Understanding High-Dose Therapy with Stem Cell Rescue

A publication of the International Myeloma Foundation

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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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Melphalan, a chemotherapy agent, is a very effective treatment for myeloma, but it can also permanently damage normal blood stem cells. High dosages of melphalan can be especially helpful in eradicating myeloma cells from the bone marrow. High-dose melphalan is known as myeloablative therapy because the high dose of chemotherapy ablates (wipes out) the bone marrow (the Greek prefix for bone marrow is “myelo”). Thus melphalan kills myeloma cells in the bone marrow and also kills all the blood-making stem cells (known in Greek-derived medical terms as “hematopoietic” stem cells) that are also present in the marrow. To circumvent the problem of simultaneous severe damage to, and potential destruction of, normal blood stem cells in the bone marrow, the blood stem cells can be “harvested” (collected) and saved before melphalan is administered.

Normal blood stem cells are collected from the patient or donor through a process called apheresis. The harvested normal blood stem cells are frozen at –80 degrees Celsius and can be stored indefinitely at that temperature. After the patient receives high-dose melphalan, the frozen stem cells are defrosted and returned to the patient’s blood circulation by a process similar to blood transfusion. The stem cells pass from the circulating blood back into the bone marrow, where they divide and grow to repopulate, or “re-seed,” the normal bone marrow space. Approximately 36 to 48 hours after the melphalan is administered, the blood and tissue levels of melphalan are very low and do not harm the new stem cell growth. This whole process of harvest and re-infusion is called stem cell rescue, or stem cell transplant, because the stem cells “rescue” the bone marrow from the effects of the high-dose chemotherapy.

Types of stem cell transplant

- **Autologous stem cell transplant (ASCT):** More accurate terminology is “HDT with stem cell rescue.” Stem cells are harvested from a patient with myeloma following initial therapy and re-infused after high-dose melphalan therapy has been administered. This is the most common type of stem cell transplant. The procedure can be performed once (single autotransplant) or twice (double or tandem transplant), although tandem transplantation has become less common in the era of effective novel therapies.

### What you will learn from this booklet

High-dose therapy (HDT) with stem cell rescue, or “stem cell transplant,” as it is sometimes known, is an important treatment option for eligible patients with myeloma. Whether it is done as part of a first treatment regimen or is done at the time of disease relapse, it can provide significant remission and survival benefits. This booklet explains the rationale for, and process of, receiving HDT with stem cell rescue as a treatment option for myeloma. Questions addressed include:

- What are blood stem cells?
- Why are blood stem cells collected and used for transplant?
- What are the benefits and risks of HDT with blood stem cell rescue as part of the treatment for myeloma?
- What is the role of HDT since the introduction of novel therapy approaches in the last decade? Can they be used in combination?

### Background rationale for use of HDT and blood stem cell transplant or rescue

Myeloma cells and normal blood stem cells are in the same bone marrow microenvironment. As myeloma cells build up in the bone marrow, they become intermixed with normal blood stem cells responsible for the production of red blood cells (RBC, erythrocytes) and white blood cells (WBC) and platelets. Any anti-myeloma drugs reaching the bone marrow microenvironment can therefore damage both the myeloma cells and the normal blood stem cells. To circumvent the problem of simultaneous severe damage to, and potential destruction of, normal blood stem cells in the bone marrow, the blood stem cells can be harvested and saved before melphalan is administered.

Normal blood stem cells are collected from the patient or donor through a process called **apheresis**. The harvested normal blood stem cells are frozen at –80 degrees Celsius and can be stored indefinitely at that temperature. After the patient receives high-dose melphalan, the frozen stem cells are defrosted and returned to the patient’s blood circulation by a process similar to blood transfusion. The stem cells pass from the circulating blood back into the bone marrow, where they divide and grow to repopulate, or “re-seed,” the normal bone marrow space. Approximately 36 to 48 hours after the melphalan is administered, the blood and tissue levels of melphalan are very low and do not harm the new stem cell growth. This whole process of harvest and re-infusion is called stem cell rescue, or stem cell transplant, because the stem cells “rescue” the bone marrow from the effects of the high-dose chemotherapy.

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### Figure 1. Blood vessel

![Blood vessel](image-url)
Allogeneic stem cell transplant: Stem cells are harvested from a human leukocyte antigen (HLA) matched family member who is not an identical twin. Usually, the best match is a sibling. Again, the stem cells are infused after HDT. Part of the anticancer effect of this type of transplant derives from the high-dose chemotherapy, and part from the grafted (or transplanted) cells. The transplanted immune system cells recognize the recipient's cancer cells as foreign, and attack and kill them. This is called the "graft-versus-myeloma effect." The problem with donor immune system stem cells is that they also see the recipient's normal cells as foreign, and attack them too, causing graft-versus-host disease (GVHD). Some cases of GVHD are controllable, and some are not. When GVHD cannot be controlled, it is lethal. Myeloablative allogeneic transplant is seldom used for myeloma patients, because their risk of death from GVHD is approximately 45%. Full allogeneic transplant was largely abandoned for myeloma patients in the early 1990s.

"Mini" or non-myeloablative allogeneic transplant: This is a newer and safer procedure than full allogeneic transplant. It involves the use of reduced-intensity chemotherapy in combination with a donor stem cell transplant. A single autologous transplant is performed first, to reduce the number of myeloma cells in the bone marrow, and then, within 180 days, a reduced dose of chemotherapy is administered before the patient receives donor blood stem cells. Although GVHD and the graft-versus-myeloma effect still occur, they are usually not as severe as with full allogeneic transplant. Nevertheless, the International Myeloma Working Group (IMWG) recommends that an allogeneic transplant be performed for a myeloma patient only within the context of a clinical trial.

Matched Unrelated Donor (MUD) stem cell transplant: Stem cells are harvested from a non-family member. A MUD transplant carries a much higher risk of GVHD than a related-donor transplant, because the stem cells are rarely a 100% tissue (HLA) match. A MUD transplant is a high-risk procedure.

Syngeneic stem cell transplant: Stem cells are harvested from an identical twin. In this case, the stem cells from the identical twin are infused after HDT, which can be melphalan or other agents.

How HDT with stem cell rescue is used as a part of myeloma therapy

Overview

HDT with stem cell rescue has been used as a treatment for myeloma for more than two decades. Transplant doctors attempt to kill as many myeloma cells – or "reduce the tumor burden" – as much as possible before collecting stem cells and administering HDT. Patients therefore receive induction or "frontline" therapy with various drugs before they begin the process of HDT with stem cell rescue. Even if there is minimal response to frontline therapy, however, patients can proceed to harvest, HDT, and stem cell rescue and still have an excellent result. Response after HDT is far more important than response before, as long as the disease is not still progressing.

Frontline options

Several options are available for initial or frontline therapy. Typical frontline regimens currently utilized are:

- Velcade® (bortezomib) plus dexamethasone with or without a third drug, such as Revlimid® (lenalidomide), thalidomide, or cyclophosphamide. The acronyms for these common regimens are, respectively, VRD, VTD, and VCD (which is also known as CyBorD). The definitive results of the SWOG S0777 study comparing VRD to Revlimid + dexamethasone (Rd) in newly diagnosed patients were presented at the American Society of Hematology (ASH) meeting in December 2015 by IMF Chairman Dr. Brian G.M. Durie. Progression-free survival (PFS) and overall survival (OS) were a year longer with VRD than with Rd. These data firmly establish the superiority of triplet frontline therapy and confirm the efficacy of the combination of a proteasome inhibitor and an immunomodulatory drug.

- Two-drug regimens such as thalidomide + dexamethasone or Revlimid + dexamethasone can also be used. Since longer-term use of Revlimid may impair stem cell harvest, doctors advise that patients on frontline Revlimid + dexamethasone therapy who are candidates for autologous transplant harvest stem cells after four cycles of treatment.

Full details of these treatments are discussed in other publications of the International Myeloma Foundation.

Frontline options to consider and avoid

In general, stem cell transplant is an option for all myeloma patients upon completion of frontline therapy. However, since transplant is an intensive approach, older patients (often defined as those over the age of 65 years) and/or those with other medical conditions may not be able to tolerate the procedure and/or may run the risk of serious complications.

If stem cell transplant is considered a potential option, the most important caution is to avoid use of melphalan prior to stem cell harvesting, since this can lead to damage of normal bone marrow stem cells. Thus, avoiding melphalan initially and keeping all options open is the most commonly recommended strategy.

Conversely, if stem cell transplant can never be an option or is not preferred, for
whatever reason, melphalan taken orally (in pill form) as part of initial therapy can be a simple and very effective treatment.

**Details of frontline therapy**

Stem cells are harvested, HDT is administered, and transplant is performed after initial or frontline therapy. Two major points about frontline therapy are:

- Initial therapy for three to six months should be with drugs that do not damage normal blood stem cells.
- Ideally, response to induction therapy should provide a >50% reduction in myeloma protein (M-protein) levels and/or other indicators of active myeloma prior to the collection of normal blood stem cells. However, even lesser degrees of response may be sufficient to allow safe and effective stem cell collection.

**What are the benefits of HDT with blood stem cell rescue?**

**Enhancement of depth of response**

Further improvement in the level of response achieved with frontline therapy is a major advantage of HDT with stem cell rescue. Over half the time, partial responses will be improved to either VGPR (very good partial response, with ≥90% myeloma protein reduction) or CR (complete response, with disappearance of measurable myeloma protein).

**Updates from clinical trials**

Results from studies in the US and Europe indicate that the use of novel agent induction therapy followed by HDT and ASCT in newly diagnosed myeloma patients increases progression-free survival and may also induce a higher rate of MRD-negative status. However, at this time there are no data to demonstrate that upfront ASCT improves overall survival. We await long-term overall survival data from the IFM 2009/DFCI randomized phase III clinical trial comparing 5 cycles of VRD induction followed by HDT with stem cell rescue, two cycles of VRD consolidation, and one year of Revlimid maintenance therapy to 8 cycles of VRD followed by one year of Revlimid maintenance therapy. As of January 2017, the survival rates for the two arms of the study are still equivalent.

Perhaps the most significant finding among studies of ASCT in 2016 was presented at the 2016 ASH meeting. Representing a group of investigators from centers across the US, Dr. Edward Stadtmauer (University of Pennsylvania) presented the data from the StaMINA trial, in which 758 transplant-eligible patients who were within 12 months of having started induction therapy and had no disease progression were randomized to one of three study arms: (1) single auto transplant followed by 4 cycles of RVD consolidation and Revlimid maintenance until disease progression; (2) tandem ASCT followed by Revlimid maintenance until disease progression; or (3) single ASCT followed by Revlimid maintenance until disease progression. The surprising preliminary results of the largest randomized US transplant trial in myeloma demonstrated comparable progression-free survival and overall survival in all three arms after 38 months of follow-up. The addition of RVD consolidation or a second ASCT was not superior to a single ASCT followed by Revlimid maintenance in the frontline treatment of myeloma.

**Role of consolidation and maintenance**

A long-term update on the CALGB/DCOG/BMT CTN trial of maintenance therapy with Revlimid following single ASCT for newly diagnosed myeloma was published in May 2015. The updated data reinforce the prior conclusion that both PFS and OS are improved with Revlimid maintenance. PFS is doubled with Revlimid versus placebo, and no median OS had yet been reached in the Revlimid arm versus 76 months median OS for the placebo arm. The PFS and OS were improved for patients who took Revlimid regardless of whether they were in complete remission or not following transplant. There is, however, an increased risk of second primary malignancies for the Revlimid maintenance arm, although the risk of death is significantly higher for lack of maintenance therapy than for a second malignancy.

Based on the data from the CALGB and an IFM Revlimid maintenance trials, the National Comprehensive Cancer Network (NCCN) upgraded the use of single-agent maintenance Revlimid from category 2A (which means that the results of clinical trials have not yet undergone full peer review, and that the safety and efficacy data are still preliminary), to category 1 (which means that it is based upon high-level evidence, and there is uniform NCCN consensus that the intervention is appropriate).

It is still an important concern, however, that the CALGB and IFM phase III post-transplant Revlimid maintenance clinical trials reported higher rates of second malignancies among patients who were in the Revlimid maintenance arms. The increase in second malignancies in these clinical trials remains an area of study, since there has been no increase in second cancers reported among relapsed/refractory patients treated with Revlimid in the absence of an alkylating agent. A prevailing theory, reinforced by a 2014 meta-analysis by Palumbo et al. of 3,218 patients in seven clinical trials, is that the increase in second hematologic cancers could arise from the combined use of Revlimid and melphalan, an alkylating agent that was used as HDT in both the CALGB and IFM clinical trials.

Given the obvious advantages but potential risks of post-transplant maintenance therapy with Revlimid, each patient must discuss the use of this type of maintenance therapy with his or her oncologist, who will evaluate individual risk factors and the response to transplant before making a recommendation. Such factors as disease characteristics, other illnesses, and genetic risk profile must be taken into consideration. Although there is currently little published data on the use of Velcade as maintenance therapy, a single Dutch
myeloma group trial did demonstrate its safety and efficacy when given every other week. A clinical trial is now ongoing in which ixazomib, now approved as Ninlaro®, the first oral proteasome inhibitor, is being tested as post-transplant maintenance therapy.

Role of a second transplant

If CR or ≥ VGPR are not achieved with a single autologous transplant, then a second autologous transplant can be offered. Continuing in the attempt to achieve ≥ VGPR with the second transplant appears to confer benefit.

A second transplant at the time of relapse remains a viable option for patients who had remissions of at least 18 months to two years following a first ASCT. In June 2015, a publication of the Nordic myeloma group comparing the use of HDT and ASCT at first relapse versus conventional cytotoxic drugs or novel agents without ASCT concluded that both median OS and time to disease progression were significantly longer with a second ASCT.

Factors influencing outcomes

It has been generally accepted that patients achieving better responses, such as CR or VGPR, have better outcomes (versus, for example, partial response or PR). However, further studies are required. Having a durable response at a particular level, whether that is a simple PR (≥ 50% improvement), VGPR (≥ 90%) or CR (100%), is more important than the level of the response in itself. Response lasting ≥ two years is particularly beneficial. The relative benefit of stable disease at the PR, VGPR, or CR level is under further study.

Practical steps in considering HDT with stem cell rescue as a treatment option

I. Confirm the diagnosis of active myeloma requiring anti-myeloma treatment.

II. If there is any doubt about the diagnosis or approach to treatment, it is an important time to seek a second opinion before going ahead with a frontline strategy.

III. Proceed with initial or frontline therapy to bring the myeloma under control and achieve an initial response.

Make sure to avoid melphalan or other therapy that may reduce the success of normal blood stem cell harvesting. Radiation therapy to the pelvis, for example, can reduce stem cell reserves and should be avoided if possible.

IV. Assess the response to treatment with each cycle of therapy (usually every three to four weeks).

After 3 to 4 cycles of treatment, more complete re-evaluation is recommended, including bone marrow testing plus x-ray/scans as needed to determine the level of response.

Review with the physician the pros and cons of HDT with stem cell rescue (and/or stem cell harvesting without immediate transplant).

If ≥ 50% response (PR: ≥ 50% reduction in myeloma protein level in blood and/or urine) is achieved, stem cell harvesting can be planned if the patient and the physician concur that this is the best approach. If there is no plan for harvest and/or HDT, a plan for ongoing maintenance (“continuous therapy”) or follow-up treatment is required.

If there is < 50% response, then other therapy may be required before proceeding to transplant.

How stem cells are collected

Blood stem cells are located in the bone marrow. Until about 20 years ago, the only way to collect these stem cells was to have the patient or donor receive a general anesthetic and undergo as many as 50 to 100 bone marrow aspirations from the back of the pelvic bone to remove enough bone marrow and stem cells to use for future transplant. This was obviously painful, invasive, and inconvenient. The discovery that stem cells could be collected from the bloodstream by giving a patient or donor injections of stem cell growth factors (“colony-stimulating factors” or “CSFs”) such as Neupogen® (filgrastim), Neulasta® (pegfilgrastim), or Leukine® (sargramostim) to trigger the release of bone marrow stem cells into the bloodstream was a major breakthrough. With refinements over the years, this has become the standard method. It is rarely necessary to use the old method of direct bone marrow harvesting from the pelvic bone.

Protocols for collecting stem cells from the blood stream

There are three main protocols for collecting stem cells from the blood stream (peripheral blood stem cells [PBSC]):

- giving standard growth factors alone,
- giving growth factors with chemotherapy, or
- giving growth factors with an additional mobilizing agent.

1. Giving growth factors alone

Growth factors stimulate the blood stem cells in the bone marrow to multiply and to be released into the bloodstream. These medications are administered subcutaneously (under the skin). This procedure is commonly known as a “shot.” The white cell growth factors (filgrastim, pegfilgrastim, sargramostim) are the ones used in high doses for stem cell harvest or “mobilization.” The injections are given daily for three or more days. Stem cells are usually collected on the fourth or fifth day

Figure 2. Bone marrow aspiration

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after starting the injections. The collections and injections are continued daily until sufficient stem cells are obtained. Typically, there is a plan to collect enough stem cells for at least two transplants, at a rate of at least 2–3 million (4–6 million total for two transplants) stem cells per kilogram of the patient’s body weight.

2. Using chemotherapy plus growth factors
Cyclophosphamide is the most commonly used chemotherapy agent in the setting of stem cell harvest to enhance the release of stem cells from the bone marrow into the bloodstream. However, there are also other chemotherapy agents that can be used. The doctor will explain why it may or may not be appropriate to use chemotherapy, such as cyclophosphamide, in addition to growth factors. The doctor will explain the potential benefits and side effects of cyclophosphamide if it is administered to mobilize the blood stem cells. Primarily, cyclophosphamide is used to increase the stem cell yield and so is recommended if there is a concern that the stem cell harvest might be low. An additional advantage of the cyclophosphamide is that it is actually treatment for the myeloma. A disadvantage of cyclophosphamide is that at many institutions it is given in the in-patient setting during mobilization. Further, it lowers blood counts and, when the white blood cells (the body’s immune system) are at very low levels, infection might result, possibly requiring yet another hospitalization.

Following chemotherapy for stem cell mobilization, one of the white cell growth factors will be given by injection under the skin daily for approximately 10 days. This procedure is therefore longer and much more intensive than using growth factors alone. The patient or someone who agrees to be responsible may be taught how to give the growth factor injection so that it can be administered at home. If a family member is not willing or available to give the injections, patients may receive their injections at a clinic or hospital, or they may receive them at home from a visiting nurse. Once the number of stem cells in the blood stream is high enough, they will be collected over the course of two to five days, while the patient is still receiving the growth factor injections.

3. Using a mobilization agent plus growth factors
Mozobil® (plerixafor) was approved by the FDA in 2008 as an additional agent for stem cell mobilization. Mozobil is used in combination with growth factors to release stem cells into the blood so they can be collected and used for transplant in patients with myeloma (as well as patients with non-Hodgkin’s lymphoma). Patients are treated with growth factors for four days prior to receiving Mozobil. Mozobil is injected subcutaneously approximately 11 hours before the planned stem cell collection for up to four consecutive days. Mozobil increases the number of stem cells that can be collected and is particularly helpful for patients who, for a variety of reasons (such as increased age or intensive prior treatment regimens), have difficulty generating stem cells for harvest.

Clinical trials have demonstrated several benefits to using Mozobil in addition to growth factors compared to growth factors alone for the mobilization of stem cells. Particular benefits of adding Mozobil are:

- Higher success rates for mobilizing more stem cells for transplant. More patients achieve the minimum and target number of stem cells, and are able to proceed to transplant. Collecting and rein fus ing more stem cells into the patient can result in longer-lasting (often termed “durable”) recovery of white blood cells, red blood cells, and platelets.
- There is the likelihood of fewer apheresis procedures, with reduced number of days on the apheresis machine.
- Virtually all myeloma and non-Hodgkin’s lymphoma patients receiving cells mobilized with Mozobil in combination with growth factors have successful engraftment. Adel et al. from Memorial-Sloan Kettering Cancer Center demonstrated that, despite the cost of Mozobil, using Mozobil upfront for stem cell mobilization may be more cost effective than the current widely used approach employing the less expensive agent cyclophosphamide, not only because Mozobil requires fewer days of apheresis, but because patients who use Mozobil do not require hospitalization for either infusions or infections.

The collection or harvesting procedure
In medical language, the harvesting is called apheresis or leukapheresis – literally the removal of white cells from the blood stream. Apheresis is a procedure by which blood from the patient or donor passes through a special machine that separates (using a centrifuge technique) and then removes the blood-making stem cells. The rest of the blood is immediately returned to the patient or donor. Compared to direct bone marrow harvesting, this is a remarkably simple and pain-free procedure.

Apheresis
Prior to the start of apheresis, a thin flexible plastic tube called a catheter, usually with two or three lumens, or tubular openings, is inserted through the skin and into a vein so that blood can be taken out and then given back. The catheter is usually inserted into the chest just below the collarbone. Insertion of the catheter is usually done as an outpatient procedure, and only a local anesthetic is necessary. The site where the catheter enters the skin may be sore for a few days; the discomfort may be relieved with medications like acetaminophen. The catheter may be kept in place for several weeks because it can be used to give HDT after stem cells have been collected. Sometimes the same catheter is used during the stem cell rescue procedure as well. Apheresis will last three to four hours each day for one to five days. Apheresis is usually done as an outpatient procedure.
The most common side effects experienced during apheresis are slight dizziness and tingling sensations in the hands and feet. Less common side effects include chills, tremors, and muscle cramps. These side effects are temporary and are caused by changes in the volume of the patient’s blood as it circulates in and out of the apheresis machine, as well as by blood thinners added to keep the blood from clotting during apheresis.

Processing stem cells
After collection, the stem cells are taken to the processing laboratory, which is usually located within the hospital or local blood bank. In the processing laboratory, the cells are prepared for freezing (cryopreservation) by being mixed with a solution containing the chemical DMSO (dimethyl sulfoxide). The stem cells are then frozen and stored in liquid nitrogen. The stem cells remain frozen until they are needed for rescue. They can be stored frozen for as long as necessary. There is some deterioration with time, but excellent function of stem cells is retained for at least 10 years.

How many stem cells do I need?
Over the years, a number of studies have been completed to determine the number of stem cells you need to safely undergo HDT. The number of stem cells is quantified by a special laboratory technique called “CD34+ cell analysis by flow cytometry.” A small sample of the stem cell collection is tested for the number of CD34+ cells in the product. We know that a minimum number of stem cells to safely complete a transplant is 2 million CD34+ cells per kilogram of body weight. The number of CD34+ cells is checked in each daily collection and the number tallied. The stem cell collection process continues daily until the planned number of stem cells is collected – usually from one to four days. Some transplant centers check the number of CD34+ cells BEFORE starting leukapheresis to make certain there will be a good collection that day. Most transplant physicians collect enough stem cells for two transplants (as mentioned above, over 4 million CD34+ cells per kilogram of weight).

Administering HDT
After the stem cells are frozen and stored, the patient is ready to receive HDT. This treatment is designed to destroy myeloma cells more effectively than standard-dose chemotherapy. The purpose of HDT is to kill myeloma cells inside the patient’s body, particularly in the bone marrow, where the myeloma cells grow. The most common type of HDT used to treat myeloma is melphalan, administered at a dose of 200 milligrams per square meter (mg/m²) of body surface area (size of patient). Depending on the type of myeloma and other factors, some patients may receive a second transplant three to six months after the first transplant (double or tandem transplant). A patient should discuss with the doctor the pros and cons of more than one transplant planned and performed back-to-back versus the possibility that the cells will be stored for a potential second transplant at a later time.

Autologous stem cell rescue, also called ASCT
The previously collected stem cells will be unfrozen and given back (infused) through a catheter into the bloodstream (as one would receive a blood transfusion) one to two days after administration of the HDT. This procedure is often referred to as the “transplant,” but that is something of a misnomer, since patients receive their own stem cells back. These blood cell-making cells are not “transplanted” from another source. The infusion of stem cells takes place in the patient’s room: it is not a surgical procedure. The frozen bags of blood cells are thawed in a warm water bath, and then injected into the bloodstream through the catheter. Upon thawing, the DMSO freezing agent evaporates into the air and creates a distinct and somewhat unpleasant garlic smell. Most centers infuse one bag at a time. It usually takes one to four hours for the infusion. Infused stem cells travel through the bloodstream, and eventually, to the bone marrow, where they begin to produce white blood cells, red blood cells, and platelets. It takes 10 to 14 days for the newly produced blood cells to enter the bloodstream in substantial numbers. Growth factors may again be given to the patient to speed up this process.

In addition to obliterating the bone marrow, HDT can cause other severe side effects, which may require that some patients be admitted to the hospital for treatment during this period. Not all transplant centers require that patients remain in the hospital after the infusion of stem cells. Some transplant centers have facilities close by where patients may stay and be monitored daily at the hospital on an out-patient basis, while others allow patients who live close to the hospital to sleep at home and come back to the hospital daily to be monitored. The average time in the hospital (or a nearby facility) for the chemotherapy, stem cell infusion, and recovery is approximately three weeks. Shortly before starting chemotherapy, patients usually are given large amounts of fluid to prevent dehydration and kidney damage from the chemotherapy. Some of the more common side effects of chemotherapy include nausea, vomiting, diarrhea, mouth sores, skin rashes, hair loss, fever or chills, and infection. Medications designed to prevent or lessen some of the expected side effects of treatment are given routinely. Patients are very closely monitored during and after the administration of HDT. Monitoring includes daily weight measurement as well as frequent measurements of blood pressure, heart rate, and temperature.

Preventing infection
During the first two to three weeks after transplantation, the re-infused stem cells migrate to the bone marrow and begin the process of producing replacement blood cells, a process called engraftment. Until engraftment of the stem cells takes place, patients are very susceptible
to developing infections. Even a minor infection like the common cold can lead to serious problems because the body’s immune system is so weakened by the effects of HDT. Therefore, special precautions are necessary during recovery. Since the patient’s immune system is very weak, patients may remain in the hospital until the white blood cell counts reach a level safe enough for the patient to be discharged.

To prevent infection, the following supportive care measures may be required:
- Antibiotics are often prescribed to help prevent infection.
- Visitors should wash their hands and may be asked to wear masks and rubber gloves to protect the patient.
- Fresh fruits, vegetables, and flowers may be prohibited from the patient’s room as these can carry infectious agents (bacteria and fungi).
- If infection and/or fever occurs (as the result of lowered white cell counts), the patient may be admitted to the hospital and receive intravenous antibiotics.

**Engraftment and recovery**

Once the stem cells have been re-infused, it will take about two weeks for blood counts to recover. Many transplant centers will again use white blood cell growth factors (filgrastim, pegfilgrastim, sargramostim) after the transplant to help stimulate the bone marrow to produce normal blood cells. These injections (under the skin) will continue until the white blood count returns to normal. During this time, red blood cell and/or platelet transfusions may also be necessary.

Waiting for the infused stem cells to engraft, for blood counts to return to safe levels, and for side effects to disappear is often the most difficult time for patients and their families and friends. During this period patients will feel weak and very fatigued. Having a support network is very important. Recovery can be like a roller coaster ride: one day a patient may feel much better, only to awake the next day feeling as sick as ever. It is important during this period to take things one day at a time. Once new blood cells are being made, symptoms will resolve, the risk of serious infections will be reduced, and transfusions will no longer be needed.

After being discharged from the hospital, a patient continues recovery at home for two to four months. Although patients may be well enough to leave the hospital, their recovery will be far from over. For the first several weeks the patient may be too weak to do much more than sleep, sit up, and walk a little around the house. Frequent visits to the hospital will be required to monitor progress. Patients usually cannot resume normal activities or return to full-time work for up to three to six months after the transplant, although this varies from individual to individual.

**Are you a candidate for HDT with stem cell rescue?**

HDT with stem cell rescue is a treatment option for many myeloma patients; however, it is very rarely a cure. It can improve the duration of remission and survival. It can also provide a better quality of life for most patients. Not all patients with myeloma are candidates for this type of therapy. Many factors must be taken into consideration. These include factors related to the myeloma itself and patient-related factors.

**Myeloma-related factors**
- disease stage
- disease aggressiveness
- responsiveness to treatment
- serum albumin
- beta-2 microglobulin (β2M)
- chromosomal (genetic) analysis

**Patient-related factors**
- age
- health status
- kidney, heart, lung, and liver function
- patient preference
- family situation
- work situation

We cannot stress enough that myeloma is a highly individualized disease. While there are similarities between patients, each patient’s disease has its own distinct characteristics. Many variables will be weighed before determining whether HDT with stem cell rescue is appropriate for you. Therefore, general statements regarding patient outcomes both during the procedure and post-procedure are inappropriate.

**Possible restrictions**

Eligibility for HDT with autologous stem cell rescue varies across countries and institutions. The operative age cut-off for ASCT in European clinical trials is 65 years. The 2014 IMWG consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem cell transplantation, however, states that the arbitrary age of 65 years is no longer sufficient to define an elderly patient. European specialists are presenting data demonstrating that not only age, but concurrent illnesses and a general assessment of a patient’s fitness should be evaluated to determine appropriate treatment, stressing that physiologic age is more important than chronological age. They recommend that decisions regarding transplant eligibility should be made for individual patients based on a risk-benefit assessment and the needs and wishes of the patient.

In the United States, there is no upper age limit set in Medicare’s National Coverage Determination for ASCT in myeloma. While such transplants used to be covered only up to the age of 77, the Centers for Medicare & Medicaid Services (CMS) has now removed the upper age limit on coverage, leaving the question of eligibility to the patient’s physician and the Medicare administrative contractor within the patient’s jurisdiction. CMS currently denies all coverage for tandem autologous transplants and for allogeneic transplant, even within the context of clinical trials. IMF advocacy efforts are addressing these issues.
What goes on at a transplant center?

To understand what goes on at a transplant center, it is important to remember that even if someone is a good candidate for HDT with stem cell rescue, the ultimate decision about whether or not, and when, to undergo this type of therapy is the patient’s.

Psychosocial issues

HDT and autologous transplantation can place an enormous stress on patients and families. Physical, psychological, emotional, and financial stresses can be overwhelming. Patients and families may experience feelings of anger, depression, and anxiety over an unknown future and a lack of control. Support services offered through the hospital and many other organizations, including myeloma support groups, are very important during this time. We urge you to take advantage of these services, or to seek a referral from your oncologist for psychological counseling and/or a psychiatric consultation.

Questions and answers about HDT with stem cell rescue

Listed below are some of the questions frequently asked by people with myeloma who have had or are considering a stem cell transplant. These questions and other concerns should be discussed with the doctor and members of the healthcare team before making any final decisions about the patient’s treatment plan.

Q. Why is a stem cell transplant necessary for a myeloma patient?
A. The transplant procedure allows the patient to receive high doses of chemotherapy to kill more myeloma cells. This therapy is so potent that it destroys all of the bone marrow. Without bone marrow, the body is unable to manufacture blood cells needed to carry oxygen, help blood clot, and defend against infection. Therefore, a stem cell transplant replaces the destroyed marrow, rescuing the patient from the effects of HDT.

Q. Am I a candidate for HDT with stem cell rescue?
A. Medical experts have yet to arrive at a set of fixed guidelines for selecting patients who will benefit the most from a transplant. Long accepted as a part of myeloma treatment protocols, successful transplantation is a function of the patient’s age, general physical condition, stage of disease, and responsiveness to prior treatments. Only the patient’s physician can provide a patient with the best assessment of his or her chances for long-term survival.

Q. Does taking alkylating agents such as melphalan, busulfan, and cyclophosphamide reduce my suitability for a transplant?
A. Alkylating agents are one of the most effective ways of killing myeloma cells inside the body. However, their prolonged use – more than four to six months – will reduce the ability to easily harvest a patient’s stem cells. Therefore, when considering a transplant, a patient should first discuss the total treatment plan to ensure that there are as many short-term and long-term treatment options available as possible. It should be emphasized, however, that collection should ideally be done before using any alkylating agents.

Q. How do I select a transplant center?
A. A transplant is a complicated medical procedure that requires an expert team of doctors, nurses, social workers, psychologists, and allied health professionals who understand the procedure, have performed it successfully many times, and are equipped to respond when medical and emotional problems arise. Today, medical centers that meet these criteria can be found throughout the country. Many of these centers specialize in treating patients with many different types of cancer. To find the one best suited for patients with myeloma, you should talk with your doctor, other myeloma patients, and International Myeloma Foundation InfoLine specialists.

Q. What goes on at a transplant center?
A. To understand what goes on at a transplant center, we strongly suggest a visit to one or more centers. Meet with the staff – doctors, nurses, and other members of the myeloma treatment team – and learn more about how they approach a transplant. See the room where your transplant will occur and where you’ll be spending your recuperation time. Find out what part of your procedure will be performed in a clinic or a doctor’s office and what part will be done in the hospital. You should be comfortable with the center before you begin your transplant. Many centers have a nearby motel or apartment complex where they house patients after they receive their HDT and while they are recuperating from the effects of the chemotherapy. Not only are patients less at risk of infection outside the walls of the hospital and in a smaller, better-controlled space, but the costs of private lodging are far less than those of being in the hospital for two weeks or more. Patients return to a safe area of the

Timing

When to perform HDT and stem cell rescue is also an important consideration. Most transplant physicians believe it is better to perform the transplant early in the disease course. However, there is no absolute clinical data to suggest that transplantation earlier in the treatment regimen is better than waiting until later. Kumar et al. studied 290 transplant-eligible patients who had received upfront treatment with dexamethasone plus an immunomodulatory drug (thalidomide or Revlimid), and who either had HDT with stem cell rescue right away or delayed their transplants until relapse. They compared the overall survival of these two groups of patients and found that “in transplant-eligible patients who receive immunomodulatory drugs as initial therapy followed by early stem cell mobilization, delayed SCT results in similar overall survival compared with early SCT.” Because this study was not randomized and because it examined only the two-drug combination of an immunomodulatory drug and dexamethasone, we await the final results of the IFM-DFCI trial comparing VRD with and without ASCT.
hospital daily to have their blood work done, and are close-by should an emergency arise.

Q. If my doctor agrees that a stem cell transplant is an appropriate treatment for my disease, what can I do now to prepare for the experience?
A. The patient can do a lot to get ready for the transplant. By reading this booklet, a patient has already taken the most important step: learning as much as possible about the procedure. A patient should speak with the doctor, seek out fellow survivors, and read as much as possible, including the publications and newsletters from the International Myeloma Foundation. Patients should ask questions about what they’ve learned and strive to read all the newest information coming from research. We suggest that patients bring a tape recorder or a friend along to the doctor’s office so that they can give full attention to the doctor. Patients should share what they learn with family and loved ones so that they will know what to expect — and how they can help in the weeks and months ahead.

The doctor will perform a series of tests to confirm that the patient is well enough to tolerate the transplant. All the data gathered on the performance of the heart, lungs, kidneys, and other vital organs will enable the doctor to compare the patient’s health before and after the procedure. In most cases, the patient won’t have to be hospitalized for these tests since they can be performed in the doctor’s office.

Q. What side effects should I anticipate from the transplant?
A. Side effects can be expected from every type of medical treatment, even the use of aspirin. Each patient reacts differently to chemotherapy and other drugs given during the transplant. No two patients share exactly the same side effect profile. The most common side effects experienced following HDT include nausea, mouth sores, hair loss, and fatigue. Patients should seek a transplant center where the doctors, nurses, and allied health professionals have performed a number of transplants on myeloma patients and have the experience and expertise to care for each individual myeloma patient’s needs.

Q. What happens during re-infusion?
A. After chemotherapy the patient receives a re-infusion of his or her own stem cells. The stem cells will be thawed and infused into the patient’s catheter either through a syringe or from an intravenous infusion bag. While the re-infusion takes place the patient may feel warm or lightheaded. The chemical used to keep the stem cells fresh has a garlic smell that the patient might be able to taste. The oncologist may re-prescribe or adjust the patient’s medication to make him or her feel more comfortable during this procedure.

Q. Can a patient die from the transplant itself?
A. Every medical procedure carries risk, and HDT for patients with myeloma is riskier than most. Nonetheless, medical studies have shown that over 95% of patients (usually closer to 99%) survive HDT with stem cell rescue.

Q. Can the patient relapse after a transplant?
A. Yes. Unfortunately, the majority (at least 50%) of all patients with myeloma experience a relapse 18 to 36 months after their transplant is completed.

Q. I’ve heard a lot about myeloma purging. Can it help?
A. The process of purging removes myeloma cells from peripheral blood taken from the patient’s body prior to transplant. HDT is used to kill myeloma cells that are within the body. Stem cell selection, or “purging,” is used to remove myeloma cells from the collected stem cells prior to the transplant. The goal of this strategy is to reduce the number of myeloma cells both within the patient’s body as well as in the peripheral blood that will be re-infused into the patient. Scientific evidence indicates that this technology is not effective in myeloma. Therefore, transplant centers currently do not use stem cell purging for patients with myeloma.

Q. How long will the transplant patient stay in the hospital or a nearby facility?
A. Patients stay in, or nearby, the hospital for about two to three weeks. The length of stay varies from patient to patient. Some patients may have several short admissions.

Q. When will the stem cells start to grow again?
A. Stem cells start to grow back or “engraft” within 10 to 14 days after re-infusion.

Q. What will the patient’s quality of life be after transplant?
A. On average, patients take 3 to 6 months to recover from a transplant. By this time, the immune system will once again fight infections because the bone marrow is producing healthy blood cells. Hair will grow back, but the taste buds might still be a little quirky. Foods that tasted good before a transplant might not taste good now. However, in most cases, patients should be able to return to normal daily activities. It can take as long as a year for some patients to fully recover normal functioning. Patients and their caregivers must take one day at a time. There will be bad days and good days, and they won’t necessarily come in that order. Patients should prepare themselves to feel differently each day during the recovery process.

Q. What alternative and complementary therapies can be taken during and after transplant?
A. Some patients believe that alternative and complementary therapies are an important part of their treatment program. Because all drugs, synthetic and natural, interact, and may create unanticipated side effects, patients should always consult their doctors about their use. The doctor should be informed of the names of all the alternative and complementary therapies being taken so that he or she can adjust the regimen accordingly. It is important to note that even seemingly innocuous over-the-counter drugs, such as ibuprofen, may be harmful to a patient with myeloma.

Q. Should transplant patients expect changes in their emotions?
A. Yes. Transplant is more than just a medical procedure. Because it forces the patient to rely upon the oncologist and other members of the transplant team, as well as on family and friends, there is often a loss of the sense of independence and control. Feelings of isolation, depression, and helplessness are common to transplant patients. Patients and loved ones should seek assistance from a trained professional who has experience in counseling. Help may also be found through patient support groups.
Questions for the doctor
These are questions we suggest be discussed with the doctor to provide better understanding of the transplant procedure and its effects on the patient’s life. Space is provided for notes.

Am I a candidate for stem cell transplant?

What does HDT with transplant hope to achieve that can’t be achieved by standard chemotherapy?

What treatment protocols are there at your institution and how do you decide which one is right for me?

Does taking alkylating agents such as melphalan, busulfan, and cyclophosphamide reduce my suitability for a transplant?

How do I select a transplant center?

How many transplants has this center performed for myeloma and what are the success rates?

How long do patients transplanted in your center live after the transplant itself?
How does this compare with national averages?

Will you be the doctor who performs the transplant and who are the other members of the team?

Will you be the doctor who provides my ongoing care?

What goes on at a transplant center?

If we decide that transplant is an appropriate treatment for my disease, what can I do now to prepare for the procedure?

When does the transplant procedure begin?

What drugs will be prescribed for use before, during, and after the transplant? What do they do and what are their side effects?
How long is the entire treatment cycle, from preparation for the transplant to recovery?

How long will I have to be in the hospital? How often are my follow-up visits going to be?

How will the transplant procedure affect my ability to function? How can I expect to feel during and after the transplant?

What side effects of my transplant should I anticipate?

What are the risks of the transplant procedure? Is there a high survival rate for HDT with stem cell transplant?

Additional notes:

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

Alkylating agent: A chemotherapeutic agent such as melphalan or cyclophosphamide. Alkylating refers to the way in which these agents cross-link the DNA of myeloma cells and block cell division.

Apheresis: Sometimes called leukapheresis, apheresis is a procedure in which blood is taken from a patient or donor and the portion of the blood containing plasma, white blood cells, and platelets is separated. Red blood cells are transfused back into the donor. The portion containing white blood cells includes the rare stem cells.

Beta-2 microglobulin (also called β2-microglobulin, β2M, or β2M): A small protein found in the blood. High levels occur in patients with active myeloma. Low or normal levels occur in patients with early myeloma and/or inactive disease. Approximately 10% of patients have myeloma that does not produce β2M. At the time of relapse, β2M can increase before there is any change in the myeloma protein level. Factors such as viral infection can sometimes produce elevated serum β2M levels.

Blood stem cells: Stem cells derived from the blood which result in faster hematologic recovery.

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.

Bone marrow aspiration: The removal, by a needle, of a sample of fluid and cells from the bone marrow for examination under a microscope.

Bone marrow biopsy: The removal, by a needle, of a sample of tissue from the bone. The cells are checked to see whether they are cancerous. If cancerous plasma cells are found, the pathologist estimates how much
of the bone marrow is affected. Bone marrow biopsy is usually done at the same time as bone marrow aspiration.

**Catheter:** A tube that is placed in a blood vessel to provide a pathway for drugs or nutrients. A central venous catheter (CVC) is special tubing that is surgically inserted into a large vein near the heart and exits from the chest or abdomen. The catheter allows medications, fluids, or blood products to be given; and blood samples to be taken.

**CD34+:** The laboratory marker used to single out and quantify the number of stem cells in your blood stream. A certain minimum number of CD34+ stem cells are required to safely support a transplant procedure.

**Chemotherapy:** Any drugs used to kill cancer cells. “Combination chemotherapy” uses more than one drug in a cancer treatment regimen.

**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.

**Colony-stimulating factor (CSF):** Proteins that stimulate the development and growth of blood cells. Neupogen® (filgrastim), Neulasta® (pegfilgrastim), and Leukine® (sargramostim) are colony-stimulating factors that are used to mobilize stem cells from the bone marrow into the bloodstream prior to apheresis. These may also be used after the transplant to hasten blood count recovery.

**Efficacy:** The power to produce an effect; in cancer research ‘efficacy’ refers to whether the treatment is effective.

**Engraftment:** The process by which stem cells in the transplanted bone marrow or peripheral blood migrate to the patient’s bone marrow and begin to grow and produce new white blood cells, red blood cells, and platelets.

**Flow cytometry:** A technology used in cell counting, cell sorting, and biomarker detection by suspending cells in a stream of fluid and passing them through a laser.

**Graft-versus-host disease (GVHD):** A reaction of donated bone marrow cells against the recipient’s own tissue.

**Growth factors:** Drugs that stimulate blood stem cells both to grow and to be released into the bloodstream.

**Human leukocyte antigen (HLA) test:** A blood test used to match a blood or bone marrow donor to a recipient for transfusion or transplant.

**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.

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

**M-proteins (M-spike):** Antibodies or parts of antibodies found in unusually large amounts in the blood or urine of multiple myeloma patients. M-spike refers to the sharp pattern that occurs on protein electrophoresis when an M-protein is present. Synonymous with monoclonal protein and myeloma protein. See “Monoclonal.”
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.

Mobilizing agent: An agent injected into a patient or donor to trigger the release of bone marrow stem cells into the bloodstream.

Monoclonal: A clone or duplicate of a single cell. Myeloma develops from a single malignant plasma cell (monoclonal). The type of myeloma protein produced is also monoclonal; a single form rather than many forms (polyclonal). The important practical aspect of a monoclonal protein is that it shows up as a sharp spike (M-spike) in the serum electrophoresis test.

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

Myeloablation: The killing of bone marrow by radiation or chemotherapy. This term usually refers to the complete or near-complete destruction of the bone marrow.

Oncologist: A doctor who specializes in treating cancer. Some oncologists specialize in a particular type of cancer.

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 blood stem cells (PBSC): Stem cells collected from the blood. These cells are similar to stem cells found in the bone marrow. The term “peripheral” means that the cells come from blood outside of the marrow.

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.

Recurrence: The reappearance of a disease after a period of remission.

Red blood cells (RBC, erythrocytes): Cells in the blood that contain hemoglobin and deliver oxygen to and take carbon dioxide from all parts of the body. Red cell production is stimulated by a hormone (erythropoietin) produced by the kidneys. Myeloma patients with damaged kidneys don’t produce enough erythropoietin and can become anemic. Myeloma patients can also become anemic because of myeloma cells’ effect on the ability of the bone marrow to make new red blood cells.

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.

Regression: The shrinkage in size of a cancer or tumor.

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.

Stem cells (hematopoietic stem cells): The immature cells from which all blood cells develop. Normal stem cells give rise to normal blood components, including red cells, white cells, and platelets. Stem cells are normally located in the bone marrow and can be harvested for transplant.

Stem cell selection: A cell processing technology that is used to obtain a stem cell-enriched product and thereby reduce cancer cells in the transplant. Not used successfully for myeloma patients.
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.

**Tumor**: An abnormal mass of tissue that results from excessive cell division.

**White blood cells (WBC)**: General term for a variety of cells responsible for fighting invading germs, infection, and allergy-causing agents. These cells begin their development in the bone marrow and then travel to other parts of the body. Specific white blood cells include neutrophils, granulocytes, lymphocytes, and monocytes.

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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.