Understanding The Immune System in Myeloma

A publication of the International Myeloma Foundation

Improving Lives Finding the Cure®
About the International Myeloma Foundation

Founded in 1990, the International Myeloma Foundation (IMF) is the oldest and largest myeloma-specific charity in the world. With more than 350,000 members in 140 countries, the IMF serves myeloma patients, family members, and the medical community. The IMF provides a wide range of programs in the areas of Research, Education, Support, and Advocacy:

**RESEARCH** The IMF is the leader in globally collaborative myeloma research. The IMF supports lab-based research and has awarded over 100 grants to top junior and senior researchers since 1995. In addition, the IMF brings together the world’s leading experts in the most successful and unique way through the International Myeloma Working Group (IMWG), which is publishing in prestigious medical journals, charting the course to a cure, mentoring the next generation of innovative investigators, and improving lives through better care.

**EDUCATION** The IMF’s educational Patient & Family Seminars, Medical Center Workshops, and Regional Community Workshops are held around the world. These meetings provide up-to-date information presented by leading myeloma specialists and researchers directly to myeloma patients and their families. Our 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** Our toll-free InfoLine at 800-452-CURE (2873) is staffed by coordinators who answer questions and provide support and information via phone and email to thousands of families each year. The IMF sustains a network of more than 150 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 Advocacy program trains and supports concerned individuals to advocate on health issues that affect the myeloma community. Working both at the state and federal level, the IMF leads two coalitions to advocate for parity in insurance coverage. Thousands of IMF-trained advocates make a positive impact each year on issues critical to the myeloma community.

Learn more about the way the IMF is helping to improve the quality of life of myeloma patients while working toward prevention and a cure. Contact us at 800-452-CURE (2873) or 818-487-7455, or visit myeloma.org.
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 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.

Immune system basics

This booklet will help you understand immune system basics. The immune system is extremely complex. It is made up of 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. 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; and
- 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 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 bloodstream 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 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 cytokotyes, 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 cytokotyes. 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 multi-clonal disease during the course of the disease and treatments. As more and more treatments successfully eliminate dominant clones, smaller subclones 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 cytokotyes that are secreted to trigger an immune response in fact stimulate the growth of myeloma cells.

Thus normal immunoglobulins 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, dendritic cell therapies, vaccine therapies, engineered T-cells, 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 borrows 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. Please see the IMF publications Understanding Darzalex (daratumumab) Injection and Understanding Empliciti (elotuzumab) for detailed information about these new therapies.

- 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 SLAM F7, and does not directly attack the myeloma cells. Rather, it attaches to NK cells and stimulates them to attack and attack myeloma cells via the SLAM F7 receptor. Elotuzumab “revs up” the immune response by activating NK cells.

**Vaccine therapies**

Using a vaccine to cure cancer is not a new idea. For more than two decades, researchers have been trying to refine this method for attacking cancer cells, without much success. Several vaccine studies of myeloma patients have been done over the years, and some clinical trials are still active.

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 (which release toxic chemicals and/or prompt cancer cells to self-destruct). Sometimes, additional substances (“adjuvants”) are added to vaccines to enhance the immune response to the antigen.

In one promising type of vaccine therapy for myeloma, specially designed antigens derived from each patient’s unique myeloma cells are introduced into the patient’s body via dendritic cells (antigen-presenting cells) to trigger a strong immune response.

**Oncolytic virotherapy**

Using viruses to kill cancer cells is a new and exciting method that may provide a “one-shot cure.” Oncolytic viruses are engineered to directly target and kill cells within the tumor, leaving non-cancerous cells unharmed.

A phase I clinical trial at the Mayo Clinic used a very high concentration of specially engineered measles virus in myeloma patients. This study captured international headlines by producing a complete and durable remission in a single patient who had very advanced disease. The only patients who could respond to this treatment, unfortunately, were those who had no antibodies to measles (from prior infection or a vaccine), which is rare occurrence; most people have measles antibodies because they have either been immunized or had the measles in childhood. If antibodies to the virus are present, the antibodies will kill the virus before the virus can kill the myeloma.

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

**Figure 3. Using your NK (Natural Killer) cells to attack myeloma with elotuzumab (anti-SLAM F7)**
There was clearly a need to find a virus to which human beings do not make antibodies. The vesicular stomatitis virus, which produces mouth sores, is one such virus. Preclinical research in the laboratory successfully used an engineered vesicular stomatitis virus (VSV) to kill myeloma cells in a single shot. An oncolytic VSV clinical trial for patients with myeloma, acute myeloid leukemia, or T-cell lymphoma is now under way at the Mayo Clinic.

**Immune cell therapies**

One of the most promising lines of research in hematologic cancers is an immunotherapy technique called chimeric antigen receptor (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. Early trials with CAR T-cells directed to CD19, an antigen not often expressed on myeloma cells, included only five myeloma patients. Of these five, three had stable disease control and one had a stringent complete response (sCR) with no minimal residual disease (MRD) detectable. More recent research uses CAR T-cells directed to the B-cell maturation antigen (BCMA), which is present on every myeloma cell. Early reports show that eight of nine patients in one trial had serious immune system side effects caused by the massive release of cytokines, but one patient achieved, and maintains a stringent complete response. Further studies will help researchers better understand and manage the immune-mediated side effects of CAR T-cell therapy.

**Combination therapies**

Combining immunomodulatory drugs – thalidomide, lenalidomide, Pomalyst® (pomalidomide) – with monoclonal antibodies and new immune therapies called “checkpoint inhibitors” shows signs of becoming a successful strategy. Checkpoint proteins limit the strength of immune responses. These proteins normally keep immune responses in check to protect us from strong responses that might damage normal cells. In cancer cells, however, these checkpoint proteins may be abnormal and may help tumors evade the immune response. As single therapies, checkpoint inhibitors are not prompting strong responses in myeloma patients, but in combination with other agents, there is greater efficacy.

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 bortezomib and carfilzomib increase dendritic cell-activated T-cell cytotoxicity. Using multiple immune system components, rather than a single target or pathway, to attack myeloma seems to be the most effective way forward.

**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 on the inside of the cancer cell. 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, checkpoint inhibitors, vaccine therapies, 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 immunoncology 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 up-to-date information about myeloma, and to contact the IMF InfoLine with your myeloma-related questions and concerns. The IMF InfoLine consists of skilled professionals who can be reached at InfoLine@myeloma.org, or 800-452-CURE (2873) or 818-487-7455.

**Terms and definitions**

**Antibody:** A protein produced by white blood cells called plasma cells that helps fight infection and disease.

**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 to cause myeloma.
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.


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 gets 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, and in addition, they 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 become standard-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 V 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.

Cytokines: Proteins secreted by cells which can stimulate or inhibit growth/activity in other cells. Cytokines are produced locally (i.e., in the bone marrow) and circulate in the bloodstream. They 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.

Multiple myeloma: A cancer arising from the plasma cells in the bone marrow. 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 large amounts of abnormal antibodies that lack the capability to fight infection. These abnormal antibodies are the monoclonal protein, or M-protein, that functions as a tumor maker for myeloma. Plasma cells also produce other chemicals that can cause organ and tissue damage (i.e., anemia, kidney damage, and nerve damage).

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, and so forth, 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 immunofluorescence 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. VGPS 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).

**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 stem cells from a patient’s circulating blood system (not from the bone marrow) and store them before the patient receives high-dose chemotherapy to destroy the cancer cells. The stem cells are then returned to the patient, where they can produce new blood cells to replace cells destroyed by the treatment. Using PBSC for autologous transplantation allows for easier and safer collection of stem cells and faster recovery after the transplant than bone marrow transplant.

- **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 or 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.

- **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 transplants. This may be two autologous transplants or an autologous transplant followed by an allogeneic (donor) transplant. Tandem transplants are usually planned with 3- to 6-month intervals between transplants. Tandem transplantation has become less common 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.

- **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.

**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. Infection with a virus can cause a person to develop symptoms. The disease and symptoms that are caused depend on the type of virus and the type of cells that are infected.

One of the most daunting aspects of being diagnosed with multiple myeloma is learning about – and understanding – an unfamiliar disease that is quite complicated. From diagnosis to long-term survival, the 10 Steps to Better Care® will guide you through the myeloma journey:

1. **Know what you’re dealing with. Get the correct diagnosis.**
2. **Tests you really need.**
3. **Initial treatment options.**
4. **Supportive care and how to get it.**
5. **Transplant: Do you need one?**
6. **Response Assessment: Is treatment working?**
7. **Consolidation and/or maintenance.**
8. **Keeping Track of the Myeloma: Monitoring without mystery.**
9. **Relapse: Do you need a change in treatment?**
10. **New Trials: How to find them.**

Visit 10steps.myeloma.org to gain a better understanding of the disease and diagnosis, and proceed through the steps to learn the best tests, treatments, supportive care, and clinical trials currently available.

As always, the International Myeloma Foundation (IMF) urges you to discuss all medical issues thoroughly with your doctor. The IMF is here to equip you with the tools to understand and better manage your myeloma. Visit the IMF website at myeloma.org or call the IMF InfoLine at 800-452-CURE (2873) or 818-487-7455 to speak with our trained information specialists about your questions or concerns. The IMF is here to help.