide enough stem cells for an adult transplant, the risk of graft-versus-host disease is increased with this type of transplant, making it even riskier for myeloma patients.

Vaccine: A preparation of killed microorganisms, living attenuated organisms, or living fully virulent organisms that is administered to produce or artificially increase immunity to a particular disease.

Virus: A small living particle that can infect cells and change how the cells function. The disease and the symptoms caused by a viral infection vary based on the type of virus and the type of cells that are infected.

INTERNATIONAL MYELOMA FOUNDATION

You are not alone. The IMF is here to help.

Myeloma is a cancer that is not known to most patients at the time of diagnosis. To be empowered to play an active role in your own medical care and to make good decisions about your care with your doctor, it is vital for you to learn as much as possible about myeloma and its treatments.

The IMF produces and maintains a library of publications to help arm you with one of the most important weapons in the fight against myeloma: INFORMATION. The following is a partial list of publications available in English, and selected titles are also available in other languages.

- *Patient Handbook*
- *Concise Review of the Disease and Treatment Options*
- *Understanding Clinical Trials*
- *Understanding Dexamethasone and Other Steroids*
- *Understanding DARZALEX® (daratumumab)*
- *Understanding EMPLICITI® (elotuzumab)*
- *Understanding Fatigue*
- *Understanding High-Dose Therapy with Stem Cell Rescue*
- *Understanding the Immune System in Myeloma*
- *Understanding KYPROLIS® (carfilzomib)*
- *Understanding MGUS and Smoldering Multiple Myeloma*
- *Understanding NINLARO® (ixazomib) capsules*
- *Understanding POMALYST® (pomalidomide)*
- *Understanding REVLIMID® (lenalidomide)*
- *Understanding Treatment of Myeloma Bone Disease*
- *Understanding Treatment of Myeloma-Induced Vertebral Compression Fractures*
- *Understanding VELCADE® (bortezomib)*
- *Understanding Your Test Results*

All IMF publications and periodicals are always free of charge. Visit **publications.myeloma.org** to read, download, or order printed copies. Subscribe to IMF periodicals at **subscribe.myeloma.org** or by contacting the IMF.

As always, the IMF urges you to discuss all medical issues with your doctor, and to contact the IMF's InfoLine specialists with your myeloma questions and concerns.

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