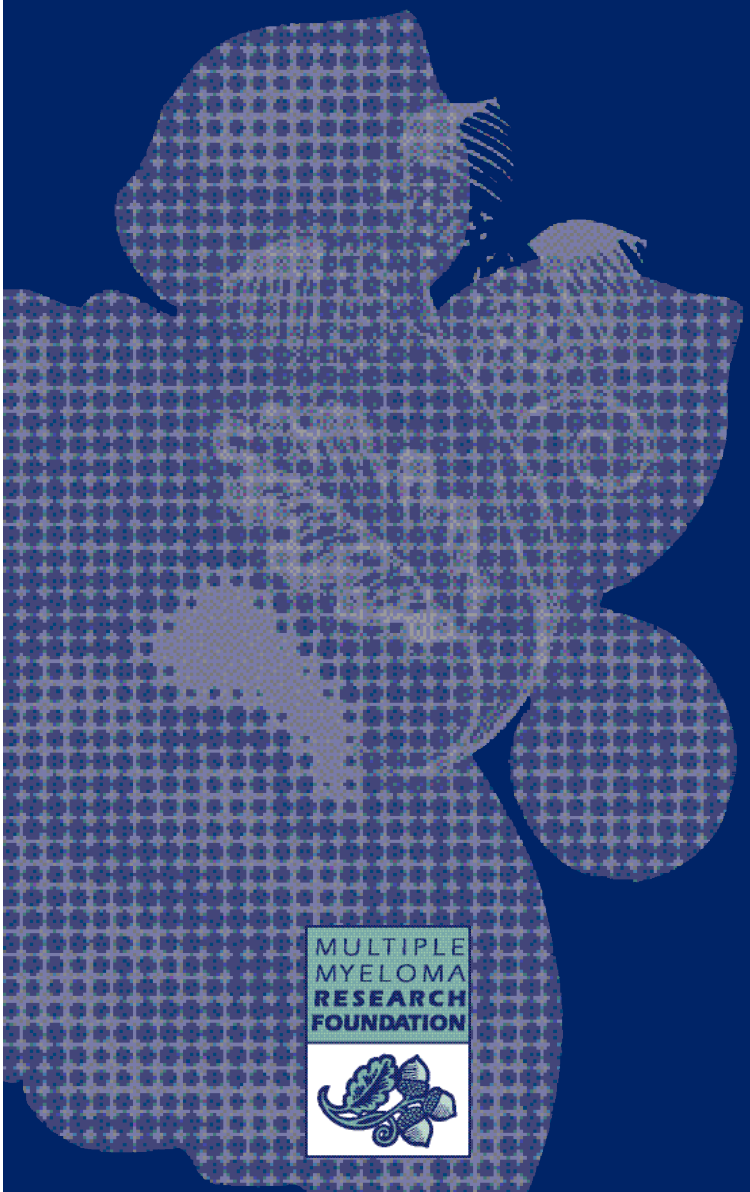

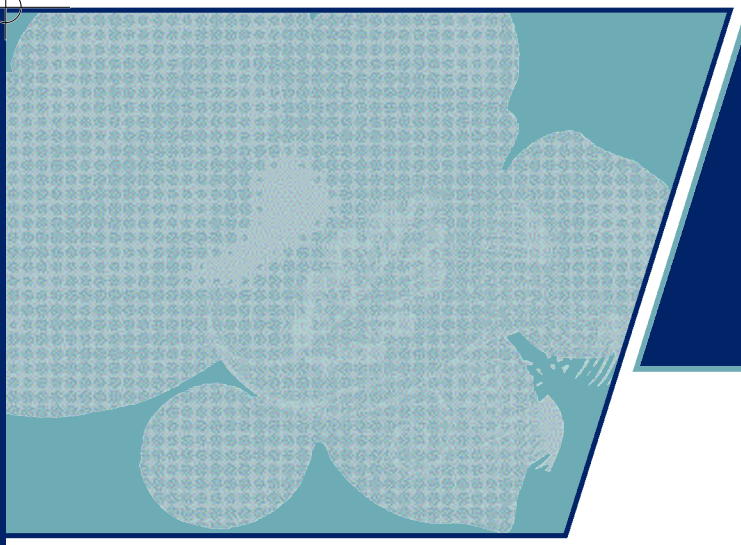

Multiple Myeloma: Stem Cell Transplantation

MMRF
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The Multiple Myeloma Research Foundation (MMRF)

is an international
nonprofit foundation
driven by a single purpose:

to accelerate the search
for a cure
for multiple myeloma.

The MMRF focuses on 5 goals:

- Raising awareness of multiple myeloma
- Funding the most promising myeloma research
- Fostering collaborations among researchers worldwide
- Educating the myeloma community
- Advocating for optimal patient care

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Celgene, Millennium, and NeoRx,
which have provided an unrestricted educational
grant to support this brochure.

What Is Multiple Myeloma?

Multiple myeloma is a cancer of the plasma cells, important cells of the immune system that produce and release antibodies (immunoglobulins) to help fight infection. Malignant plasma cells produce an abnormal immunoglobulin, making myeloma patients susceptible to infection.

What causes multiple myeloma?

While the specific cause of multiple myeloma has not been identified, possible associations include a decline in the immune system, genetic factors, and exposure to certain chemicals, radiation, and viruses.

What are the common symptoms of myeloma?

- Pain in the lower back or ribs, which is the result of accumulations of plasma cells that cause tiny fractures in the bones
- Unusual tiredness due to anemia
- Frequent, recurrent infections such as bacterial pneumonia, urinary tract infections, or shingles
- Hypercalcemia and kidney failure may also be seen in myeloma patients

How common is multiple myeloma?

- Multiple myeloma, the second most common blood cancer, represents 1% of all cancers and 2% of all cancer deaths
- According to the American Cancer Society, 15,270 Americans will be diagnosed with multiple myeloma and 11,070 Americans will die of the disease this year
- The incidence of multiple myeloma is higher in African Americans than it is in whites (11.3 versus 5.3 per 100,000)
- Multiple myeloma is a top 10 cancer killer of African Americans

What Is the Multiple Myeloma Research Foundation?

The MMRF is a nonprofit organization driven by a single purpose—to accelerate the search for a cure for multiple myeloma.

Incorporated in 1998, the MMRF remains dedicated to improving therapeutic options for people with multiple myeloma by:

Raising awareness of multiple myeloma

The MMRF has reached millions of Americans with feature segments on NBC's *Today*, *CNBC*, *CNN/SI*, *CBS This Morning*, *Fox News*, and *Inside Edition*.

Funding the most promising myeloma research

The MMRF is the world's leading private funder of myeloma research, offering Senior Research Awards of $100,000, Fellows' Awards of $50,000, and Collaborative Research Program Grants of $1.5 million.

Fostering collaborations among researchers worldwide

The MMRF conducts Research Roundtables—worldwide symposia serving as think tanks for top myeloma specialists to discuss cutting-edge science topics, such as cell signaling, the microenvironment, genomics, and targeted therapeutics.

Educating the myeloma community

The MMRF provides the myeloma community with the latest research information fast and free of charge via its Web site, Web casts, e-mail updates, newsletters, teleconferences, and educational symposia.

Advocating for optimal patient care

The MMRF held the first congressional hearing on blood cancers and spearheads an annual advocacy day.

Multiple Myeloma: Stem Cell Transplantation

Introduction

Stem cell transplantation, performed as support for high-dose chemotherapy, is a treatment option for many patients with multiple myeloma. This treatment regimen achieves a high response rate and provides significant benefits for many patients with myeloma, especially when a complete response is achieved. It may prolong the duration of response as well as provide a better quality of life.

In 2002, approximately 4,300 stem cell transplants of various types were performed in patients with myeloma in North America and were reported to the International Bone Marrow Transplant Registry/American Bone Marrow Transplant Registry (IBMTR/ABMTR).[1] However, the actual number of transplants performed is likely to be higher, since not all transplants are reported to the IBMTR/ABMTR.

This booklet will help you better understand the process of stem cell transplantation. It explains why high-dose chemotherapy and stem cell transplantation are used in the treatment of myeloma. In addition, it discusses the factors that are considered when determining whether a patient is a candidate for the procedure. It goes on to explain the different types of stem cell transplants in use today. Finally, the process of stem cell transplantation is described in detail.

Words you may not be familiar with are **bolded** and defined in the *Words You Need To Know* section beginning on page 26 of this booklet.

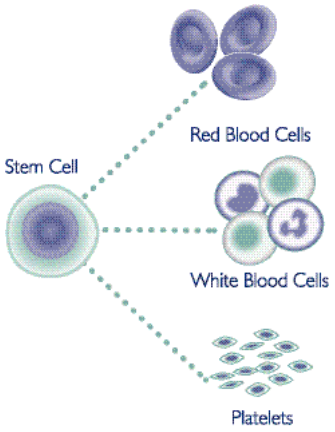
Why Does a Patient Need a Stem Cell Transplant?

In some patients with myeloma, higher doses of chemotherapy than those given as standard therapy are useful in treating their disease. Although high-dose chemotherapy is frequently more effective in killing myeloma cells, it also destroys normal cells in the bone marrow—the soft, spongy tissue inside bone where blood cells are produced. When bone marrow cells are destroyed, blood cell production stops. Therefore, a stem cell transplant is required following high-dose chemotherapy in order to replenish the bone marrow with stem cells. The replacement of stem cells by a stem cell transplant usually allows a patient to resume normal blood cell production following high-dose chemotherapy.

What Are Stem Cells and Why Are They So Important?

Stem cells normally reside in the bone marrow and occasionally circulate in the blood. They are truly remarkable cells. A stem cell can be thought of as a "mother cell" that can divide and develop into any one of the 3 main types of mature cells found in the blood.

- **Red blood cells**—cells that carry energy-giving oxygen from the lungs to the entire body
- **White blood cells**—immune cells that play an important role in fighting bacteria and viruses that cause infection
- **Platelets**—structures that help blood to clot when bleeding occurs



Stem cells constitute only a small fraction (less than 1%) of all cells in the bone marrow and an even smaller percentage of cells in the peripheral blood.

What Would Happen Without Stem Cells?

As mentioned earlier, high-dose chemotherapy destroys not only myeloma cells, but also stem cells in the bone marrow. When this happens, the reduced supply of blood cells can cause severe problems, including:

- Fatigue and difficulty breathing from lack of red blood cells that carry oxygen throughout the body
- Infection from lack of white blood cells that attack invading germs
- Bleeding from lack of platelets that help the blood to clot

Fortunately, a stem cell transplant replenishes stem cells that are lost during high-dose chemotherapy. Thus, a stem cell transplant restores the production of blood cells, including immune cells, in patients who have received high-dose chemotherapy.

How Does a Patient Know if a Stem Cell Transplant Is the Right Treatment?

High-dose chemotherapy with stem cell support is appropriate therapy for many patients with myeloma. Because each patient with myeloma is different, the appropriateness of this therapy is determined on an individual basis.

Many factors are taken into consideration, particularly a patient's age and general physical condition. A doctor will assess the functioning of various organs, such as the kidneys, liver, heart, and lungs, to ensure that the patient is healthy enough to undergo the procedure. In the past, transplants were limited to younger patients in good physical condition. However, they are now performed in a more diverse group of patients. A doctor will also consider the stage of the disease, how aggressive it is, and the responsiveness of the cancer to prior treatment in deciding whether to recommend the procedure and, if so, the specific type of transplant.

What Are the Different Types of Stem Cell Transplants?

There are several types of stem cell transplants, and they are defined by the source of the stem cells.

- **Bone marrow transplants** refer to transplants where the stem cells are obtained from the bone marrow. Historically, these were the first type of stem cell transplants performed. However, they are rarely performed today in myeloma because of the ability to collect stem cells from the peripheral blood
- **Peripheral blood stem cell (PBSC) transplants** refer to stem cells obtained from the peripheral blood. Peripheral blood is the source of stem cells for most transplants in myeloma. Compared to bone marrow transplants, PBSC transplants are easier to collect, they provide a more reliable number of stem cells, the procedure puts less strain on the donor's system, and the patient recovers more quickly

Stem cell transplants are further categorized based on the donor who provides the stem cells.

- **Autologous stem cell transplants (autografts)** refer to stem cells that are collected from an individual and given back to that same individual. With this type of transplant, the patient's stem cells are collected prior to high-dose chemotherapy, frozen and stored if necessary, and are then returned after high-dose chemotherapy. Most stem cell transplants in myeloma are autologous PBSC transplants
- **Allogeneic stem cell transplants (allografts)** refer to stem cells that are taken from one person and given to another. Currently, this type of transplant is performed very infrequently in myeloma and when performed, is often in the context of a clinical trial
- **Syngeneic stem cell transplants** refer to stem cells that are taken from an identical twin of the recipient

Lastly, there are also several types of transplants and strategies under investigation in clinical trials.

- A **tandem autologous transplant**, also known as a double autologous transplant, requires the patient to undergo 2 autologous stem cell transplants within 6 months
- A **mini (non-myeloablative) allogeneic transplant** involves the use of reduced-intensity chemotherapy in combination with an allogeneic stem cell transplant
- **Radiopharmaceuticals** (radiolabeled, bone-targeted therapeutics) are being used in conjunction with high-dose chemotherapy as a means to increase response rates

These transplants will be described in more detail in the sections that follow.

Autologous transplants

High-dose chemotherapy with autologous stem cell transplant is considered to be the current standard of care for patients who meet specific criteria. Several studies have shown that compared with conventional chemotherapy, high-dose chemotherapy with autologous stem cell transplantation offers a higher rate of complete response (undetectable disease; also referred to as complete remission) in patients under the age of 65 and is associated with improved survival.[2,3]

Following high-dose chemotherapy and autologous transplantation approximately 20% to 40% of patients achieve a complete response. Since myeloma is not necessarily curable, patients will eventually have recurrence or progression (also referred to as relapse) of their disease. Individual patient factors play a role in the duration of response. Approximately 40% to 50% of patients who achieve a complete response may expect to remain in remission for 5 years or longer, as do approximately 20% to 40% of patients who do not initially achieve a complete response.* The survival rate within the first 3 months following autologous transplantation is over 95%.

*Estimates of rates/lengths of disease remission in myeloma vary widely; the figures presented in this booklet may not necessarily represent a consensus among the entire myeloma community.

Who Is a Candidate?

High-dose chemotherapy with autologous stem cell transplantation is a treatment option for both patients with newly diagnosed disease and for those who have already received other treatments. Patients under the age of 65 in good physical condition with adequate kidney, lung, and heart function are potential candidates. Older patients may be eligible if they meet the performance and function criteria. Because the superiority of high-dose chemotherapy with stem cell transplantation over conventional chemotherapy in patients over the age of 65 has not been definitively established, older patients who are being considered for the procedure may be best served in the context of a clinical trial.

In some instances, prior treatment with certain chemotherapy drugs (for example, the alkylating agents melphalan or BCNU [carmustine]) or with radiation therapy to the spine or pelvis may reduce the number of stem cells that can be collected for an autologous transplant. For this reason, an autologous transplant may not be an option for some patients who have received these therapies.

When Is the Best Time for an Autologous Stem Cell Transplant?

Prior to an autologous stem cell transplant, patients first receive several cycles of conventional chemotherapy (referred to as **induction therapy**) to reduce the tumor burden. Although alkylating agents such as melphalan are commonly used as initial therapy for myeloma, candidates for an autologous transplant should receive an alternative agent for induction therapy, such as dexamethasone, VAD (vincristine, Adriamycin® [doxorubicin], and dexamethasone), or thalidomide plus dexamethasone, which will not compromise stem cell collection.

After induction therapy, the stem cells are collected. Patients may then go straight to high-dose chemotherapy and transplant ("early transplantation") or continue to receive chemotherapy until the myeloma relapses ("late transplantation"). Although overall survival is similar whether transplantation is early or late,[4] some patients prefer early transplants because they receive a shorter period of chemotherapy.

Greater benefit may be achieved when an autologous stem cell transplant is performed when a patient has received treatment for less than 1 year.[5] Greater benefit may also be achieved when a transplant is performed after a patient has achieved a complete response or near complete response following initial therapy.[6]

Improving Outcome

Researchers are investigating ways to improve the outcome of autologous transplants. One strategy is the use of novel therapies or other chemotherapy regimens to improve the outcome of initial therapy prior to transplant, which may lead to greater benefit following the transplant.

Another strategy is the use of bone-seeking, targeted radiopharmaceuticals in conjunction with high-dose chemotherapy and autologous transplantation as a means of improving response rates. These agents consist of a bone-seeking drug coupled with a radioactive compound. The radioactivity is delivered directly to the bone where it

provides a therapeutic effect. Examples of radiopharmaceuticals being investigated for use in myeloma include Skeletal Targeted Radiotherapy (STR™, 166Ho-DOTMP, NeoRx) and Quadramet® (Samarium Sm-153 lexidronam, Cytogen).

Data from a Phase I/II trial of STR demonstrated that the complete response rate (35%) and survival (approximately 60% at 3 years) with this strategy compare favorably to other published transplantation regimens. A Phase III trial opened for enrollment in March 2004. The trial, which is expected to enroll about 240 patients in up to 40 sites in the US and Canada, is designed to evaluate the safety and efficacy of STR in patients with myeloma who did not respond to initial therapy.

Researchers are also investigating the use of double or tandem autologous transplants as a means to improve outcome (see the box below). Novel therapies are also being investigated for use in maintaining a response following autologous transplantation.

Tandem Autologous Transplants

A tandem autologous transplant incorporates a second round of high-dose chemotherapy and an autologous transplant to enhance the response rate and duration achieved with the first transplant. The second transplant is performed after recovery from the first procedure, usually within 6 months.

In one study in newly diagnosed myeloma, 71% of patients were able to proceed with both transplants.[7] Mortality rates were 3% during initial chemotherapy, 1% during the first transplant, and 4% during the second transplant.

Although the relative merit of this technique has yet to be determined, it may offer a survival advantage over the long term. One important study in newly diagnosed patients showed improved overall 7-year survival with double compared to single transplantation (42% vs 21%).[8] Results of this study and others suggest that a second transplant is of most benefit to those patients who do not achieve a very good response after the first transplant.

Preliminary results of 3 other randomized comparative trials that have had shorter follow-up appear to support the survival advantage of the highly demanding tandem procedure. Ongoing studies will help determine the optimal regimen and who might benefit most.

Allogeneic transplants

High-dose chemotherapy and allogeneic stem cell transplants, also known as allografts, are now performed very infrequently in myeloma because the risks outweigh the potential benefits of the procedure. In the US, such transplants are typically performed in the context of a clinical trial.

With allografts, the donor's cells must match the recipient's tissue type. In many cases, the stem cell donor is related to the recipient, typically a sibling. However, stem cells from a **matched, unrelated donor (MUD)** can also be used.

Studies have shown that conventional allogeneic stem cell transplantation leads to prolonged survival in a relatively small percentage of patients. In addition, the percentage of patients who remain in remission for 5 years or longer (approximately 50% to 70%) is higher than that seen with autologous transplants. However, allogeneic transplants are associated with a greater risk of complications than autologous transplants, including infections and graft-versus-host disease (GVHD), which can lead to death. During GVHD, the donor immune cells may attack specific organs of the host such as the skin, liver, or gastrointestinal tract. Although GVHD can be prevented or controlled in some cases with **immunosuppressive drugs**, severe organ failure can result. This is because cells from the donor are considered foreign to the patient. Because GVHD can have serious consequences, allografts are associated with significant mortality within the first year (20% to 50%, depending on the duration of therapy prior to transplantation).

A potential benefit of allogeneic transplants is their ability to help the patient fight against the myeloma tumor **(graft-versus-myeloma effect)**. It is thought that this effect may account in part for the lower rate of disease recurrence/progression seen following allografts compared with autografts. However, one must still consider the significantly higher mortality seen with allografts.

Who Is a Candidate?

Within the last 10 years, there have been improvements in the support given to patients who undergo conventional allogeneic transplants. Although these improvements, as well as use of the procedure earlier in the course of the disease, have reduced the risks somewhat, the conditions required

for allografts are rigorous and the potential for adverse events or death is high. Therefore, these transplants are usually performed in the context of a clinical trial and are restricted to patients aged 55 or younger who are in good overall health.

Improving Outcome: Mini-transplants

Conventional allogeneic transplants have largely been replaced by allogeneic mini-transplants, a type of transplant being evaluated in clinical trials. With a mini-transplant, patients receive lower doses of chemotherapy than those used with a conventional allograft. Patients may also receive radiation. Because these doses of chemotherapy and/or radiation do not destroy the bone marrow completely, mini-transplants are also referred to as **non-myeloablative transplants**.

Because they are allografts, the graft-versus-myeloma effect helps destroy tumor cells. However, mini-transplants are associated with lower transplant-related mortality than conventional allografts (approximately 10% to 15% within the first year). Patients receive immunosuppressive drugs to prevent GVHD, and may receive an additional infusion of white blood cells from the donor to enhance the graft-versus-myeloma effect.

Mini-transplants can be used alone or in combination with an autologous stem cell transplant. In this type of **tandem transplant**, patients first undergo an autograft, which may provide substantial antitumor effects. This is followed by a mini-transplant, using peripheral blood stem cells from a matched donor, 2 to 4 months later. This strategy is designed to provide a sequential antitumor effect from the 2 transplants and a potential graft-versus-myeloma effect from the allogeneic mini-transplant. Mortality with this approach is approximately 20%.

These procedures are still being investigated in clinical trials. Although preliminary results suggest that mini-transplants improve the response rate when used after autologous transplants, there are still high risks with the procedures and there are no long-term data regarding their efficacy and safety.

Syngeneic transplants

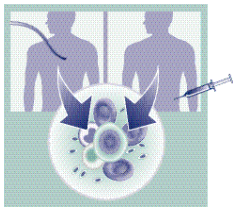
The rarest type of transplant—syngeneic transplants—are considered to be the safest type. This is because the transplant is taken from a patient's twin, who is genetically identical to the recipient. In addition, a syngeneic transplant does not contain any potentially contaminating myeloma cells as an autologous transplant might. Thus, one is less likely to give anything back to the patient that might adversely affect him or her. The survival rates for syngeneic transplants are similar to those seen with autografts, thus the mortality is lower than that seen with allogeneic transplants. The rate of disease recurrence/progression following syngeneic transplants has been reported to be equal to or lower than autologous procedures. The advantages and disadvantages of each procedure are summarized below.

Advantages and Disadvantages of the Various Types of Stem Cell Transplants

Transplant	Advantages	Disadvantages
Autologous	· Considered to be a standard of care for certain eligible patients · Safer than allogeneic; higher survival rate · Lower complication rate · Less infection · In many instances, much of the procedure can be done on an outpatient basis · No need for immuno-suppressive drugs	· No graft-versus-myeloma effect; higher rate of disease recurrence/progression than allogeneic · Prior treatment with certain drugs or radiation may impair ability to collect stem cells · Potential contam-ination of graft with tumor cells
Allogeneic	· Lower rate of disease recurrence/progression attributable in part to graft-versus-myeloma effect · Contain no tumor cells	· Higher mortality rates · Need matched donor · Graft-versus-host disease · Need immuno-suppressive drugs · Takes longer to recover immune function; higher risk of infection · Limited to younger and healthy patients
Syngeneic	· Safest procedure · Contain no tumor cells · Survival rate similar to autologous · Disease recurrence/progression rate equal to or lower than autologous	· Twins are rare · No graft-versus-myeloma effect

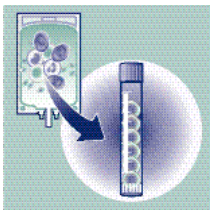
What Is Involved in the Stem Cell Transplant Process?

Stem cell transplantation is a complex process that involves 6 major steps.



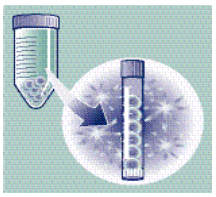
Collection

The stem cells are collected.



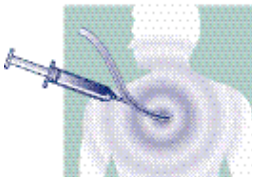
Processing

The stem cells are processed in the laboratory.



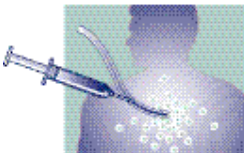
Cryopreservation

The processed stem cells are cryopreserved (frozen) and stored until needed. This step is usually omitted with donor (allogeneic or syngeneic) stem cells because the cells can be obtained fresh at the time they are needed.



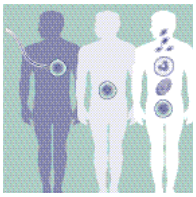
Chemotherapy

The patient receives high-dose chemotherapy.



Infusion

The stem cells are thawed and infused into the patient.



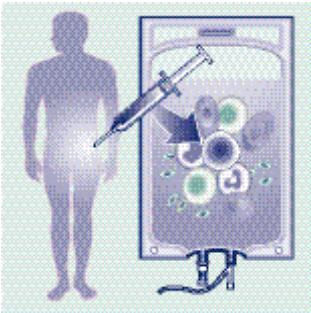
Engraftment and Recovery

The transplanted stem cells begin to produce new blood cells.

Each of these steps is described in detail on the following pages. In the case of autologous stem cell transplantation, the patient will undergo the stem cell collection procedure. In allogeneic or syngeneic stem cell transplants, the stem cell donor, rather than the patient, will undergo the collection procedure and cryopreservation of the cells is usually not performed.

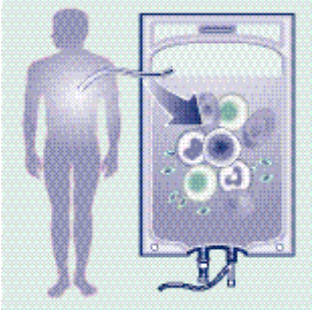
Collection

Most of the stem cells in the human body reside in the bone marrow. Until recently, the only way to obtain stem cells for transplantation was to remove a portion of the bone marrow. However, through recent medical advances, it is now possible to collect stem cells from blood for transplantation. At present, most stem cells for myeloma transplants are collected from the blood. However, there may be rare cases where stem cells may need to be collected from both the blood and bone marrow in order to obtain a sufficient number of cells.



Collecting stem cells from bone marrow

Collecting or "harvesting" bone marrow is usually done in a hospital operating room under general anesthesia. Using a needle and syringe, a surgeon will take bone marrow from several different areas of the hipbone (pelvis). The bone marrow, which appears as a thick red liquid, is typically frozen and stored until high-dose chemotherapy is completed. However, allogeneic bone marrow transplants need not be frozen if they are used right away.



Collecting stem cells from peripheral blood

Stem cells that are collected from peripheral blood are referred to as peripheral blood stem cells or PBSC. Harvesting stem cells from the blood takes approximately 1 week, and it often can be done in an outpatient setting so an overnight hospital stay is not necessary. Stem cells sufficient for 2 transplants are usually collected.

Because most stem cells reside in the bone marrow, it is necessary to move the stem cells from the bone marrow to the bloodstream prior to their collection. This procedure is called **mobilization**.

A commonly used mobilization technique is to administer a medication specifically designed to increase the number of stem cells in the blood. This medication is called a **colony-stimulating factor** or "growth factor" and it is usually injected under the skin. In the case of autografts, a cycle of chemotherapy may be administered along with a growth factor to increase the number of stem cells that can be recovered and to reduce the patient's tumor burden as well.

Once a sufficient number of stem cells are mobilized from the bone marrow into the bloodstream, the stem cells are collected using a nonsurgical procedure called **apheresis**. Apheresis is a procedure in which blood from the donor passes through a cell separator machine. The white blood cell component enriched for stem cells is separated out and the rest of the blood flows back into the donor.

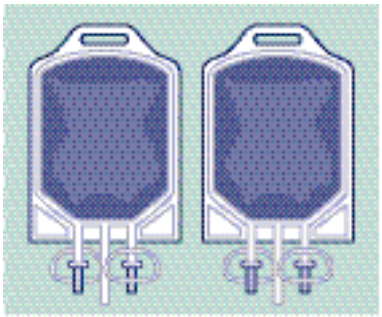
Apheresis is a relatively painless procedure. For allogeneic transplants, the donor undergoes a PBSC collection process that is similar to a regular blood donation. A needle is placed in a vein (typically in the arm) to collect the blood. Another needle is placed in the opposite arm to return the remaining blood components.

In the case of an autologous transplant, where the patient serves as his or her own donor, the collection process is slightly different. Prior to starting apheresis, a flexible plastic tube called a catheter is inserted through the skin and into a large vein so that blood can be collected without the need for needles. 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 needed. The site where the catheter enters the skin may be sore for a few days, and can be relieved with medications like acetaminophen (Tylenol®). The catheter can also be used to give chemotherapy or other drugs and to obtain blood samples. It may be kept in place for several weeks.

Once the needle or catheter is in place, the donor can undergo apheresis. He or she sits in a comfortable chair and the needle or catheter is connected to the apheresis machine with special tubing. Blood circulates through the apheresis machine, which removes a portion of the blood containing the mobilized stem cells, and returns the other blood cells back to the donor.

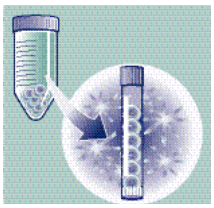
Donors usually do not need to be hospitalized for apheresis, but must come in for 1 to 3 sessions, lasting 2 to 4 hours each, in order to ensure that enough stem cells are collected.

Harvested Blood or Marrow



Processing

After collection, the peripheral blood or bone marrow is taken to the processing laboratory, which is usually located within the hospital or local blood bank. In the processing laboratory, the blood or bone marrow stem cells are prepared for freezing (**cryopreservation**) if they are not to be used right away, as is the case with autografts.



Cryopreservation

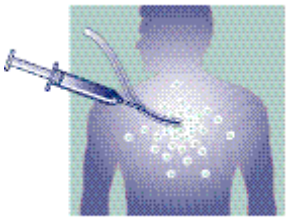
Following collection and processing, blood or bone marrow (now referred to as the stem cell transplant) must be preserved to keep the stem cells alive until it is time to infuse the cells into the patient's bloodstream. In order to preserve the cells, they are frozen and stored in liquid nitrogen or a special freezer. A chemical called **DMSO** (dimethyl sulfoxide) is mixed with the blood or bone marrow before freezing. DMSO keeps the water in the cells from forming ice crystals that would damage the cells during the freezing process. The blood or bone marrow can be stored in a frozen state as long as necessary. If donor (allogeneic or syngeneic) stem cells are collected at the time they are needed, this step is omitted.

Chemotherapy

After the stem cells are frozen and stored, the patient is ready to receive high-dose chemotherapy. Sometimes called dose-intensive chemotherapy, this treatment is

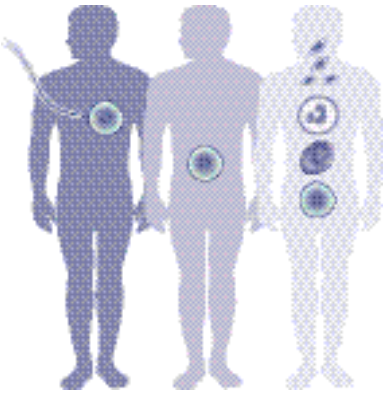
designed to destroy cancer cells more effectively than standard chemotherapy by giving patients higher doses of anticancer medicines. Depending on the type of cancer and other factors, some patients may receive 1 or more treatments of high-dose chemotherapy over a period of several days.

The most common type of high-dose chemotherapy used to treat myeloma is melphalan, administered at a dose of 200 mg/mg^2. However, the kind of high-dose chemotherapy a patient receives depends upon a number of factors, such as how far advanced the cancer is. Some patients may need only one cycle of treatment, while others may require several cycles with rest periods in between. In some cases, radiation may also be administered.



Infusion

Within a few days after completing the high-dose chemotherapy, the stored blood or bone marrow is transplanted, or infused, into the patient's bloodstream. The infusion process is similar to a blood transfusion. The frozen bags of stem cells are thawed in a warm water bath and infused through the catheter over a period of 2 to 4 hours. The infused stem cells travel through the bloodstream and settle in the bone marrow, where they begin to produce new white blood cells, red blood cells, and platelets.



Engraftment and Recovery

During the first few days after transplantation, the reinfused stem cells migrate to the bone marrow and begin the process of producing replacement blood cells, a process called **engraftment**. The stem cells start to produce new blood cells within 10 to 14 days following infusion. **Colony-stimulating factors** may be administered during this time to stimulate the process of blood cell production.

Until engraftment is complete, a transplant recipient is susceptible to infection, **anemia**, and bleeding caused by low blood cell counts. Therefore, special precautions are necessary during recovery. Patients may be given red blood cell and platelet transfusions during the recovery period to help prevent anemia and bleeding.

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 and the loss of blood cells.

Several precautions may be taken to help prevent infection.

Preventing Infection

- Antibiotics are often prescribed to help prevent infection
- Visitors and family may be asked to wash their hands and wear masks and gloves to minimize contact with the patient
- Fresh fruits, vegetables, and flowers may be prohibited from the patient's room, as these can carry germs (bacteria and fungi)
- If infection and fever occur, the patient may be admitted to the hospital and given intravenous antibiotics

The doctors, nurses, and other members of the healthcare team will do everything possible to ensure a successful recovery. However, it is also important that the patient and the patient's family or caregivers are also active participants in the recovery process. Patients are asked to come in for frequent check-ups and tests during the early recovery period, which typically lasts about 6 weeks.

Outpatients need to stay near the treatment center so recovery can be closely monitored. Some patients are admitted to the hospital during the recovery period. Each medical center has its own specific guidelines for patient care, including removal of the catheter, during recovery. The healthcare team will explain these to the patient and family members.

Patients receiving autologous transplants can expect to stay in the hospital for about 2 weeks or less following a stem cell transplant. On the average, it takes about 2 to 3 months to recover normal physical performance after an autologous procedure. However, it can take as long as a year for a patient to get back to his or her normal routine.

Because there is greater potential for adverse events following an allograft, the recovery period is longer than that of an autograft. Allograft recipients can expect to stay in the hospital for about 4 to 6 weeks (longer in cases of GVHD), with a recovery period of up to 6 months, depending on whether any late complications occur.

What Are the Side Effects of Stem Cell Transplantation?

As with most medical treatments, there are side effects associated with the process of stem cell transplantation. Everyone is different, and so is his or her side effect profile. Some of the side effects that are associated with the process are listed below.

Collection

In the majority of cases, when collecting stem cells from the bone marrow, the only side effect of the collection procedure is some soreness in the hip area for a few days.

When collecting PBSCs using apheresis, the most common side effects 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. These temporary side effects are relieved by medications.

Catheter insertion may be associated with pain or bleeding at the insertion site. Uncommonly, there may be infection at the catheter site that can spread to the bloodstream. Occasionally, blood clots may form around the catheter inside the vein.

Chemotherapy

High-dose chemotherapy can cause side effects that may require some patients to be admitted to the hospital for treatment. Some patients can receive chemotherapy as outpatients, but will need to stay close to the hospital so they can be carefully monitored.

Shortly before starting chemotherapy, patients are usually given large amounts of fluid to prevent dehydration and kidney damage. Medications designed to prevent or lessen some of the expected side effects of treatment are also given.

Some of the more common temporary side effects caused by the high-dose chemotherapy are nausea, vomiting, diarrhea, mouth sores, skin rash, and hair loss. The severity of side effects such as nausea and vomiting can be reduced by medication. Patients are very closely monitored during high-dose chemotherapy, with daily weight measurements, as well as frequent measurements of blood pressure, heart rate, and temperature.

Infusion

The most common temporary side effects of the stem cell infusion process are caused by DMSO, the preservative used in the cell freezing process. Side effects related to DMSO include nausea and vomiting, abdominal cramping, chilling, and an unusual odor and taste of garlic. In rare cases, DMSO may cause low blood pressure, a fast heart rate, or shortness of breath. Medications are given before the infusion process to prevent or lessen some of the expected effects of DMSO infusion. The more DMSO that is infused, the greater the possibility that the patient will react

to this chemical. Therefore, concentrating the stem cells into a smaller volume during processing and prior to freezing dramatically reduces the amount of DMSO that is needed.

Engraftment and Recovery

As mentioned previously, a transplant recipient is susceptible to infection and bleeding, caused by low blood cell counts, until engraftment is complete.

In allogeneic transplants, there may be complications that arise because the donor stem cells are from a different individual. One complication is GVHD, a condition where immune cells in the transplant attack the recipient's cells. In some cases, the recipient may reject the graft and not allow the new stem cells to grow.

How Does One Choose a Transplant Center?

A stem cell transplant is a complex medical procedure that requires an expert team of specialized healthcare professionals. There are several medical centers that specialize in stem cell transplants for patients with myeloma. Some are conducting clinical trials that are investigating new protocols for intensive therapy and stem cell transplantation. Your doctor and the MMRF will be able to direct you to a suitable center.

Where Can I Get More Information?

In addition to the MMRF, there are several organizations that can provide you with more information about stem cell transplants, as well as counseling, referrals, insurance information, and financial assistance. These include Cancer Care, several leading bone marrow transplant organizations, the Blood and Marrow Transplant newsletter, and several patient advocacy groups. Contact information for these organizations can be found on page 30 of this booklet. A variety of support services are also provided directly through the transplant center.

Hope for the Future

Stem cell transplants, performed as support for high-dose chemotherapy, offer hope to many patients with myeloma. There is much ongoing research to make stem cell transplants safer and more effective. High-dose chemotherapy with stem cell transplantation significantly reduces the tumor burden, providing a platform upon which new immune therapies can be tested. It is in this context that such immune therapies are most likely to be successful.

We would like to thank the following MMRF Scientific Advisors for their contributions to this brochure.

William Bensinger, MD
Jean-Luc Harousseau, MD
Sundar Jagannath, MD

Words You Need to Know

Allogeneic stem cell transplantation: A procedure in which bone marrow or peripheral blood stem cells from a donor (usually related) are collected, stored, and infused into a patient (recipient) following high-dose chemotherapy.

Allograft: An allogeneic stem cell transplant.

Anemia: A decrease in the normal number of red blood cells. This can cause shortness of breath, weakness, and fatigue.

Apheresis: A procedure in which blood is taken from a donor, a blood component (such as white blood cells, red blood cells, or plasma) is separated out, and the remaining blood components are reinfused back into the donor. With PBSC transplantation, the white blood cell component, which also contains the stem cells, is collected. In this case, the procedure may also be referred to as leukapheresis.

Autograft: An autologous stem cell transplant.

Autologous stem cell transplantation: A procedure in which a patient's own stem cells from bone marrow or peripheral blood are collected, stored, and reinfused following high-dose chemotherapy.

Bone marrow transplantation: A procedure in which stem cell-containing bone marrow is collected, stored, and infused following high-dose chemotherapy.

Colony-stimulating factor (CSF): A protein that stimulates the development and growth of blood cells, sometimes called growth factor. Granulocyte colony-stimulating factor is a CSF that is used to mobilize stem cells from the bone marrow into the bloodstream prior to apheresis.

DMSO: Dimethyl sulfoxide, a colorless chemical used for cryopreservation of stem cells. When introduced into the body, it may cause unpleasant or even serious toxic effects.

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

Graft-versus-host disease (GVHD): A complication of allogeneic transplants caused by donor leukocytes recognizing the recipient's cells as foreign and mounting an attack against them.

Graft-versus-myeloma effect: A beneficial effect of allogeneic transplants resulting from the donor cells mounting an attack on the recipient's myeloma cells.

Hematopoiesis: The formation and development of blood cells in the bone marrow.

Immune system: A network of related cells, tissues, and organs that protect the body from disease organisms, other foreign bodies, and cancers.

Immunosuppressive drug: A drug given to suppress a patient's immune system, such as one given to prevent rejection of transplanted tissue.

Induction therapy: The administration of 3 to 4 cycles of chemotherapy to reduce tumor burden prior to stem cell transplant.

Lymphocytes: Small white blood cells produced in the lymphoid organs (the lymph nodes, spleen, thymus, and tonsils) that are essential for normal function of the immune system.

Matched unrelated donor: An allogeneic stem cell transplant donor who is not a member of the patient's family but whose tissue type matches that of the patient.

Mini-allograft: A type of allogeneic stem cell transplant that uses lower doses of chemotherapy, sometimes in combination with radiation, and thus does not completely destroy the bone marrow; also known as mini-transplant or non-myeloablative transplant.

Mini-transplant: See *Mini-allograft*.

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.

Neutropenia: A below-normal number of neutrophils.

Neutrophil: A type of white blood cell that functions to destroy bacteria.

Non-myeloablative transplant: See *Mini-allograft*.

Peripheral blood stem cell (PBSC): Stem cells collected from the blood. The term "peripheral" means that the cells come from outside the bone marrow.

Peripheral blood stem cell (PBSC) transplantation: A procedure in which blood containing mobilized stem cells is collected by apheresis, stored, and infused following high-dose chemotherapy.

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

Remission: The period during which no evidence of disease is present.

Stem cell: A parent cell that grows and divides to produce red blood cells, white blood cells, and platelets. They are found primarily in the bone marrow, but also in the peripheral blood.

Syngeneic stem cell transplantation: A procedure in which bone marrow or peripheral blood stem cells from a patient's identical twin are collected, stored, and infused into the patient following high-dose chemotherapy.

Tandem autologous transplant: A double transplantation technique whereby a patient receives 2 planned autologous stem cell transplants within a relatively short period of time.

Tandem transplant: A double transplantation technique whereby a patient receives 2 planned stem cell transplants within a relatively short period of time. This may involve 2 autologous transplants or an autologous transplant followed by a mini-transplant.

White blood cell: One of the major cell types in the blood. It is responsible for immune defenses and is also called a leukocyte.

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Patient Resources

We hope you have found this booklet helpful. Your healthcare provider can answer any additional questions you may have. You may also contact the following organizations for more information.

Blood and Marrow Transplant Information Network
Susan Stewart
Executive Director
2900 Skokie Valley Road
Suite B
Highland Park, IL 60035
1-847-831-1913
www.bmtinfonet.org

Cancer Care, Inc
275 7th Ave, 22nd Floor
New York, NY 10001
1-800-813-HOPE (4673)
www.cancercare.org

Thompson CenterWatch
Clinical Trials Listing Service™
22 Thomson Place, 36T1
Boston, MA 02210-1212
1-617-856-5900
www.centerwatch.com

The Bone Marrow Foundation
337 E. 88th Street, Suite 1B
New York, NY 10128
1-800-365-1336
www.bonemarrow.org

The Marrow Foundation
400 Seventh Street NW
Suite 206
Washington, DC 20004
1-202-638-6601
www.themarrowfoundation.org
e-mail: tmf@nmdp.org

Patient Advocate Foundation
700 Thimble Shoals Blvd
Suite 200
Newport News, VA 23606
1-800-532-5274
www.patientadvocate.org

National Marrow Donor Program
3001 Broadway Street NE
Suite 500
Minneapolis, MN 55413
1-612-627-5817
www.themarrowfoundation.org

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