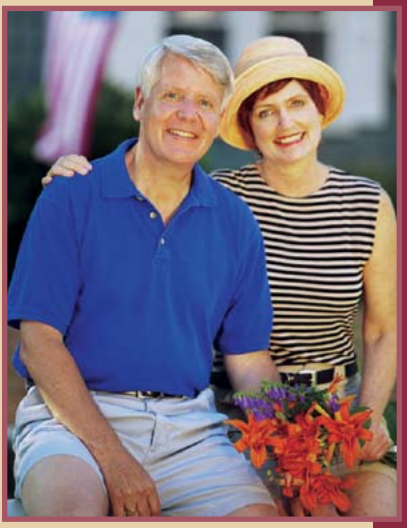
Understanding Stem Cell Transplant



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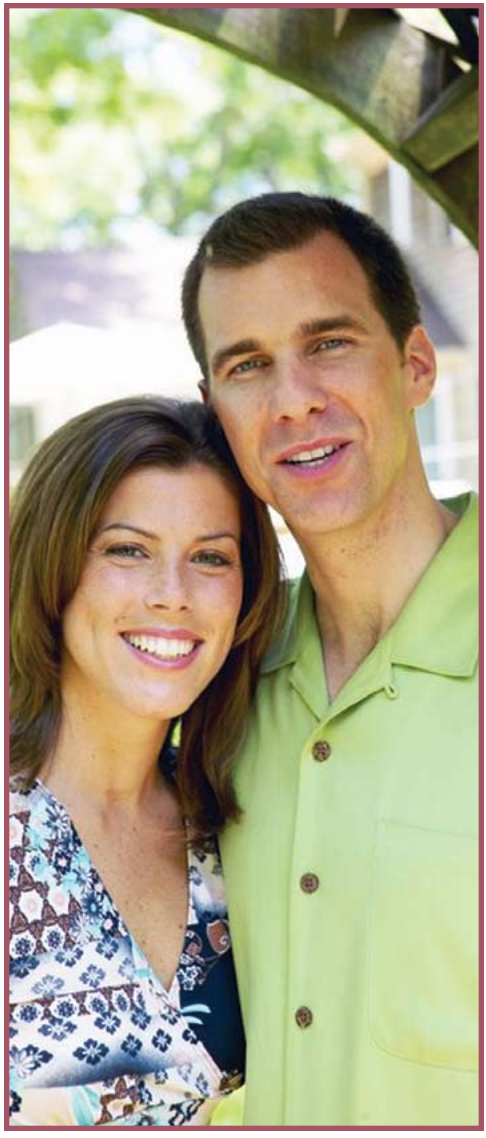


Introduction

This booklet explains important details about the **transplant** of **blood stem cells**. 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 high-dose chemotherapy with blood stem cell rescue as part of the treatment for myeloma?
- What is the role of high-dose chemotherapy versus novel therapies? Can they be used in combination?

The booklet is meant to provide you with general information only. It is not meant to replace the advice of your doctor, nurse, or other healthcare practitioners. Your healthcare team can answer specific questions related to your personal treatment plan. All words that appear in **bold type** are defined in the glossary at the back of this booklet.

What is Multiple Myeloma?

Multiple myeloma (also known as myeloma and **plasma cell** myeloma) is a cancer of the **immunoglobulin**-producing plasma cells found in the **bone marrow**. It is a cancer that involves the **immune** system. The cancerous plasma cells, or myeloma cells, rarely enter the blood stream. The myeloma cells accumulate in the bone marrow, causing the following:

- Disruption of normal bone marrow function, most commonly causing **anemia** (a low level of **red blood cells** in the bloodstream),

although reduction in **white blood cell** and **platelet** counts can also occur

- Damage to bone surrounding accumulated myeloma cells
- Release of an abnormal protein, **monoclonal protein** (**M protein**), into the blood stream and/or urine
- Suppression of normal immune function, observed as reduced levels of normal immunoglobulins and increased susceptibility to infection

Myeloma cells can also grow in the form of localized tumors or **plasmacytomas**. Plasmacytomas may be single or multiple and either medullary (confined within bone marrow and bone) or extramedullary (outside of the bone). When there are multiple plasmacytomas inside or outside bone, this condition is also called *multiple myeloma*.

The Stages of Multiple Myeloma

Confronted with a diagnosis of multiple myeloma, a doctor (usually a hematologist/oncologist) must determine the stage of the disease. Disease staging will help determine which parts of the body have been affected and how severely. This will allow the doctor to decide upon the best treatment options.

Stage I (low cell mass): Early disease. The bone structure appears normal or close to normal on x-ray images; the number of red blood cells and amount of calcium in the blood are normal or close to normal; and the amount of M protein is very low.

Stage II (intermediate cell mass): An intermediate stage between stage I and stage III.

Stage III (high cell mass): More advanced disease. One or more of the following are present:

- Anemia
- A high level of calcium in the blood
- More than 3 areas of advanced **lytic bone lesions** (destructive holes in the bones)
- A high level of M protein in the blood or urine

A new prognostic factor system called the **International Staging System (ISS)** was recently introduced. It is based upon the levels of two blood proteins: **beta-2 microglobulin ($ß_2$M)** and albumin; the levels of these proteins predict overall outcome with myeloma treatment.

Stage I (best outcome)

- Serum albumin ≥ 3.5 g/dl
- $ß_2$M of < 3.5 mg/l

Stage II

- Serum albumin and $ß_2$M both < 3.5 or
- Serum $ß_2$M between 3.5 and 5.5 mg/l

Stage III

- Has more elevated serum $ß_2$M of ≥ 5.5mg/l

Multiple myeloma is a serious cancer, but it is very treatable. Many patients experience a series of responses, relapses, and remissions. New treatments may extend the average survival of 5 years or more for patients diagnosed with multiple myeloma. Patients with myeloma can live over 10 years; some live over 20 years.

Background Rationale for Use of High-Dose Chemotherapy 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 normal red and white cells as well as platelets. Any drugs reaching the bone marrow microenvironment can therefore damage both the myeloma cells and the normal blood stem cells.
- **High-dose melphalan seriously damages normal stem cells.** High-dose melphalan is a very effective treatment against myeloma, but 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, techniques for collecting and saving normal blood stem cells before administering the melphalan have been developed.
- **Stem cells can be collected (harvested) and infused after treatment to replace those damaged by treatment.** Normal blood stem cells are collected or "harvested" from the patient or donor before administration of the melphalan. The harvested normal blood stem cells are returned to the blood circulation by a process similar to blood transfusion. By a seeding process, the stem cells pass from the circulation back into the bone marrow where they divide and grow to repopulate the normal bone marrow space. Approximately 36–48 hours after administering the melphalan, 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 at the best time is called "stem cell transplant."

Types of Stem Cell Transplant

- **Autologous stem cell transplant.** Stem cells are harvested from a myeloma patient 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 high-dose therapy, 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. Again, the stem cells are infused after the high-dose therapy.
- **"Mini" or non-myeloablative allogeneic transplant** is a newer and safer procedure than full allogenic transplant. It involves the use of reduced intensity chemotherapy in combination with an allogeneic stem cell transplant.
- **Matched Unrelated Donor (M.U.D.) 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.

How Stem Cell Transplant is Used as a Part of Myeloma Therapy

- Following diagnosis, several options are available for initial or front-line therapy.

  Typical frontline regimens currently utilized are:

  - Thalidomide plus dexamethasone
  - Dexamethasone alone
  - Various dexamethasone combinations incorporating an anthracycline (e.g., Adriamycin® or Doxil® as part of VAD or VDD), Velcade®, or more recently Revlimid® combinations. Cytoxan® can also be used as part of the initial approach.

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

- **In general, stem cell transplant is a potential 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 to be a potential option, the most important caution is to avoid use of melphalan by mouth 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 pills as a part of initial therapy can be a simple and very effective treatment.
- **Stem cells are harvested and transplant is performed after initial or frontline therapy.** This means that treatment is used to achieve response and at least some degree of remission before proceeding to therapy with high-dose melphalan and blood stem cell rescue.

Major details include:

- **Initial therapy for 3–6 months** with drugs that do not damage normal blood stem cells.
- **Ideally, response is achieved with >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 to be performed.

What are the Benefits of High-Dose Chemotherapy with Blood Stem Cell Rescue?

■ **Further improvement in the level of response** achieved with frontline therapy is a major advantage of high-dose therapy with stem cell transplant. 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).

■ **Enhanced benefit in patients who have already achieved VGPR or CR.** With the advent of more frequent VGPR or CR with novel frontline therapies, the added benefit of high-dose therapy in this setting is coming under closer scrutiny. High-dose chemotherapy has conferred statistically significant benefit following traditional chemotherapy induction using, for example, VAD chemotherapy. However, novel therapy combinations can produce high levels of VGPR and CR. The additional benefit of high-dose therapy for a patient who has already achieved VGPR or CR is under investigation.

■ **Enhanced response without the necessity of maintenance.** A particular benefit of high-dose therapy 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 maintenance anti-myeloma therapy. Patients undergoing high-dose therapy 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 individual details, including chromosome testing, maintenance therapy and/or other (consolidation) therapy may be recommended after transplant.

■ **Potential benefit with double or tandem transplantation.** If CR or ≥VGPR are not achieved with a single autologous transplant, then a second autologous (or an alternate transplant such as "mini allogeneic" [see above]) can be offered. Continuing in the attempt to achieve ≥VGPR with the second transplant does appear to confer benefit.

■ **Significance of achieving CR or VGPR.** 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 Stem Cell Transplant as a Treatment Option

STEP ONE

- **Confirm the diagnosis** of active myeloma that requires 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 TWO

- **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 THREE

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

STEP FOUR

- **Review with the physician the pros and cons of stem cell transplant** (and/or stem 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 it is agreed to proceed. If there is no plan for harvest and/or transplant, 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 stem cell transplant 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 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 50–100 **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, frightening, 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 such as Neupogen®, Neulasta®, or Leukine® 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.

Methods of Collecting Stem Cells from the Blood Stream (Peripheral Blood Stem Cells [PBSC])

There are two main methods for collecting stem cells: 1) giving growth factors alone or 2) giving growth factors with chemotherapy.

1. Growth factors alone.

Growth factors are drugs that stimulate blood stem cells both to grow and to be released into the blood stream. There are red cell and white cell growth factors. These medications are administered subcutaneously (under the skin). Growth factors are often used for patients receiving chemotherapy to hasten their white and red cell count recovery. The white cell growth factors (Neupogen, Neulasta, Leukine) used in high doses stimulate the release of stem cells from the bone marrow into the bloodstream. This process is called "mobilization." The injections are given daily for three or more days. Stem cells are usually collected on the 4th or 5th day after starting the injections. The collections and injections will continue daily until sufficient stem cells are obtained.

2. Using chemotherapy plus growth factors.

Chemotherapy with growth factors may also be used to release stem cells from the bone marrow into the bloodstream. The doctor will explain why it may or may not be appropriate to use chemotherapy in addition to growth factors. The doctor will explain the chemotherapy that will be administered to mobilize the blood stem cells and its potential benefits and side effects. Following chemotherapy for stem cell mobilization, a white cell growth factor is given by injection under the skin daily for approximately ten 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 the clinic/hospital or from visiting nurses. Once the number of stem cells in the blood stream is high enough, they will be collected over 2–5 days, while the patient is still receiving the growth factor injections.

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. Apherisis is a procedure whereby 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 chemotherapy after stem cells have been collected. Sometimes the same catheter is used during the transplant procedure as well. During this procedure, blood is collected through the catheter and processed through a blood-processing machine to remove the stem cells. The rest of the blood is returned through part of the same catheter (the lumen not being used in a double lumen catheter) or by using a different catheter. The apheresis procedure will last 3–4 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.

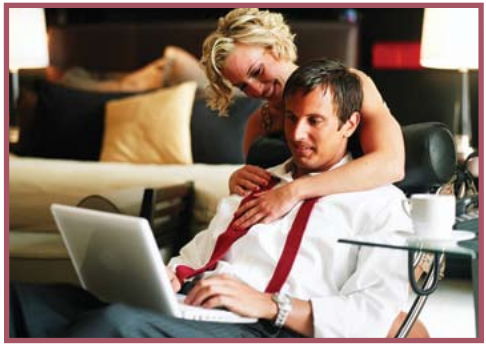
Processing stem cells: After collection, the peripheral blood (or occasionally direct bone marrow material) is taken to the processing laboratory, which is usually located within the hospital or local blood bank. In the processing laboratory, the bone marrow or blood cells are prepared for freezing (cryopreservation). 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 will be frozen until the time they will be needed for the transplant. 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 high-dose therapy. 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 trans-

plant 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 1–4 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 body weight). In situations where a sufficient number of blood stem cells cannot be harvested, patients may qualify for a compassionate use program of AMD-3100 (Mozobil®), an experimental drug that boosts stem cell production.

Administering High-Dose Chemotherapy

After the stem cells are frozen and stored, the patient is ready to receive high-dose chemotherapy. This treatment is designed to destroy myeloma cells more effectively than standard-dose chemotherapy. The purpose of high-dose



chemotherapy is to kill myeloma cells inside the patient's body. The most common type of high-dose chemotherapy used to treat myeloma is melphalan administered at a dose of 200 milligrams per square meter (mg/m^2) of body surface area (size of patient). Depending on the type of myeloma and other factors, some patients may receive a second transplant 3 to 6 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 Transplant or Infusion

Since high-dose treatment destroys the normal bone marrow in addition to the myeloma cells, the blood stem cells must be given back to restore the bone marrow. The previously collected stem cells will be unfrozen and given back, through a catheter, into the bloodstream (as one would receive a blood transfusion) one to two days after administration of the high-dose chemotherapy. This procedure is often referred to as the transplant. The transplant takes place in the patient's room: it is not a surgical procedure. The frozen bags of bone marrow or 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 1–4 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 10–14 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, high-dose chemotherapy 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, transplant, and recovery is approximately 3 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 high-dose chemotherapy. Monitoring includes daily weight measurement as well as frequent measurements of blood pressure, heart rate, and temperature.

Preventing Infection

During the first 2–3 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 the high-dose chemotherapy. 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 be necessary.

Waiting for the transplanted 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 both the patient and his or her family and friends. During this period patients will feel weak and very fatigued. Having a support network is very important during this period. 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.

Am I a Candidate for an Autologous Transplant?

A stem cell transplant 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 a stem cell transplant. 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

We cannot stress enough that myeloma is a highly individualized disease. While there are similarities between patients, each case has its own distinct characteristics. There will be testing to determine how much myeloma there is in your body and how aggressive it is. All of these variables will be weighed before determining whether a transplant is appropriate for you. Therefore, general statements regarding patient

outcomes both during the transplant procedure and post transplant are inappropriate.

When to transplant 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. Remember, in most cases, unlike a heart attack, myeloma gives the patient the luxury of 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 transplant candidate, the ultimate decision about whether or not to have a transplant is the patient's.

Transplants and Clinical Trials

A single autologous stem cell transplant is currently considered the standard of care for patients with multiple 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 high-dose therapy 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 achieve either VGPR or CR following first autologous transplant.

Radiopharmaceuticals (radioactive bone-targeted therapy) are combined with high-dose chemotherapy and autologous stem cell transplant as a means to increase response rates. This approach allows for a two-pronged attack on the myeloma through high-dose chemotherapy plus a radioactive compound that only attacks the bone marrow. There is currently a radiopharmaceutical agent in myeloma clinical trials: Quadramet (samarium Sm-153 lexidronam).

A "mini" (non-myeloablative) allogeneic transplant involves the use of mild therapy (chemotherapy and/or radiation therapy) to suppress the patient's immune system to allow for donor stem cells to grow. This dose of chemotherapy does not destroy the bone marrow but does allow for the donor's blood cells and immune system to grow. After the lowered dose of chemotherapy is administered, the patient receives the donor's stem cells. Once the allogeneic stem cells grow, the donor's immune cells attack the myeloma. This is a form of immunotherapy. The risk of this procedure is that the donor's immune system will "overreact" and attack more than the myeloma cells. This reaction is called "graft-versus-host disease," which can be very serious and potentially life threatening.

Sequential autologous transplant followed by a mini allogeneic transplant. Pilot studies using sequential transplants have shown promise.

This involves high-dose chemotherapy 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. As with a single mini allogeneic transplant, there is a risk of graft-versus-host disease, which can be very serious and potentially life threatening.

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 include thalidomide, Revlimid, prednisone, and dexamethasone, alone or in combinations.

Psychosocial Issues

High-dose chemotherapy 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 Stem Cell Transplantation

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 multiple 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 high-dose chemotherapy.

Q. Am I a candidate for bone marrow or peripheral blood stem cell transplant?

A. Medical experts have yet to arrive at a set of fixed guidelines for selecting patients who will benefit the most from a transplant. Increasingly accepted as a part of multiple 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 multiple myeloma, you should talk with your doctor, other multiple 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 multiple 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.

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 brochure, 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 know 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.

Patients should therefore seek a transplant center where the doctors, nurses, and allied health professionals have performed a number of transplants and appear competent 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 a transplant for multiple myeloma patients is

riskier than most. Nonetheless, medical studies have shown that over 95% of patients (usually closer to 99%) survive transplant.

Q. Can the patient relapse after a transplant?

A. Yes. Unfortunately, the majority (at least 50%) of all multiple myeloma patients 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. High-dose chemotherapy 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 myeloma patients.

Q. How long will the transplant patient stay in the hospital?

A. Patients stay in the hospital for about 2 to 3 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 10–14 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 to 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, e.g., ibuprofen, may be harmful to a myeloma patient.

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 high-dose chemotherapy 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 multiple 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 high-dose therapy with stem cell transplant?

About the IMF

"One person can make a difference,
Two can make a miracle."

Brian D. Novis
IMF Founder

Myeloma is a little-known, complex, and often misdiagnosed bone marrow cancer that attacks and destroys bone. Myeloma affects approximately 75,000 to 100,000 people in the United States, with more than 19,000 new cases diagnosed each year. Although there is presently no known cure for myeloma, doctors have many approaches to help myeloma patients live better and longer.

The International Myeloma Foundation (IMF) was founded in 1990 by Brian and Susie Novis shortly after Brian's myeloma diagnosis at the age of 33. It was Brian's dream that future patients would have easy access to medical information and emotional support throughout their battle with myeloma. He established the IMF with the three goals of treatment, education, and research. He sought to provide a broad spectrum of services for patients and, their families, friends, and health- care providers. Although Brian died four years after his initial diagnosis, his dream did not. Today, the IMF reaches out to an international membership of more than 145,000. The IMF was the first organization dedicated solely to myeloma, and today it remains the largest.

The IMF provides programs and services to aid in the research, diagnosis, treatment, and management of myeloma. The IMF ensures that no one must brave the myeloma battle alone.

We care for patients today, while working toward tomorrow's cure.

How Can the IMF Help You?

PATIENT EDUCATION

INFORMATION PACKAGE

Our free IMF InfoPack™ provides comprehensive information about myeloma, treatment options, disease management, and IMF services. It includes our acclaimed Patient Handbook.

INTERNET ACCESS

Log on to www.myeloma.org for 24-hour access to information about myeloma, the IMF, education, and support programs.

ONLINE MYELOMA FORUM

Join the IMF Internet Discussion Group at www.myeloma.org/listserve.html to share your thoughts and experiences.

MYELOMA MINUTE™

Subscribe to this free weekly email newsletter for up-to-the-minute information about myeloma.

IMF PATIENT & FAMILY SEMINARS™

Meet with leading experts in myeloma treatment to learn more about recent advances in therapy and research.

MYELOMA MATRIX™

On our website and in print, this document is a comprehensive guide to drugs in development for myeloma.

MYELOMA TODAY™ NEWSLETTER

Our quarterly newsletter is available free of charge by subscription.

SUPPORT

MYELOMA HOTLINE: 800-452-CURE (2873)

Toll-free throughout the United States and Canada, the IMF Hotline is staffed by trained information specialists and is in frequent interaction with members of our Scientific Advisory Board.

SUPPORT GROUPS

A worldwide network of more than 100 myeloma support groups hold regular meetings for members of the myeloma community. The IMF conducts annual retreats for leaders of myeloma support group leaders.

RESEARCH

BANK ON A CURE®

This DNA bank will provides genetic data research in new drug development.

THE INTERNATIONAL STAGING SYSTEM (ISS)

This updated staging system for myeloma enhances physicians' ability to select the most appropriate treatment for each patient.

RESEARCH GRANTS

Leading the world in collaborative research and achieving extraordinary results, the IMF Grant Program supports both junior and senior researchers working on a broad spectrum of projects. The IMF has attracted many young investigators into the field of myeloma; they have remained in the field and are actively pursuing a cure for this disease.

Glossary

Alkylating agent: A chemotherapeutic agent such as melphalan (Alkeran) or cyclophosphamide (Cytoxan). Alkylating refers to the way in which these agents cross-link 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 high-dose chemotherapy.

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

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

Blood stem cells: Stem cells, derived from the blood, that 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.

Creatinine: A small chemical compound normally excreted by the kidney. If the kidneys are damaged, the serum level of creatinine builds up, resulting in elevated serum creatinine. The serum creatinine test is used to measure kidney function.

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.

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 protein (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 multiple 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.

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.

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

Transplantation: 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).

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