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Understanding **High-Dose Therapy with Stem Cell Rescue**



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A publication of the **International Myeloma Foundation**



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

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

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

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

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

Learn more about the ways the IMF is helping to improve the quality of life of myeloma patients while working toward prevention and a cure.

**Contact us at 818.487.7455 or 800.452.CURE,
or visit myeloma.org.**

Improving Lives **Finding the Cure®**

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What you will learn from this booklet

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

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

Understanding High-Dose Therapy with Stem Cell Rescue explains the rationale for, and process of, an important treatment option for some patients with myeloma. For eligible patients, high-dose therapy (HDT) with **stem cell** rescue (also known as "stem cell **transplant**") may be performed as part of a first treatment regimen or at the time of disease **relapse**. Transplant can provide significant **response** and survival benefits.

Background rationale for use of HDT with stem cell rescue

Myeloma cells and normal blood stem cells (known in medical terms as "hematopoietic" 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.

Melphalan, a **chemotherapy** agent belonging to the drug class of **alkylating agents**, 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 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.

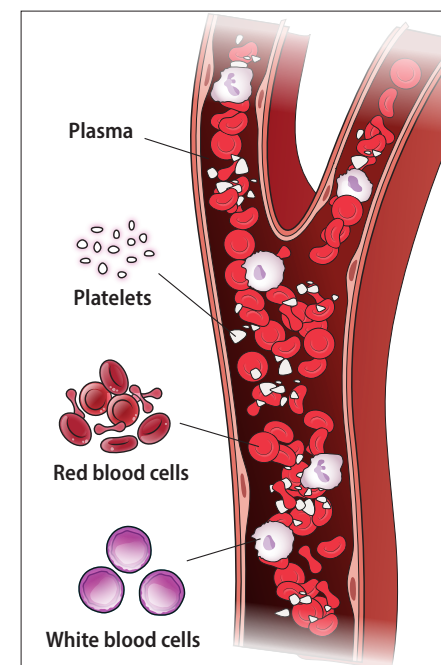
Normal blood stem cells are collected from the patient or donor through a process called **apheresis**. The harvested normal blood stem cells are frozen at -80 degrees Celsius and can be stored indefinitely at that temperature. After the patient receives high-dose melphalan, the frozen stem cells are 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 levels of melphalan in the blood and tissue 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)

"HDT with stem cell rescue" is the more accurate terminology. 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 autologous transplant) or twice (double or tandem transplant), although tandem transplantation has become less common in the era of effective novel therapies.

Figure 1. Blood vessel



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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 anti-cancer 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 stem cell 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. First, a single autologous transplant is performed to reduce the number of myeloma cells in the bone marrow. 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

HDT with stem cell rescue has been used as a treatment for myeloma for more than two decades. Transplant doctors attempt to "reduce the **tumor burden**" – to kill as many myeloma cells as possible – before collecting stem cells and administering HDT. Patients, therefore, receive **induction** therapy with various drugs before they begin the process of HDT with stem cell rescue. Even if there is minimal response to frontline therapy, 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 frontline therapy of transplant-eligible patients.

- The definitive results of the SWOG S0777 study comparing Velcade® (bortezomib) + Revlimid® (lenalidomide) + dexamethasone (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**. Therefore, VRd is the preferred frontline therapy currently recommended by the National Comprehensive Cancer Network (NCCN).

Other NCCN preferred options are:

- Revlimid + dexamethasone (Rd)
- Velcade + cyclophosphamide + dexamethasone (VCD, which is also known as CyBorD).

Other NCCN recommended therapies include:

- Velcade + Adriamycin® (doxorubicin) + dexamethasone (PAd)
- Kyprolis® (carfilzomib) + Revlimid + dexamethasone (KRd)
- Ninlaro® (ixazomib) + Revlimid + dexamethasone (IRd).

The NCCN also lists the following as "useful in certain circumstances":

- Velcade + dexamethasone (Vd)
- Velcade + thalidomide + dexamethasone (VTd)
- Velcade + thalidomide + dexamethasone + cisplatin + doxorubicin + cyclophosphamide + etoposide (VTD-PACE).

Since longer-term use of Revlimid may impair stem cell harvest, doctors advise that patients who are candidates for ASCT who are on frontline regimens that include Revlimid + dexamethasone should harvest stem cells after four cycles of treatment.

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

Important considerations

In general, stem cell transplant is an option for most myeloma patients upon completion of frontline therapy. However, since transplant is an intensive approach, older, frail patients, 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, initial therapy for three to six months should be with drugs that do not damage normal blood stem cells. 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. The Velcade + melphalan + prednisone (VMP) regimen, though not commonly used in the US, is an affordable and effective regimen still used outside the US.

Depth of response to induction therapy has generally been thought to influence the depth of response post-ASCT. Transplant doctors usually require a > 50% reduction in **monoclonal protein (myeloma protein, M-protein, M-spike)** 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. A Hackensack University Medical Center study of 496 patients, which was presented in December 2017 at the annual meeting of the American Society of Hematology (ASH), demonstrated that while having



progressive disease (PD) after induction therapy predicts for poorer overall survival, all other responses to induction therapy – complete response (CR), very good partial response (VGPR), partial response (PR), and stable disease (SD) – did not lead to statistically significant differences in overall survival.

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. More than half the time, PR will be improved to either VGPR or CR. The ultimate goal of transplant is to eliminate all residual myeloma cells that have not been killed during induction therapy. The state of having no minimal residual disease (MRD) is called “MRD-negative.” Many transplant clinical trials now include MRD testing of bone marrow using either a new type of flow cytometry (Next Generation Flow, or NGF) or a new type of DNA sequencing (Next Generation Sequencing, or NGS). Studies have demonstrated that patients who are MRD-negative have improved overall survival.

Updates from clinical trials

Results from the IFM 2009 randomized phase III clinical trial of 5 cycles of VRD induction followed by HDT with stem cell rescue, 2 cycles of VRD consolidation, and one year of Revlimid maintenance therapy versus 8 cycles of VRD followed by one year of Revlimid maintenance therapy indicate that the use of VRd followed by HDT and ASCT in newly diagnosed myeloma patients increases progression-free survival. In 2016, at 3 years of post-therapy follow-up, however, the overall survival curves for the patients who had VRd and then proceeded to ASCT were the same as those for patients who had VRd and did not proceed to transplant. The study data demonstrate that patients who were MRD-negative had improved overall survival, regardless of which arm of the study they were on. We await the 5-year overall survival data, which should be available in 2018.

A significant finding among studies of ASCT 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 clinical trial, with 758 transplant-eligible patients who were within 12 months of having started induction therapy and had no disease progression. These patients 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/ECOG/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, a 7.5% risk of **second primary malignancies (SPM)** 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 current NCCN preferred maintenance therapy is Revlimid. The NCCN guidelines list Velcade + dexamethasone maintenance therapy as “useful in certain circumstances.”

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 cancers among patients who were in the Revlimid maintenance arms. The increase in second cancers 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, the 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 clinical trial did demonstrate its safety and efficacy when given every other week. Clinical trials are now ongoing in which Ninlaro® (ixazomib), the first oral proteasome inhibitor, is being tested as post-transplant maintenance therapy.

Role of a second transplant

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

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

Step 1

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

Step 2

- **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.

Step 3

- **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 imaging studies as needed to determine the level of response.

Step 4

- **Review with the physician the pros and cons of HDT with stem cell rescue** (and/or stem cell harvesting without immediate transplant).
- 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 the response to induction therapy is deemed inadequate, then other therapy may be required before proceeding to transplant.

“Questions and answers” about HDT, as well as “Questions to ask the doctor” about the potential procedure, are listed later in this booklet.

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 filgrastim, pegfilgrastim, or 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** or **PBSC**):

- Giving standard growth factors alone.
- Giving growth factors with chemotherapy.
- 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 blood stream. These medications are administered subcutaneously (under the skin). This procedure is commonly known as a “shot.” The white cell growth factors 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

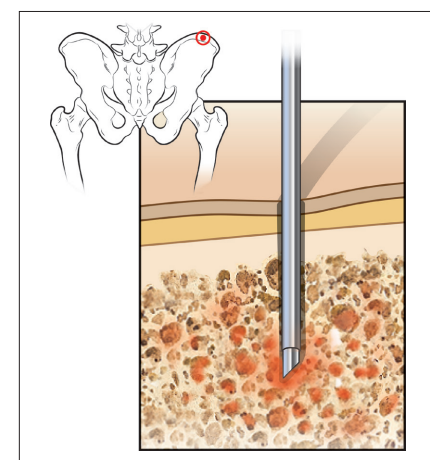
fourth or fifth day after starting the injections. The collections and injections are continued daily until sufficient stem cells are obtained. Typically, there is a plan to collect enough stem cells for at least two transplants, at a rate of at least 2–3 million (4–6 million total for two transplants) 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, so it 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 inpatient 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.

Figure 2. Bone marrow aspiration



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 reinfusing 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.

Is there a risk posed by myeloma cells that may be among the cells harvested for transplant?

To definitively answer this question, the European Bone Marrow Transplant (EMBT) group conducted a large, randomized clinical trial to evaluate any differences in relapse rate seen between transplant patients whose harvested stem cells were purged of myeloma cells and those whose harvested cells were not purged. The results, published in 2007 in *Haematologica*, definitively demonstrated that there was no difference in relapse rate between patients who received grafts with detectable tumor cells versus those receiving grafts with no detectable tumor cells. The prevailing theory is that it is not the myeloma cells among the harvested stem cells that cause relapse, but the myeloma cells that remain in the body (minimal residual disease, or MRD) that cause recurrence.

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 (blood-making stem 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 are 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 new 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?

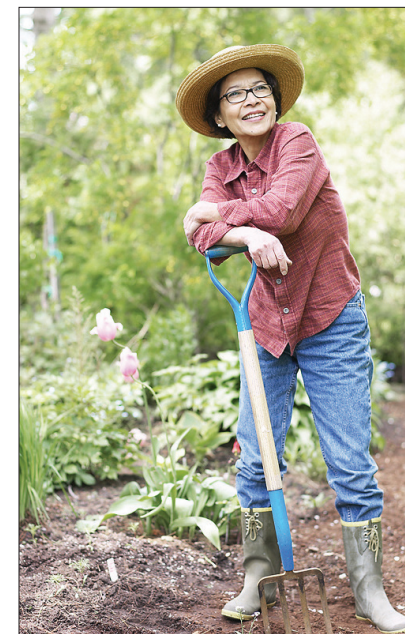
HDT with stem cell rescue is a treatment option for many myeloma patients; however, it is very rarely a cure. It can improve the duration of remission and survival. It can also provide a better quality of life for most patients. Not all patients with myeloma are candidates for this type of therapy. Many 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

- 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. A Hackensack Medical Center study of post-transplant outcomes for Hackensack patients who were fit and aged 75 to 81 years was presented at the 2017 ASH meeting. The study found that there was no difference in overall survival for fit patients 75 years and older at the time of transplant compared to patients younger than age 75.

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.

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. We await the final results of the previously referenced IFM 2009 trial comparing VRD plus Revlimid maintenance with and without ASCT. The long-term follow-up of this trial will clarify whether the timing of ASCT has an impact upon survival.

Most myeloma patients can take the time to gather the information needed to make an informed decision about what's right for him or her. Whether and when to have a transplant are questions to discuss with your doctor. 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 standard of care for transplant-eligible patients, 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 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 friend or a family member 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 light-headed. 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, current data from the Health Resources and Services Administration (HRSA) demonstrate that 99.1% of myeloma patients in the US are alive at 100 days following HDT with autologous stem cell transplant.

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.

- 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?

In closing

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

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

We encourage you to visit myeloma.org for more information about myeloma and to contact the IMF InfoLine with your myeloma-related questions and concerns. The IMF InfoLine consistently provides callers with the most up-to-date and accurate information about myeloma in a caring and compassionate manner. IMF InfoLine specialists can be reached at InfoLine@myeloma.org or 818-487-7455 or 800-452-CURE.

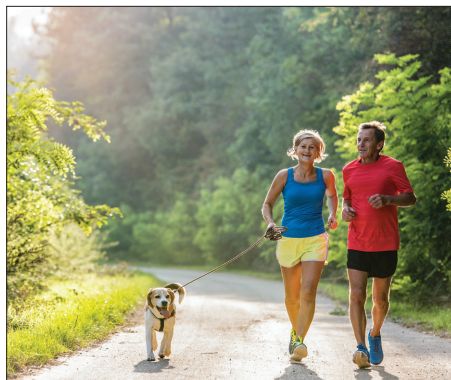
Terms and definitions

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 from red blood cells. The red blood cells are transfused back into the patient or donor. The portion containing white blood cells includes the rare blood cell-making (hematopoietic) stem cells.

Beta-2 microglobulin (also called β 2-microglobulin, β 2M, or β 2M):

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 β 2M. At the time of relapse, β 2M can increase before there is any change in the myeloma protein level. Factors such as viral infection can sometimes produce elevated serum β 2M levels.



Blood stem cells: Stems cells in the bone marrow that are responsible for making all the blood cells. The medical term is “hematopoietic” stem cells.

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

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 hollow-bore 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.

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

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 CD34-positive laboratory marker on the surface of hematopoietic stem cells is used to select and to quantify the stem cells. A specified minimum number of CD34+ stem cells is 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 receives the standard treatment or placebo (no treatment).
- **Experimental group** – The arm of a randomized trial that gets the new treatment.
- **Randomized clinical trial** – A research study in which subjects are randomly assigned to receive a particular treatment or not.
- **Arm** – One of the treatment groups of a randomized trial. The majority of randomized trials have two, but some have more.

- **End point** – The goal of the trial; what a clinical trial is trying to measure or find out. Typical end points include measurements of toxicity, response rate, and survival.
- **Double blind** – Aspect of a randomized trial in which neither the participant nor the investigator knows the arm of the trial to which the patient is assigned. The purpose is to eliminate any bias in the reporting of results.
- **Phase I trial** – A trial designed to determine the maximum-tolerated dose (MTD) of a new drug or a new combination of drugs. It is usually the first human testing of a new treatment, although in phase I trials of combination therapies, the individual elements may already have been well tested. Patients in phase I trials generally have advanced cancer that is refractory to all standard treatment. In a typical phase I trial, successive groups (“cohorts”) of 3 to 6 patients are given the treatment. All patients in a cohort get the same dose. The first cohort typically gets a very low dose, and the dose is raised in each subsequent cohort until a set number of patients experience dose-limiting toxicity (DLT). The dose level used for the previous cohort is then taken to be the MTD. This dose is then used in a phase II trial.
- **Phase II trial** – A trial designed to determine the response rate of a new therapy that has already been tested in phase I trials. Typically, 14 to 50 patients with one type of cancer are treated to see how many have a response. Patients are usually required to have advanced cancer that is refractory to any standard treatment. In addition, patients must have measurable disease. If results from a phase II trial are promising enough, the treatment may then be tested in a phase III trial. If the results are obviously much better than the standard treatment, then it may not be necessary to do a phase III trial, and the treatment may be approved based on phase II trial results.
- **Phase III trial** – A trial designed to compare two or more treatments for a given type and stage of cancer. The end point of a phase III trial is usually survival or disease-free survival. Phase III trials are usually randomized, so patients don’t choose which treatment they receive. A typical phase III trial has 50 to thousands of patients. Some phase III trials compare a new treatment that has had good results in phase II trials with an older, well known, standard treatment. Other phase III trials compare treatments that are already in common use. Some treatments in phase III trials may be available outside the clinical trial setting.
- **Phase IV trial** – Even after a drug has been approved by the United States Food and Drug Administration (FDA) for use in a particular

indication, there may be need for additional studies. Phase IV clinical trials may be required by regulatory authorities or may be undertaken by the sponsoring company for a variety of reasons. For example, safety surveillance is designed to detect any rare or long-term side effects over a larger patient population and longer time period than was possible during the phase I-III clinical trials.

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, or to treat low white cell count caused by therapy.

Efficacy: 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): An immune-related reaction of donated tissue against the recipient’s own tissue.

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

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

Immune system: The body’s defense system from pathogens and foreign substances destroys infected and malignant cells, and removes cellular debris. The immune system includes white blood cells and organs and tissues of the lymphatic system.

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: A specific term used for the initial treatment given to a patient in preparation for an autologous stem cell transplant (ASCT). Also see **“Frontline therapy”** and **“Line of therapy.”**

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

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

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 cells are derived from a “monoclonal,” a single malignant plasma cell in the bone marrow. 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) on the protein electrophoresis test.

Monoclonal protein (myeloma protein, M-protein, M-spike):

An abnormal protein produced by myeloma cells that accumulates in and damages bone and bone marrow. Antibodies or parts of antibodies found in unusually large amounts in the blood or urine of myeloma patients. A monoclonal spike (M-Spike), the sharp pattern that occurs on protein electrophoresis, is the telltale indicator of M-protein in the blood, a marker for the activity of myeloma cells. See **“Monoclonal.”**

Multiple myeloma: A cancer of the bone marrow plasma cells, white blood cells that make antibodies. 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): The median number of individuals in a group who are alive after a particular duration of time. OS is often used as a measure of treatment efficacy in clinical trials. The lengthening duration of OS in myeloma trials makes it a difficult endpoint to use, leading to the effort to validate minimal residual disease status as a new endpoint.

Peripheral blood stem cells (PBSC): Stem cells collected from the circulating 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 abnormal antibodies that lack the ability to fight infection. These abnormal antibodies are the monoclonal protein, or M-protein, that functions as a tumor marker for myeloma. The presence of malignant plasma cells in the bone marrow can lead to organ and tissue damage (anemia, kidney damage, bone disease, and nerve damage).

Platelets: One of the three major types of blood cells, the others being 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 length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. In a clinical trial, measuring the PFS is one way to determine how well a new treatment works. Also called PFS. See **“Progressive disease.”**

Progressive disease: Myeloma that is becoming worse or relapsing, as documented by tests. Defined as an increase of $\geq 25\%$ 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, deliver oxygen to all parts of the body, and take away carbon dioxide. 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 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 $\leq 5\%$ plasma cells in bone marrow. CR is not the same as a cure.
- **Very good partial response (VGPR)** – VGPR is less than CR. VGPR is serum M-protein and urine M-protein detectable by immunofixation but not on electrophoresis, or 90% or greater reduction in serum M-protein, plus urine M-protein less than 100 mg per 24 hours.
- **Partial response (PR)** – PR is a level of response in which there is at least a 50% reduction in M-protein, and reduction in 24-hour urinary M-protein by at least 90% (or to less than 200 mg per 24 hours).

Second primary malignancy (SPM): A second, unrelated primary cancer that is diagnosed after a person has been treated for cancer. Certain types of treatment may increase the risk of a second primary malignancy.

Side effect: Unwanted effect caused by a drug. Also known as adverse reaction or adverse event (AE).

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 blood-making stem cells from a patient's circulating blood (not from the bone marrow), which are then frozen and stored. The patient receives high-dose chemotherapy to destroy the cancer cells, but healthy blood cells are also destroyed. The frozen stem cells are then defrosted and returned to the patient, where they can produce new blood cells to replace cells destroyed by the treatment.
- **Autologous transplant** – A procedure in which stem cells are removed from a patient's blood and then are given back to the patient following intensive treatment.
- **Bone marrow transplant** – This term refers to the process of collecting stem cells from the bone marrow and infusing them into a patient. This term is used less frequently today in myeloma as stem cells are now collected from the peripheral (circulating) blood.
- **Allogeneic (allograft) transplant** – The infusion of bone marrow or stem cells from one individual (donor) to another (recipient). A patient receives bone marrow or stem cells from a compatible, though not genetically identical, donor. An HLA blood test is done to determine if a patient has a potential donor match. A donor may be a family member or may be obtained through a donor registry such as the National Marrow Donor Program (NMDP). Rarely, donor cells may be obtained from an umbilical cord blood bank. The donor's immune system cells recognize the recipient's myeloma cells as foreign, and attack them. Unfortunately, the donated cells also attack other tissues in the

recipient's body, causing graft-versus-host disease (GVHD), which may be fatal.

- **Reduced-intensity conditioning (RIC) allo transplant** – A newer and, for myeloma, safer technique than an allogeneic transplant. RIC is a non-myeloablative, reduced-intensity “mini-allo” transplant performed within 180 days after a standard autologous transplant.
- **Tandem transplant** – A term used to indicate two autologous transplants done in succession. Tandem transplants are usually planned with 3-month to 6-month intervals between transplants. Tandem transplantation has become less common in the US in the era of effective novel therapies.
- **Matched unrelated donor (MUD) transplant** – Refers to a stem cell transplantation procedure in which the patient and the stem cells are genetically matched but are not from family members. This procedure is not recommended for myeloma patients because it carries an unacceptably high mortality rate from graft-versus-host disease (GVHD).
- **Syngeneic transplant** – The infusion of bone marrow or stem cells from one identical twin into another.
- **Umbilical cord blood transplant** – Stem cells obtained from the umbilical cords of newborns. These are frozen and stored in cord blood banks. Because multiple cords are needed to provide enough stem cells for an adult transplant, the risk of graft-versus-host disease is increased with this type of transplant, making it even riskier for myeloma patients.

Tumor: An abnormal mass of tissue that results from excessive cell division. In myeloma, a tumor is referred to as a plasmacytoma.

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 bone marrow and then travel to other parts of the body. Specific white blood cells include neutrophils, basophils, eosinophils, lymphocytes, and monocytes.



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

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

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

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

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

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

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