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Improving Lives • Finding the Cure®

Understanding High-Dose Therapy with Stem Cell Rescue

A Publication of the International Myeloma Foundation

Dedicated to improving the quality of life of myeloma patients while working toward prevention and a cure.

Multiple Myeloma
Cancer of the Bone Marrow

Improving Lives • Finding the Cure®

About the International Myeloma Foundation

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

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

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

SUPPORT Our toll-free InfoLine at 800-452-CURE (2873) is staffed by coordinators who answer questions and provide support and information via phone and email to thousands of families each year. The IMF sustains a network of more than 150 support groups and offers training for the hundreds of dedicated patients, caregivers, and nurses who volunteer to lead these groups in their communities.

ADVOCACY The IMF Advocacy program trains and supports concerned individuals to advocate on health issues that affect the myeloma community. Working both at the state and federal level, the IMF leads two coalitions to advocate for parity in insurance coverage. Thousands of IMF-trained advocates make a positive impact each year on issues critical to the myeloma community.

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

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The *Understanding* series

The IMF's *Understanding* series of booklets encompasses the 10 Steps to Better Care® template. This means that on the IMF website myeloma.org and in other formats, the information is distributed into appropriate "steps" categories. Articles referencing clinical trial results, guidelines, videos of authors discussing data, and much more can be viewed or downloaded electronically.

For any questions or concerns, or to request a hard copy of any of our publications, the IMF InfoLine is available by calling 800-452-CURE (2873), toll-free in the US and Canada, or 818-487-7455 from other parts of the world, or via email at TheIMF@myeloma.org. We look forward to hearing from you.

This *Understanding* booklet is intended only to provide you with general information that will guide you in discussions with your healthcare team. It is not meant to replace the advice of your doctor or nurse. Your doctor or nurse can answer questions related to your specific treatment plan. Words appearing in **bold type** are explained in the "Terms and definitions" section at the end of this booklet.

Introduction

High-dose therapy (HDT) with stem cell rescue is an important treatment option for eligible patients with **multiple myeloma** (which will be referred to as "myeloma" for the sake of brevity). 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. HDT with stem cell rescue, or "stem cell transplant," as it is sometimes known, is Step 5 in the IMF's 10 Steps to Better Care. 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 and white blood cells 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, 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. 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 collected and saved before melphalan is administered.

Normal blood stem cells are collected or "harvested" from the patient or donor through a process called **apheresis**. The harvested normal blood stem cells are frozen at –80 degrees Celsius. They 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 transplant," or "stem cell rescue," 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, or, more accurately, 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**).
- **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.
- **Allogeneic stem cell transplant:** Stem cells are harvested from a family member who is not an identical twin, but is well-matched by tissue (HLA) typing. Usually the best match is a sibling. Again, the stem cells are infused after HDT. Part of the anti-cancer effects of this type of transplant derive from the effect of high-dose chemotherapy on the disease, and part from the effect of the grafted (or transplanted) cells. The transplanted cells recognize the cancer cells as foreign, and attack and kill them. This is called "graft versus myeloma effect." The problem with donor 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. This procedure is seldom used in 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 myeloma burden, 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
- **Matched Unrelated Donor (MUD) stem cell transplant:** Stem cells are harvested from a non-family member. In this case, the stem cells are rarely a 100% tissue (HLA) match. Hence the term "mismatch" is frequently used in this situation. A MUD transplant carries a much higher risk of GVHD than does a related donor transplant, and is a much higher-risk procedure overall.

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 over 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 "front-line" 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 front-line therapy. **Typical frontline regimens currently utilized are:**

- Velcade® (bortezomib) plus dexamethasone with or without a third drug, such as Revlimid®/lenalidomide (R), Thalomid®/thalidomide (T), or Cytoxan®/cyclophosphamide (C). The acronyms for these common regimens are, respectively, VRD, VTD, and VCD (which is also known as CyBorD).
- Two-drug IMiD® (**immunomodulatory agent**) regimens such as Thalomid or Revlimid plus dexamethasone can also be used. Since longer-term use of Revlimid may impair stem cell harvest, doctors advise that patients on frontline Revlimid plus 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, patients 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 more 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 3 to 6 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 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 level).

Improved outcomes

With the advent of more frequent VGPR or CR with novel frontline therapies, the added benefit of HDT in this setting is coming under closer scrutiny. HDT has conferred statistically significant benefit following traditional (as opposed to novel) chemotherapy induction using, for example, VAD chemotherapy. However, novel therapy combinations can produce higher levels of VGPR and CR than traditional chemotherapy. Results from two studies comparing novel therapy alone with novel therapy plus HDT and stem cell rescue were presented at the American Society of Hematology (ASH) in December 2011. The early data suggest that despite increased toxicities, novel therapy followed by high-dose melphalan plus stem cell rescue may improve not only progression-free, but overall survival. Further studies and longer-term follow-up are needed to confirm this early data.

Role of consolidation and maintenance

A particular benefit of HDT is that added response can occur within a few weeks of the procedure. If CR or VGPR occur, then such patients can be followed and monitored without the absolute need for ongoing anti-myeloma **maintenance therapy**. Patients undergoing HDT also tend to be in remission longer and thus to have a longer period before retreatment is required. Thus, the potential ongoing toxicity, inconvenience, and expense of maintenance can be avoided. However, depending upon the patient's individual disease characteristics, including the results of chromosome testing, maintenance therapy and/or other (**consolidation**) therapy may be recommended after transplant.

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 does appear to confer benefit.

Factors influencing outcomes

It has been generally accepted that patients achieving better response, such as CR or VGPR, have better outcomes (versus, for example, partial response [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 ≥2 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.
- 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.

II.

- ***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.

III.

- **Assess the response to treatment** with each cycle of therapy (usually every 3 to 4 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.

IV.

- **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 or follow-up treatment is required.
- **If there is <50% response**, 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 the brochure.

How stem cells are collected

Blood stem cells are located in the bone marrow. Until about twenty 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 fifty to one hundred **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 – CSFs") such as Neupogen® or Neulasta® 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]): 1) giving standard growth factors alone, 2) giving growth factors with chemotherapy, or 3) 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 (Neupogen®, Neulasta®, Leukine®) are the ones used in high doses for stem cell harvest or "mobilization." The injections are given daily for 3 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, which is at least 2–3 million per transplant (4–6 million total) stem cells per kilogram of the patient's body weight.

2. Using chemotherapy plus growth factors

Cytoxan® (cyclophosphamide) is the most commonly used chemotherapy in this setting 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 Cytoxan, in addition to growth factors. The doctor will explain the potential benefits and side effects of Cytoxan if it is administered to mobilize the blood stem cells. Primarily, the Cytoxan 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 Cytoxan is that it is actually treatment for the myeloma. A disadvantage of Cytoxan 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. Some 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 2 to 5 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 4 days prior to receiving Mozobil. Mozobil is injected subcutaneously approximately 11 hours before the planned stem cell collection for up to 4 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 for a transplant, 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 incorporating Mozobil in combination with growth factors have successful engraftment.
- An ASH 2011 poster by Adel *et al* from Memorial-Sloan Kettering Cancer Center demonstrated that Mozobil upfront for stem cell mobilization may be more cost effective than the current widely used approach employing Cytoxan, 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 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/leukapheresis

Prior to the start of apheresis, a thin flexible plastic tube called a catheter is inserted through the skin and into a vein so that blood can be taken out. 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 (Tylenol®). 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 3 to 4 hours each day for 1 to 5 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 peripheral blood (or occasionally direct bone marrow material) is taken to the processing laboratory, which is usually located within the hospital or local blood bank. In the processing laboratory, the bone marrow or blood cells are prepared for freezing (cryopreservation). The stem cells are mixed with a solution containing the chemical DMSO (dimethyl sulfoxide) to prepare the stem cells for freezing. 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 1 to 4 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 (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. 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 stem cell transplant

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 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 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 be monitored at the hospital. 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 infection (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 be given 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 (Neupogen, Neulasta, Leukine) 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 fulltime 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 not 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

- type of myeloma
- disease stage
- disease aggressiveness
- responsiveness to treatment
- serum albumin
- beta-2 microglobulin
- chromosome 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.

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. Recent clinical trial results suggest that frontline therapy that includes the anti-myeloma agents thalidomide, Revlimid, and/or Velcade may result in response rates and duration of response comparable to those of HDT with stem cell rescue, allowing some patients to postpone HDT until later in the

course of the disease. This is undergoing further investigation. Remember, in most cases, having myeloma gives the patient the time to do some homework and to gather the information needed to make an informed decision about what's right for him or her. For example, one could have stem cells harvested and saved for a later treatment. This leaves the patient open to other more immediate treatment options. These are things to discuss with the doctor. It's 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.

Transplants and clinical trials

A single autologous stem cell transplant is currently considered the standard of care for patients with myeloma. However, there are a number of novel approaches that are being evaluated to try to improve patient outcomes. These are being conducted as clinical trials. These include the following:

A tandem autologous transplant is an approach that utilizes two autologous transplants. Sufficient stem cells are collected prior to the first transplant. Three to six months after the first transplant, the patient receives a second similar course of HDT followed by infusion of the other half of the stored stem cells. Preliminary data indicates that tandem transplants result in improved disease control and survival in patients who do not experience either VGPR or CR following first autologous transplant.

Sequential autologous transplant followed by a "mini" (non-myeloablative) allogeneic transplant involves HDT with an autologous transplant to destroy the majority of the myeloma cells, followed 2 to 4 months later by an allogeneic mini-transplant to allow the donor's immune cells to destroy any remaining myeloma cells. Once the allogeneic stem cells grow, the donor's immune cells attack the myeloma (the "graft vs. myeloma effect" mentioned earlier in this booklet). This is a form of immunotherapy. The risk of this procedure is GVHD, which can be very serious and potentially life-threatening. Autologous stem cell transplant followed by mini allogeneic transplant (an "auto-mini allo") has been studied in the clinical trial setting in myeloma patients for a number of years. In 2006, an IFM (French myeloma group) study reported no overall survival or progression-free survival benefit with auto-mini allo vs. tandem auto. In 2007, Bruno *et al* found improved survival for patients receiving auto-mini allo vs. tandem auto. At the ASH meeting in December 2010, a large BMT CTN study of tandem autologous transplant vs. auto-mini allo (Krishnan *et al*) with 710 patients at 43 centers found no difference in progression-free or overall survival. Given the lack of remission or survival benefit and the increase in treatment-related mortality in the auto-mini allo patients, the International Myeloma Working Group currently recommends that mini allo be performed only in the context of clinical trials.

Maintenance therapy is an approach that involves lowered doses of anti-myeloma drugs to maintain longer remission and survival after a transplant. Currently, some of the drugs being evaluated as maintenance therapies in clinical trials include Revlimid, prednisone, Velcade, and dexamethasone, alone or in combinations.

The most compelling and largest maintenance trials recently conducted are two phase III post-transplant studies from the United States (CALGB 100104) and France (IFM 2005-02) which explored the use of maintenance Revlimid. Their results were presented at the ASH meeting in December 2010, where both studies at that time demonstrated progression-free survival (PFS) twice as long for those patients who had been randomized to receive maintenance Revlimid. At the ASH meeting in December 2011, follow-up data from these trials was presented. Both trials continued to demonstrate a doubled rate of PFS for patients on the Revlimid arm over that of patients not randomized to Revlimid maintenance, and an overall survival (OS) benefit was reported in the CALGB trial.

The other notable topic of discussion and controversy regarding these trials was that both post-transplant Revlimid maintenance trials, as well as an Italian trial for non-transplant patients who were treated with Revlimid+melphalan+prednisone and then given Revlimid maintenance therapy (the MM015 trial, with MPR-R), reported higher rates of second malignancies among patients who were in the Revlimid maintenance arms. The increase in second malignancies in these trials remains an area of study, since there has been no increase in second cancers reported among relapsed and refractory patients treated with Revlimid. A prevailing theory is that the increase in second cancers could arise from the use of melphalan, an alkylating agent which was used as HDT in both the CALGB and IFM trials, and its potentially carcinogenic effect in combination with Revlimid.

Based on the evidence from these phase III trials, the National Comprehensive Cancer Network (NCCN) recently 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. Given the obvious advantages and risks of post-transplant maintenance therapy, each patient must discuss the use of maintenance therapy with his or her oncologist, who will evaluate individual risk factors and the response to transplant before making a recommendation.

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 (Cytoxan®) 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 4 to 6 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 the International Myeloma Foundation.

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 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. Recent evidence indicates that this technology is not effective in myeloma. Therefore, very few centers currently 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 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. *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.

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 (Advil®, Motrin®), may be harmful to a patient with myeloma.

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 Cytoxan 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:

Terms and definitions

Alkylating agent: A chemotherapeutic agent such as melphalan (Alkeran) or cyclophosphamide (Cytoxan). Alkylating refers to the way in which these agents crosslink the DNA of myeloma cells and block cell division.

Allogeneic (allograft) stem cell transplant: Refers to stem cells that are taken from a donor and given to the patient. Most allogeneic stem cell transplants are performed using donor peripheral blood stem cells. Conventional allogeneic transplants for myeloma patients are rarely performed in the US due to excessive risk to the patient. A newer and, for myeloma, safer technique (discussed below) is a non-myeloablative or "mini-transplant" that is currently being evaluated in clinical trials. To determine if a patient has a potential donor match, a special blood test call HLA testing is done. 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.

Anemia: A decrease in the normal number of red blood cells, usually below 10 g/dL with over 13–14 g/dL being normal. Myeloma in the bone marrow blocks red cell production, thus causing anemia, the symptoms of which are shortness of breath, weakness, and tiredness.

Apheresis/Leukapheresis: 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 contains the rare stem cells.

Autologous peripheral blood transplantation (see autologous stem cell transplantation): A procedure in which a patient's blood is collected by apheresis, stored, and re-infused following HDT.

Autologous (autograft) stem cell transplantation (ASCT) : Refers to stem cells that are collected from the patient and are given back to the same patient after he or she receives HDT. Most stem cell transplants in myeloma are autologous transplants.

Beta-2 microglobulin (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. For these patients, β2M testing cannot be used to monitor the disease. At the time of relapse, β2M can increase before there is any change in the myeloma protein level. Therefore, 90% of the time, β2M testing is very useful for determining disease activity.

Bone marrow: A soft spongy tissue, found in most large bones, that produces red and white blood cells and platelets.

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

Bone marrow aspiration: The removal, by needle, of a sample of tissue from the bone marrow.

Bone marrow transplant: Obtained from the bone marrow of the patient or the donor. Very few bone marrow transplants are currently performed due to the availability of peripheral blood stem cells. Rarely, bone marrow may be collected for patients who are unable to collect sufficient number of stem cells from the peripheral blood.

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

Chemotherapy: Drugs that are used to kill cancer cells.

Colony-stimulating factor (CSF): Proteins that stimulate the development and growth of blood cells. Neupogen, Neulasta, and Leukine 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.

Complete response (CR): CR is the absence of myeloma protein from the serum and/or urine by standard testing; absence of myeloma cells from the bone marrow and/or other areas of myeloma involvement; clinical remission and improvement of other laboratory parameters to normal. CR is not the same thing as a cure.

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.

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

Immune system: The function of a number of related body organs that protect the body from disease organisms, other foreign bodies, and cancers.

Immunomodulatory agent: Drug that affects, enhances, or suppresses the immune system.

Immunoglobulin: A protein produced by plasma cells (a type of white blood cell) which helps fight infection. Also known as an antibody.

International Staging System (ISS): the most current staging system for myeloma, the ISS is the result of the collaboration of more than twenty research institutions world-wide.

Lytic bone lesions: Holes in the bone.

M-spike: Antibodies or parts of antibodies found in unusually large amounts in the blood or urine of 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.

Monoclonal protein (M-protein): An abnormal protein produced by myeloma cells which accumulates in and damages bone marrow. A high level of M-protein indicates that myeloma cells are present in large numbers.

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.

Multiple myeloma: A cancer arising from the plasma cells in the bone marrow. The plasma cells in patients with myeloma form abnormal antibodies, possibly damaging the bone, bone marrow, and other organs.

Peripheral blood stem cell (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.

Peripheral blood stem cell (PBSC) transplant: Obtained from the patient or donor bloodstream. Using PBSC for transplantation allows for easier and safer collection of stem cells and faster recovery after the transplant than bone marrow transplant.

Plasma cell: A type of white blood cell that produces antibodies.

Plasmacytoma: A tumor made up of cancerous plasma cells.

Platelets: Granule-containing cellular fragments critical for blood clotting and sealing of wounds. Platelets also contribute to the immune response.

Red blood cell: A blood cell that carries oxygen from the lungs throughout the body.

Remission or response: Remission and response are used interchangeably. Complete remission (CR) is the common abbreviation for both. CR is defined as the absence of myeloma protein from serum and/or urine by standard testing, absence of myeloma cells from the bone marrow and/or other areas of myeloma involvement, clinical remission, and improvement of other laboratory parameters to normal.

Stem cell (hematopoietic stem cell): Normal (hematopoietic, or blood-making) stem cells give rise to normal blood components, including red cells, white cells, and platelets. These stem cells are normally located in the bone marrow and can be harvested for a 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.

Syngeneic stem cell transplant: Refers to stem cells that are taken from an identical twin of the patient.

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 3 to 6 month intervals between transplants.

Transplantation (transplant): Stem cells are used to rescue the patient's blood-forming potential following a very high-dose chemotherapy and/or radiation treatment. Transplant is not a treatment but a method of support to make high-dose chemotherapy treatment possible.

Umbilical cord blood transplant: Stem cells obtained from the umbilical cords of newborns. These are frozen and stored in cord blood banks.

Very good partial response (VGPR): A response that is not quite a complete response (that is, not 100%), but has a 90% or greater reduction in serum M-protein.

White blood cell: One of the three major cell types in the blood. There are several types of white cells (i.e., neutrophils, lymphocytes, and monocytes).

For references, please see the IMF's website myeloma.org (Step 4 in the 10 Steps to Better Care®).

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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 MM. Visit the IMF website myeloma.org or call the IMF InfoLine at 800-452-CURE (2873), which is staffed by trained information specialists, with your questions or concerns. The IMF is here to help.

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