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.

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The Understanding series and 10 Steps to Better Care

The IMF’s Understanding series of booklets is designed to acquaint you with treatments and supportive care measures for multiple myeloma (which will be referred to simply as “myeloma” for the sake of brevity).

For a general overview of myeloma, the IMF’s Patient Handbook should be your first step, while the IMF’s Concise Review of the Disease and Treatment Options is a more in-depth summary for healthcare professionals and knowledgeable readers outside the medical community. Both publications, as well as the many booklets in the IMF’s Understanding series, are available on the IMF website myeloma.org, where you will find a wealth of information. You can also order copies of IMF booklets by calling 800-452-CURE (2873) toll-free in the United States and Canada, or 818-487-7455 worldwide, or by emailing theIMF@myeloma.org.

To help you navigate the IMF website, we have organized our information according to the 10 Steps to Better Care®, which takes you from diagnosis (Step 1) through clinical trials and how to find them (Step 10). Information relevant to each step along the way, including guidelines for testing, treating, transplanting, assessing response, managing side effects, monitoring, and treating relapsed disease, is available under the appropriate step on the path to better care.

In this booklet, words in bold type are explained in the “Terms and definitions” section. A more complete dictionary of myeloma-related vocabulary, the IMF’s Glossary of Myeloma Terms and Definitions, can be found at myeloma.org/publications.

What you will learn from this booklet

Velcade® (also known by the generic drug name “bortezomib”) plays an important role throughout the disease course of the myeloma patient, from induction therapy for those who are newly diagnosed, to a possible role as part of conditioning for stem cell transplant, to consolidation and/or maintenance therapy, to treatment for those whose myeloma has become refractory to and/or relapsed on previous therapies.

What is Velcade and how does it work?

Velcade is the first in a class of drugs called proteasome inhibitors. It was first approved by the US Food and Drug Administration (FDA) for the treatment of relapsed/refractory myeloma in May 2003. In June 2008, the FDA expanded Velcade’s approval to include the frontline setting. In January 2012, the FDA approved subcutaneous (SQ) administration of Velcade. In August 2014, the FDA expanded the Velcade label to allow for retreatment of patients who previously responded to Velcade and who relapsed at least six months after completing prior Velcade treatment.

Velcade can be used alone, in combination with dexamethasone, or as part of a more complex multi-drug regimen.

Velcade works by inhibiting enzyme complexes called proteasomes. Both normal cells and cancer cells contain proteasomes, which break down damaged and unwanted proteins into smaller components. Proteasomes also carry out the regulated breakdown of undamaged proteins in the cell, a process that is necessary for the control of many critical cellular functions. These smaller protein components are then used to create new proteins required by the cell. Proteasomes can be thought of as crucial to the cell’s “recycling” of proteins.

When Velcade inhibits proteasome function, the normal balance within a cell is disrupted. This disruption results in a number of effects on the cell, some of which are still being studied. When proteasomes are inhibited in laboratory tests, myeloma cells stop dividing. Proteasome inhibition also causes myeloma cells to stop producing chemicals that stimulate other myeloma cells: the autocrine feedback loop is interrupted. Myeloma cells are more sensitive to these effects than normal cells, so myeloma cells die while normal cells can recover.

How is Velcade given?

Velcade comes in the form of a freeze-dried powder, which must be reconstituted before it is administered.

As approved in 2003, Velcade is given as an intravenous (IV, into the vein) infusion injected through either a peripheral IV line (usually in the arm) or a central IV line (usually in the chest, also known as a “central venous catheter”). Velcade is injected over a short period of 3 to 5 seconds.

In January 2012, the FDA approved a second method for administering Velcade to patients. In addition to the former method of giving Velcade as an IV infusion, it is possible to receive Velcade as a subcutaneous (SQ, under the skin) injection, commonly known as a “shot.” The SQ injection is given at the doctor’s office, at the same dose and on the same schedule as IV Velcade, and should be given alternating between the thighs and the abdomen.

SQ Velcade causes significantly less peripheral neuropathy (PN) than IV Velcade, and may also reduce the occurrence of gastrointestinal (GI) side effects. Other side effects of SQ Velcade are the same as those for IV Velcade. Approximately 6% of patients in clinical trials with SQ Velcade had site reactions (itching, swelling, pain, and/or redness at the injection site). If you have pre-existing neuropathy or GI problems, you should discuss using SQ Velcade with your doctor.

When is Velcade given, and at what dose?

In standard protocols, Velcade is given at the doctor’s office or a clinic at 1.3 mg per square meter of body mass, twice per week, for 2 weeks, followed by a 10-day rest period. Patients and their doctors typically choose a Monday + Thursday or Tuesday + Friday schedule. At least 72 hours are needed between doses, so that normal cells have a chance to recover from the effects of the drug. Therefore, changes in the administration schedule...
Palumbo and Dr. Kenneth Anderson ing Group (IMWG) members Dr. Antonio In 2011, IMF International Myeloma Work patients who are elderly and frail.  There are situations in which it may be necessary to reduce the dose of Velcade and/or administer it once, rather than twice, per week. Your doctor may order dose reductions and/or treatment schedule changes if you experience side effects. Schedule and dose changes can also be ordered preventively for patients with pre-existing medical problems or for patients who are elderly and frail. In 2011, IMF International Myeloma Working Group (IMWG) members Dr. Antonio Palumbo and Dr. Kenneth Anderson published a dosing regimen for older and/or frail patients in the New England Journal of Medicine. Among that population of patients, Dr. Palumbo recommends that dosages of Velcade and the drugs with which it is commonly combined be adjusted according to the patient’s age and concurrent illnesses and/or tolerance. Dr. Palumbo provides a helpful table for specific dose adjustments recommended for frail patients (see Table 1). His “go-go,” “moderate-go,” “slow-go” three-group system is now in use around the world.

The specific treatment algorithm for Velcade dose reductions within combinations is summarized in Table 2, which includes, at dose level “–2,” a dose reduction of Velcade to once per week (versus twice per week in the standard regimens).

Velcade is frequently given in combination with other anti-myeloma drugs, including dexamethasone, cyclophosphamide, Revlimid® (lenalidomide), thalidomide, and melphalan/prednisone. Velcade is a required component of the FDA-approved combination therapy of Farydak® (panobinostat) + Velcade + dexamethasone for patients who have had one to three prior therapies for myeloma, including Velcade and an immunomodulatory drug such as thalidomide, Revlimid, or Pomalyset® (pomalidomide). Velcade is also being tested in combination with many other agents that are still in clinical trials. Detailed information about Velcade therapy in combination with dexamethasone, thalidomide, Revlimid, or Farydak is discussed in separate IMF booklets.

**Velcade in clinical trials**

A wide range of clinical trials has been conducted with Velcade. Studies have demonstrated the efficacy of Velcade therapy for patients in the frontline, conditioning, relapsed/refractory, and maintenance settings.

At the 2015 annual meeting of the American Society of Hematology (ASH), three important myeloma studies were presented that have had profound effects on clinical practice. Each clinical trial involved a regimen containing Velcade in combination with an immunomodulatory drug:

- **IMF Chairman Dr. Brian G. M. Durie** presented the long-anticipated results of a large, randomized clinical trial known as SWOG 0777 that compared the combination of Velcade + Revlimid + dexamethasone (VRD) to Revlimid + dexamethasone alone (RD) in newly diagnosed myeloma patients who were not candidates for stem cell transplant. The trial results demonstrated that VRD extended both progression-free survival (PFS) and overall survival (OS) by a year longer than RD. These data firmly established the superiority of triplet frontline therapy over two-drug therapy and confirmed the efficacy of the combination of a proteasome inhibitor and an immunomodulatory drug. The SWOG 0777 study was published in The Lancet in December, 2016, and was named the major “practice-changing” trial for 2016 in Nature Reviews Clinical Oncology.
- Dr. Michel Attal presented the results of the Intergroupe Francophone du Myélome (IFM, French myeloma trial group) IFM 2009 clinical trial, which was designed to determine

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If a Grade 3–4 AE (adverse event, or side effect) occurs:
1. discontinue therapy; 2. wait for a Grade 1 AE; 3. restart at a lower dose

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if autologous stem cell transplant (ASCT) is still a necessary component of treatment for newly diagnosed patients in the era of powerful novel therapies. All patients were treated with VRD, and approximately half of them went on to have high-dose melphalan followed by ASCT. Patients in both arms of the study received maintenance therapy with Revlimid. Trial partners at the Dana-Farber Cancer Institute in Boston are still recruiting patients and collecting data, and are not yet ready to present their results. The results from the IFM portion of the trial demonstrate that VRD followed by upfront ASCT provides longer PFS and higher rates of MRD negativity than VRD alone, but overall survival remains the same in the transplant and non-transplant arms at the time of this writing (January 2017). Perhaps the Dana-Farber data will eventually resolve the open question of whether or not the addition of auto transplant to VRD and Revlimid maintenance therapy extends overall survival.

Dr. Philippe Moreau presented the results of another IFM study that compared the use of triplet therapies with Velcade + thalidomide + dexamethasone (VTD) and Velcade + cyclophosphamide + dexamethasone (VCD) as induction therapy prior to ASCT. The results, subsequently published in *Blood*, demonstrate the superiority of the VTD triplet combining a proteasome inhibitor and an immunomodulatory drug over VCD, which combines a proteasome inhibitor and an alkylating agent.

The data from several important clinical trials involving Velcade were presented at international meetings in 2016. The first of these was the CASTOR study of the new monoclonal antibody Darzalex® (daratumumab) in combination with Velcade + dexamethasone versus Velcade + dexamethasone alone. At the June 2016 annual meeting of the American Society of Clinical Oncology (ASCO), Dr. Antonio Palumbo presented the results of the CASTOR study, which determined that Darzalex + Velcade + dexamethasone is superior to Velcade + dexamethasone alone. The results of this study were published in *The New England Journal of Medicine* in August 2016, prompting a submission of the trial data to the FDA and the European Medicines Agency (EMA) to broaden the indication for use of Darzalex. On November 21, 2016, the FDA approved Darzalex in combination with Velcade + dexamethasone for patients who have had at least one prior therapy.

The ASH meeting held in December 2016 featured several important presentations in which Velcade was combined safely and effectively with a new therapy to treat patients with relapsed/refractory myeloma. The first of these oral presentations concerned the data from a trial that compared the efficacy of an approved HIV treatment, Viracept® (nelfinavir), in combination with Velcade + dexamethasone, versus Velcade + dexamethasone alone. All patients in the trial were refractory to previous treatment with Velcade. In this small study, 65% of the patients who received nelfinavir + Velcade + dexamethasone had at least a 50% drop in monoclonal protein (that is, at least a partial response, or PR). Among patients with high-risk cytogenetic abnormalities, 77% had at least a PR, and among patients who had received five or more prior lines of therapy, 61% had at least a PR. There will be a larger confirmatory study to ascertain that nelfinavir is capable of overcoming resistance to Velcade and that it is highly effective and safe in combination with Velcade + dexamethasone.

A second 2016 ASH presentation in which a new drug combined with Velcade + dexamethasone demonstrated benefit over Velcade + dexamethasone alone was the report of a trial with venetoclax: 68% of the patients in that study had at least a PR to venetoclax + Velcade + dexamethasone, and 40% of those responses were a drop of at least 90% in monoclonal protein. Among those who were not refractory to prior Velcade or had received only 1–3 prior therapies, the response rate was 89%. While this, too, was a small study, it does add to the mass of data on the power of triplet therapies with Velcade + dexamethasone as a platform, and to the ability of some new drugs to overcome resistance to Velcade.

Another highlight of the 2016 ASH meeting that featured Velcade + dexamethasone as a platform in combination with a new agent was the presentation of data from the STOMP trial, which explored the safety and efficacy of selinexor in combination with a number of current therapies for highly refractory disease. Best results emerged from the arm of the trial that used a combination of selinexor + Velcade + dexamethasone: 27 of the 33 patients in that trial arm had high-risk cytogenetics, yet the overall response rate of at least a PR was 77%, including patients who were refractory to prior Velcade or another proteasome inhibitor. Among patients who were not refractory to a proteasome inhibitor, the response rate was 100%.

Because of its effectiveness and broad use in myeloma, Velcade is often used as the standard of care in randomized clinical trials or as a platform drug for novel combination therapies. Velcade is currently in scores of clinical trials, including those evaluating:

- use of subcutaneous Velcade as a maintenance therapy for patients with high-risk disease
- use of Velcade along with high-dose melphalan as conditioning for autologous transplant
- use of Velcade along with Pomalyst + dexamethasone in relapsed/refractory myeloma
- use of Velcade as a stem-cell mobilizer in combination with colony stimulating factor for stem cell harvesting.
Use of Velcade in clinical practice in 2017

In the frontline setting

Numerous studies have demonstrated the efficacy of Velcade in combination with:
- melphalan + prednisone (VMP);
- dexamethasone (VD);
- cyclophosphamide + dexamethasone (VCD, also known as CyBorD);
- thalidomide + dexamethasone (VTD);
- Revlimid + dexamethasone (VRD).

It is important to discuss with your doctor the most appropriate combination and strategy in your case. The choice is determined by several factors, including plans for autologous transplantation or not; presence or absence of high-risk chromosome features (t(4;14); t(14;16); t(14;20); del 17p), and the presence or absence of kidney problems or underlying neuropathy. In addition to these medical concerns, personal preference and financial impact are also important considerations.

In other disease settings, including consolidation, maintenance, and relapse

In these settings various combinations and sequences of therapy with Velcade have been demonstrated to be effective. Details should be discussed with your doctor.

It is important to note that Velcade is active and well-tolerated in patients with relapsed myeloma with varying degrees of renal (kidney) insufficiency. Efficacy/safety in clinical trials were not substantially affected by severe-to-moderate versus none-to-mild kidney impairment. Several trials have confirmed the safety and efficacy of Velcade for patients with renal impairment.

In addition, several clinical trials using various treatment strategies incorporating Velcade have shown that Velcade can help overcome poor-risk genetic mutations and significantly improve overall survival.

Clinical trials with Velcade have also demonstrated its ability to help prevent bone loss in myeloma patients.

There is low risk of venous thromboembolism (VTE) with Velcade, and Velcade may even provide a protective effect against VTE in combination with IMiD-based regimens.

What are the possible side effects of Velcade?

Most of the side effects associated with Velcade are manageable and predictable. The most important and most frequently occurring side effects are described below. Your doctor or nurse can provide more information in greater detail about these and other possible side effects. Speak with your doctor or nurse if you notice ANY changes in your health.

Peripheral neuropathy

Peripheral neuropathy (PN) is a serious condition in which treatment affects nerves in the hands, feet, legs, and/or arms. Symptoms of PN include numbness, tingling, or even pain in the hands, feet, legs, and/or arms. Some patients may have experienced PN from the effects of the myeloma monoclonal protein itself and/or from previous treatments for myeloma. If you begin taking Velcade with this pre-existing condition, it is especially important that you pay particular attention to the extent of your discomfort, so that you can rapidly report a worsening of your condition to your doctor. If detected and managed appropriately, the neuropathy is often reversible.

Subcutaneous (SQ) Velcade causes significantly less PN than IV Velcade. Patients who received SQ Velcade in the IFM trial in which it was compared to IV Velcade had an incidence of PN of any severity of 38%, while those who received IV Velcade had a 53% incidence of any grade of PN. Only 6% of the patients who received SQ Velcade had PN of Grade 3 or 4 (on a scale where 1 is the lowest and 4 the highest grade), while 16% of the IV patients had Grade 3 or 4 PN. SQ Velcade may also have reduced side effects on the gastrointestinal system (nausea, constipation/diarrhea).

Prevention and treatment of PN

You are strongly advised to contact your doctor if you experience new or worsening symptoms of PN, as early detection and dose modification may prevent progression of this condition. Notifying your doctor also allows for appropriate modifications of the Velcade dose and/or schedule.

You should be aware that very detailed recommendations for Velcade dose and schedule modifications are available (see Tables 1 and 2). These are the key principles:
- Avoid progressive PN, especially if any significant pain develops (what is called Grade 2). Although PN can be reversible, it may be partly but not fully reversible. Prevention is the best approach. This requires early, proactive dose and/or schedule modifications.
- Discuss options for dose/schedule/method of administration changes with your doctor. The main types of modification are:
  1. Dose reduction. This is done in stepwise fashion:
     - full dose: 1.3 mg/m² of body surface area
     - first dose reduction: 1.0 mg/m²
     - half dose: 0.7 mg/m²
  2. One day per week option. Several recent studies have shown that using Velcade 1 day/week instead of the standard 2 day/week schedule can retain full efficacy (with some of the major combinations now used) and significantly reduce the risk of neuropathy of Grade 2 or higher.
  3. SQ administration option. SQ Velcade causes significantly less peripheral neuropathy than IV Velcade.
Fatigue

Fatigue is a common side effect associated with Velcade therapy. Although fatigue is generally not severe, caution is advised if you are operating machinery, including automobiles. Please see the IMF publication Understanding Fatigue for further information on this debilitating side effect and how to manage it.

Prevention and treatment of fatigue

Management of fatigue may include supportive care as determined by your doctor. The effects of fatigue may be minimized by maintaining:

- a moderate level of daily activity;
- a healthy diet and proper fluid intake;
- a consistent sleeping schedule with enough rest at night;
- regularly scheduled visits with your doctor or health care professional.

Nausea

Nausea may occur while taking Velcade and may be associated with dizziness, light-headedness, or fainting if it leads to dehydration. Medical treatment may be required for dehydration.

Prevention and treatment of nausea

Precautions should be taken to prevent dehydration caused by vomiting. You should drink a sufficient amount of water and other fluids and seek medical advice if you experience dizziness, light-headedness, or fainting. Your doctor may administer anti-emetic medication (to prevent vomiting) or IV hydration, as required.

Diarrhea

Diarrhea may occur while taking Velcade. Dizziness, light-headedness, or fainting may occur due to dehydration caused by either excessive or persistent diarrhea.

Prevention and treatment of diarrhea

Precautions should be taken to prevent dehydration caused by either excessive or persistent diarrhea. You should maintain a proper level of hydration by drinking a sufficient amount of water and seek medical advice if you experience dizziness, light-headedness, or fainting. Your doctor may administer antidiarrheal medication or IV hydration, as required.

Decreased platelet levels

Myeloma patients taking Velcade often experience a condition called thrombocytopenia – a lowered level of platelets in the blood. Platelets help blood to clot; fewer platelets can lead to bruising, bleeding, and slower healing. The platelet level falls with treatment but, after the required interval between doses, should return to the baseline level by the beginning of the next cycle.

Prevention and treatment of decreased platelet levels

You should inform your doctor if you experience excessive bruising or bleeding. Management may include platelet transfusions at the discretion of your doctor.

Low blood pressure (hypotension)

A drop in blood pressure may occur after receiving Velcade. If you have a history of fainting or low blood pressure or are taking medication that can cause low blood pressure (such as antihypertensive medication, that is, medication to treat high blood pressure), it is important that you tell your doctor about your condition before you begin receiving Velcade. Dizziness, especially when it occurs after rapidly sitting up or standing from a lying-down position, may be a sign of low blood pressure.

Prevention and treatment of low blood pressure

You should seek medical advice if you experience dizziness, light-headedness, or fainting. Caution is advised when operating machinery, including automobiles. You should take precautions to prevent dehydration (drinking plenty of water, for example), and your doctor may administer medication for the treatment of low blood pressure. It is also important to inform your doctor about any additional medications you are taking, particularly for the treatment of hypertension (high blood pressure).

Other side effects of Velcade

Other side effects that may occur with Velcade include headache, insomnia, occasional rash, fever, cough, back pain, and muscle cramps. Velcade has been shown to increase the incidence of the herpes zoster virus – also known as shingles – a painful itchy rash usually located on one side of the body. Patients with myeloma have a higher risk for developing shingles because myeloma compromises the immune response. Please talk to your doctor about taking an anti-viral medication to reduce your risk for shingles while you are receiving Velcade, and remember to discuss ANY changes in your health with a doctor or nurse on your healthcare team.

Will a reduction in dose of Velcade change the effectiveness of treatment?

It is important to communicate openly with your doctor or healthcare professional and keep regular appointments to maintain your Velcade treatment schedule. Your doctor may choose to lower your dose of Velcade as part of an overall plan to manage a particular side effect you experience. The recommended initial dose of Velcade is 1.3 mg/m². However, a lower dose of 1.0 mg/m², which is the first dose reduction your doctor is likely to try, has also been found active against myeloma. In the small study that examined both of these doses, there was no significant difference in effectiveness between the two doses. Your doctor may also choose to skip a scheduled dose to reduce the severity of a side effect before continuing treatment.
Studies have shown that administration of Velcade on a weekly schedule in combination with other anti-myeloma agents is associated with a reduction in side effects, particularly peripheral neuropathy, without significant reduction in efficacy.

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 consistently provides callers with the best information about myeloma in a caring and compassionate manner. IMF InfoLine specialists can be reached at InfoLine@myeloma.org, or 800-452-CURE (2873), or 818-487-7455.

Terms and definitions
Autocrine: Autocrine refers to the process whereby a growth factor is both produced by a cell (such as a myeloma cell) and can also stimulate myeloma cell growth, creating a positive autocrine loop. In similar fashion, in a paracrine loop, factors produced by the microenvironment surrounding myeloma cells can stimulate these cells. Stimulated myeloma cells produce factors that can in turn stimulate microenvironmental cells.

Cell: The basic unit of any living organism. Millions of microscopic cells comprise each organ and tissue in 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 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.
Conditioning: A treatment regimen given to a patient to destroy cancer cells prior to stem cell transplant. The most common conditioning regimen given to myeloma patients is 200 mg of melphalan per square meter of body mass.

Deep vein thrombosis (DVT): A condition that occurs when a blood clot (thrombus) forms in one or more of the deep veins in the body, usually in the legs. Deep vein thrombosis can cause leg pain or swelling, but may occur without any symptoms.

Enzyme: A protein molecule manufactured by a cell. An enzyme acts as a catalyst that increases the rate of a specific biochemical reaction in the body.

Gastrointestinal side effects: Side effects of medication that affect the digestive tract, such as nausea, vomiting, diarrhea, and constipation.

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

Induction therapy: The initial treatment used in an effort to achieve remission in a newly diagnosed myeloma patient. Sometimes called “frontline” therapy.

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

Multiple myeloma: A cancer arising from the plasma cells in the bone marrow. The cancerous plasma cells are called myeloma cells.

Overall survival (OS): For a group of individuals suffering from a cancer, this term denotes the chances of staying alive. It denotes the median number of individuals in the group who are likely to be alive after a particular duration of time. At a basic level, OS is representative of cure rates. OS is often used as a measure of treatment efficacy in clinical trials.

Peripheral neuropathy (PN): Numbness, tingling, and/or pain in the hands, feet, legs, and/or arms.

Plasma: The liquid part of the blood in which red blood cells, white blood cells, and platelets are suspended.

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 marker for myeloma. Plasma cells also produce other chemicals that can cause organ and tissue damage (i.e., anemia, kidney damage, and nerve damage).

Platelets: One of the three major blood elements, others being the red blood cells and white blood cells. Platelets plug up breaks in the blood vessel walls and release substances that stimulate blood clot formation. Platelets are the major defense against bleeding. Also called thrombocytes.

Progression-free survival (PFS): The improved survival of a patient that can be directly attributed to the treatment given for the myeloma. The time period during which the patient survives, and the myeloma does not regrow or relapse. See “Progressive disease.”

Progressive disease: Myeloma that is becoming worse or relapsing, as documented by tests. Defined as an increase of ≥ 25% from lowest confirmed response value in the myeloma protein level and/or new evidence of disease.

Proteasome: A joined group (or complex) of enzymes that destroy damaged or unwanted proteins and undamaged proteins that require degradation in the cell. This turnover or “recycling” of proteins is important to maintain balance within the cell and helps to regulate several functions including cell growth.

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, and so forth, as well as enzymes and antibodies.

Pulmonary embolism (PE): A condition that occurs when a blood clot in the vein (deep vein thrombosis, or DVT) breaks loose, travels through the bloodstream, and lodges in a lung, blocking blood flow.

Refractory: Disease that is no longer responsive to standard treatments. Patients with refractory myeloma have had progressive disease either during treatment or within 60 days following treatment. Most clinical trials for advanced disease are for patients with relapsed and/or refractory myeloma.

Relapse: The reappearance of signs and symptoms of a disease after a period of improvement. Patients with relapsed disease have been treated, then developed signs and symptoms of myeloma at least 60 days after treatment ended. Most clinical trials for advanced disease are for patients with relapsed and/or refractory myeloma.

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. 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).

Side effect: Unwanted effect caused by a drug. Also known as adverse event or adverse reaction.
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 at three to six month intervals between transplants.

- **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.

Venous thromboembolism (VTE): A condition that includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). Nearly two thirds of VTE events result from hospitalization. Risk factors include infection, age >75, cancer, and a history of VTE. See “Deep vein thrombosis (DVT)” and “Pulmonary embolism (PE).”

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.
9. Relapse: Do you need a change in treatment?

Visit [10steps.myeloma.org](http://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.