Multiple Myeloma
High-Dose Chemotherapy and Stem Cell Transplantation
About the Multiple Myeloma Research Foundation

The Multiple Myeloma Research Foundation (MMRF) was founded in 1998 by identical twin sisters Kathy Giusti and Karen Andrews soon after Kathy was diagnosed with multiple myeloma, an incurable blood cancer. The mission of the MMRF is to relentlessly pursue innovative means that accelerate the development of next-generation multiple myeloma treatments to extend the lives of patients and lead to a cure.

Thanks to the support and generosity of people like you, and by working closely with researchers, clinicians and our partners in the biotech and pharmaceutical industry, we helped bring multiple myeloma patients four new treatments that are extending lives around the globe. Today, we are on the cusp of the next breakthrough treatment, and are supporting a pipeline of more than 50 promising compounds and combination treatments, including more than 30 clinical trials we advanced through our affiliate organization, the Multiple Myeloma Research Consortium (MMRC).

As the multiple myeloma community’s most trusted source for information, the MMRF supports patients from the point of diagnosis throughout the course of the disease. No matter where you are in your journey with multiple myeloma, you can count on the MMRF to get you the information you need about multiple myeloma and its treatment options, including clinical trials. All information on our website, www.themmrf.org, is tailored to patients by disease stage so we can make sure you get the information you need at the right time.

To learn more about the MMRF, visit www.themmrf.org.
Introduction

This booklet is designed primarily to help individuals with multiple myeloma, and their friends and families, better understand an important treatment option, high-dose chemotherapy and stem cell transplantation. This booklet explains what high-dose chemotherapy and stem cell transplantation is and describes the types of transplants. Practical information to better inform patients in their decision-making process is included as well. Words you may not be familiar with are bolded throughout the text at first mention and defined in the Glossary (page 31).

The information in this booklet is not intended to replace the services of trained healthcare professionals or to be a substitute for medical advice. Please consult with your healthcare professional if you have specific questions relating to your health, especially questions about diagnosis or treatment.

The MMRF booklet Multiple Myeloma Treatment Overview and the MMRF website [www.themmrf.org] provide more information about current therapies for myeloma and emerging treatment options.
Overview

What is high-dose chemotherapy and stem cell transplantation?

High-dose chemotherapy and stem cell transplantation is a treatment option for some patients with multiple myeloma. With this treatment, high doses of chemotherapy are given in order to destroy more myeloma cells than would be possible with conventional (standard dose) chemotherapy. High-dose chemotherapy also destroys important cells in the bone marrow, called hematopoietic stem cells, which are responsible for the production of blood cells. Without these stem cells, blood cell production would cease. These stem cells must be replaced in order to restore blood cell production after high-dose chemotherapy. The procedure that restores the stem cells is called stem cell transplantation.

Historically, high-dose chemotherapy and hematopoietic stem cell transplantation has been considered to provide patients with a better chance for longer survival than other therapies. However, the newer, novel agents (e.g., Revlimid®, Velcade®, Thalomid®) are providing high response rates, with significantly prolonged survival as well. Thus, the role of high-dose chemotherapy and stem cell transplantation in the treatment of multiple myeloma is evolving.

Approximately 5000 patients with multiple myeloma receive high-dose chemotherapy and stem cell transplant each year in North America.
What are hematopoietic stem cells and why are they so important?

Hematopoietic stem cells are remarkable types of cells that can divide and develop into any of the three main types of cells found in the blood:

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

Hematopoietic stem cells are found in the bone marrow, an organ which is found inside almost all the bones of the body, and in the circulating blood (also called peripheral blood). 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.
How do hematopoietic stem cells differ from other types of stem cells?

Hematopoietic stem cells are entirely different from embryonic stem cells, which have received much attention in the media over the last few years.

Embryonic stem cells are immature cells that come from human embryos. They are not yet specialized to perform any particular function in the body so they can grow and develop into many types of tissues. They are being studied as possible cures for many types of chronic diseases.

In contrast, hematopoietic stem cells are specialized and can only produce blood cells. Only hematopoietic stem cells are used in the transplantation procedure for multiple myeloma.

For the remainder of this discussion hematopoietic stem cell transplantation will be referred to simply as stem cell transplantation.

Who is a candidate for high-dose chemotherapy and stem cell transplantation?

Many factors must be considered to determine whether a patient is a candidate for high-dose chemotherapy and stem cell transplant. These include:

• The type of myeloma
• The stage of disease and how aggressive it is
• How the cancer responded to prior treatment
• Age and general physical condition

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. In general, patients in overall good physical condition with adequate kidney, lung, and heart function are eligible.

In addition, recent studies have shown that high-dose chemotherapy and stem cell transplant may even be possible in patients who have reduced kidney function or kidney failure, with proper precautions and somewhat lower doses of chemotherapy.

Transplant may not be feasible in patients who have received:

• Certain types of chemotherapy, especially melphalan
• Radiation therapy to the spine or pelvis

These treatments may impact the ability to obtain the stem cells needed for the transplantation.
Although it seems counterintuitive, some experts do not recommend high-dose chemotherapy and stem cell transplant for patients who have some types of high risk disease, which accounts for approximately 25% of myeloma patients. High-risk patients include those with certain types of DNA abnormalities (e.g. chromosome 13 deletion, chromosome 17 translocation). These patients tend to have shorter periods of remission. Further, one study showed there may actually be poorer survival.

*You and your doctor will determine if high-dose chemotherapy and stem cell transplant is right for you.*

**What are the different types of stem cell transplants?**

Stem cell transplants are classified in several different ways.

- **By the type of donor (individual providing stem cells):**
  - Autologous: from the patient
  - Allogeneic: from another individual who is genetically similar or matched to the patient.
    - The donor’s cells must match the patient’s, similar to the matching process used for kidney or other organ transplantation. In many cases, the stem cell donor is related to the recipient, typically a brother or sister.
  - Stem cells from unrelated donors can also be used if there is a match. It may also be possible to use cells from banked cord blood.

- **By the way in which stem cells are obtained or collected:**
  - Peripheral blood: from the bloodstream
  - Bone marrow

The vast majority of stem cell transplants performed in multiple myeloma patients are autologous peripheral blood stem cell (PBSC) transplants. Bone marrow transplants are rarely performed today in myeloma. Historically, these were the first type of stem cell transplants performed, however peripheral blood stem cell transplants put less strain on the body and stem cells are easier to collect. Occasionally, bone marrow transplants may be used if the number of stem cells that can be obtained from the peripheral blood are insufficient.
Autologous stem cell transplants have several advantages over other types of transplants:

• The patient serves as his or her own source of stem cells. There is no need to find a donor and there is no risk of incompatibility (i.e., a mismatch).
• In many instances, much of the procedure can be done on an outpatient basis.
• They are relatively safe procedures, with low rates of complications and infections compared with allogeneic transplants. Deaths due to the transplant itself are approximately 2% to 3% in patients with newly diagnosed myeloma.

In theory, one disadvantage of autologous stem cell transplants is that the transplant could be potentially contaminated with tumor cells when a patient’s stem cells are used. However, recent studies indicate that this is not a significant problem and is not a major cause of myeloma relapse.

High-dose chemotherapy followed by an allogeneic transplant has the potential to possibly provide better long-term control of myeloma (with longer time without disease progression) than autologous transplants. However, this is a risky procedure with a high death rate due to the procedure itself (20-50%). As a result, this type of transplant is rarely performed.

A safer type of allogeneic transplant is much more common. This type of transplant is called a mini-allogeneic transplant (also called a reduced intensity or non-myeloablative allogeneic transplant). A “mini-transplant” uses lower doses of chemotherapy prior to transplant and as a result the rate of death due to the procedure is very low, similar to that of an autologous transplant.
Types of Stem Cell Transplants

<table>
<thead>
<tr>
<th>Source of Stem Cells</th>
<th>Frequency of Use</th>
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<tbody>
<tr>
<td>Peripheral Blood (bloodstream)</td>
<td>More than 95% of transplants</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Occasional; only if the number of stem cells obtained from the peripheral blood is too low</td>
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<tr>
<td>Cord blood (umbilical cord)</td>
<td>Rare: Due to limited numbers of stem cells that can be collected from each umbilical cord. New research has shown the feasibility of using multiple cord blood units from more than one donor.</td>
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<table>
<thead>
<tr>
<th>Type of Donor</th>
<th>Frequency of Use</th>
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<tbody>
<tr>
<td>Autologous (autografts): Patient</td>
<td>Majority</td>
</tr>
<tr>
<td>Allogeneic: Siblings, rarely children or parents or an unrelated individual (matched for genetic similarity)</td>
<td>Unusual, mostly in clinical trials</td>
</tr>
<tr>
<td>Syngeneic: Identical twin</td>
<td>Rare</td>
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Other Types of Stem Cell Transplantation

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
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<tbody>
<tr>
<td>Tandem autologous transplant</td>
<td>2 transplants within 6 months</td>
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<tr>
<td>Mini (non-myeloablative) allogeneic transplant</td>
<td>Uses lower doses of chemotherapy (compared to standard high-dose chemotherapy). Often performed as a tandem transplant after one autologous transplant</td>
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What are the steps in the process of high-dose chemotherapy and stem cell transplantation?

High-dose chemotherapy and stem cell transplantation is a complex process that involves several steps.

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
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<tbody>
<tr>
<td>Induction Therapy (initial treatment)</td>
<td>Several months of myeloma treatment is given first to reduce the amount of tumor present, in order to increase the chance of a successful transplant. These treatments may be the same as those given to patients who are not planning to undergo a transplant.</td>
</tr>
<tr>
<td>Stem Cell Collection</td>
<td>Following induction therapy, stem cells are obtained or harvested from a patient or donor. In most cases, patients’ own stem cells are used (autologous transplant).</td>
</tr>
<tr>
<td>Freezing and Storage</td>
<td>When a patient’s own stem cells are used, they are frozen and stored until needed.</td>
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<tr>
<td>High-Dose Chemotherapy</td>
<td>High doses of chemotherapy are given in order to eliminate as much disease as possible. High-dose chemotherapy can be given either immediately following stem cell collection or at a later date.</td>
</tr>
<tr>
<td>Stem Cell Transplantation</td>
<td>After the completion of high-dose chemotherapy, the stem cells are injected into the patient’s bloodstream. The stem cells travel to the bone marrow and begin to produce new blood cells, replacing the normal cells lost during high-dose chemotherapy.</td>
</tr>
<tr>
<td>Consider Second Transplant or Consolidation Therapy, if M Protein Level greater than 90 % (Under Investigation)</td>
<td>Patients who do have a less than ideal response (less than a very good partial response) after high-dose chemotherapy and transplant may be considered for a second transplant or additional myeloma treatments (known as consolidation therapy) in order to further reduce the amount of tumor present.</td>
</tr>
<tr>
<td>Maintenance Therapy</td>
<td>Ongoing treatment with a myeloma drug may be considered, even for patients who are in complete remission, following the completion of high-dose chemotherapy and stem cell transplant, with the goal of further reducing the chance of a relapse.</td>
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**What is induction therapy?**

Induction therapy is the initial myeloma treatment given to newly diagnosed or previously untreated myeloma patients whether or not they plan to undergo high-dose chemotherapy and stem cell transplant. Prior to high-dose chemotherapy and stem cell transplant, patients receive induction therapy to reduce the amount of tumor present. Studies have shown that patients who have fewer detectable myeloma cells prior to transplant tend to have a lower risk of relapse and longer survival.

Induction therapy is typically given for approximately 4 months (or cycles). The types of treatments given may also be appropriate for patients who may not be planning to undergo transplant.

Options for induction therapy typically include:

- **Velcade®** plus **dexamethasone** (Velcade-dex)
  - In a large clinical study, patients receiving Velcade in combination with dexamethasone had better responses and longer survival without disease progression than patients who received a type of older chemotherapy treatment (**VAD**: Vincristine, plus Adriamycin and Dexamethasone)
- **Revlimid®** plus **dexamethasone** (Revlimid-dex)
  - In a large clinical study, 90% of patients who received four cycles of Revlimid and then went on to transplant were alive after 3 years.
- **Velcade** plus **Thalomid®** plus **dexamethasone** (VTD):
  - Patients who received this treatment had higher response rates both before and after high-dose chemotherapy and stem cell transplant as compared to another common treatment (Thalomid plus dexamethasone). These patients also survived longer without any disease progression after high-dose chemotherapy and stem cell transplantation.

Thalomid plus dexamethasone (Thal-dex) is another type of induction therapy that was previously used frequently. It has now been replaced with new treatments that are more effective and have fewer side effects.

Kidney function is one factor that needs to be taken into consideration in the selection of an induction therapy. Patients who have kidney failure or poor kidney function may be better candidates for a treatment including Velcade.

There are many other induction treatments that are being studied by researchers, including:

- Velcade plus Revlimid and dexamethasone (VRD)
- **Cytoxan®** plus Velcade plus Revlimid and dexamethasone (CVRD)
- Revlimid plus Cytoxan plus dexamethasone (RCD)
- Revlimid plus Velcade plus Doxil® plus dexamethasone (RVDD)
- Velcade plus Cytoxan plus dexamethasone (VCD)

*You and your doctor will determine which induction regimen is best for you.* For information on clinical trials evaluating induction therapy visit the MMRF’s website [www.themmr.org](http://www.themmr.org).
How are stem cells collected and stored?
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 a person’s peripheral blood (the bloodstream). Today, most autologous transplants utilize peripheral blood stem cells (PBSCs). In contrast, bone marrow stem cells may be used somewhat more frequently in allogeneic transplants.

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.

Collecting stem cells from peripheral blood
Harvesting stem cells from the blood takes approximately a week and has certain advantages over collecting stem cells from bone marrow. General anesthesia is not needed for this collection method, and it often can be done in an outpatient setting so no overnight hospital stay is necessary.

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

Typically, the goal is to collect enough stem cells to permit 2-3 transplants.
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 "white blood cell growth factor," and it is usually injected under the skin, much like an insulin injection for diabetes. A drug called Mozobil® (or plerixafor) may be used in combination with colony-stimulating factors in order further enhance stem cell mobilization.

Once a sufficient number of stem cells are mobilized from the bone marrow into the bloodstream, the stem cells are collected using a non-surgical procedure called apheresis. Apheresis is a procedure in which blood is removed from the patient or a donor via a needle in the arm, similar to a blood donation. Alternatively, patients may also have blood removed via a catheter that is placed in a vein in the chest. The blood is then circulated through a machine which separates the stem cells from the blood, while the rest of the blood flows back into the patient or donor.

Apheresis is a relatively painless procedure. Patient or donors usually do not need to be hospitalized but must come in for one to three sessions, lasting two to four hours each, in order to ensure that enough stem cells are collected.

**Storing stem cells**

After the bone marrow or peripheral blood stem cells are collected from the patient, they are processed in the laboratory, frozen (cryopreserved) and stored. Stem cells can be stored indefinitely until they are needed.

*Allogeneic* stem cells typically do not require this step since they are collected just prior to transplant.
What is high-dose chemotherapy?
After the bone marrow or stem cells are collected the patient is eligible to receive high-dose chemotherapy. The higher doses of chemotherapy are designed to destroy cancer cells more effectively than standard chemotherapy. Some patients may receive one or more treatments of high-dose chemotherapy, possibly in combination with radiation therapy, over a period of several days. This combination of treatments is also referred to as a conditioning regimen. These treatments, in addition to killing cancer cells, also destroy the blood-producing cells in the bone marrow, hence the need for the stem cell transplant.

The chemotherapy drug melphalan, given alone, is the most commonly used conditioning regimen in myeloma. It is typically given at a dose of approximately 200mg/m².

High-dose chemotherapy can be given either immediately following stem cell collection or at a later date. Some patients may receive their high-dose chemotherapy on an outpatient basis.
How are stem cells “transplanted” after high-dose chemotherapy?
Within a few days after completing the high-dose chemotherapy, the stored blood or bone marrow (or recently harvested allogeneic) stem cells are transplanted, or infused, into the patient's bloodstream. The infusion process is similar to a blood transfusion, and can be done on an outpatient basis, in some cases. The frozen bags of bone marrow or blood cells are thawed in a warm water bath and infused into a vein over a period of 2 to 4 hours. The 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.

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 12 to 15 days following infusion. Growth factors (colony-stimulating factors, G-CSF) may be administered during this time to stimulate the process of blood cell production.

What is consolidation therapy?
Consolidation therapy is additional myeloma therapy given after high-dose therapy and stem cell transplantation to patients who may not have achieved a substantial response (i.e., very good partial response or complete response).

What is maintenance therapy?
Maintenance therapy is additional myeloma treatment that may be given after stem cell transplant in order to further reduce the risk of relapse.

There is growing evidence that Revlimid and/or Velcade can improve the extent and duration of response achieved with high-dose chemotherapy and stem cell transplant when used as maintenance therapy following transplant. However, it is still too early to tell if maintenance therapy will prolong survival.
The use of maintenance therapy following high-dose chemotherapy and transplantation is something that needs to be decided on a case-by-case basis. For instance, patients who are considered to have standard-risk disease who achieve a complete response or very good partial response following transplant may do very well for years without maintenance therapy. So, close observation or maintenance therapy are both viable options for these patients. In contrast, patients with high-risk disease or those with a high tumor burden following transplant generally do not have a long period of response, and thus may need continuing therapy of some kind. However, with maintenance therapy one must also consider the potential side effects that may be associated with using a drug over an extended period of time, as well as the potential risk for developing resistance to the drug. We will have to wait for additional data from clinical studies before we have all the answers we need regarding routine use of maintenance therapy.

Patients who have undergone a stem cell transplant should discuss with their doctors the pros and cons of maintenance therapy.

For information on clinical trials evaluating maintenance therapy visit the MMRF’s website www.themmrf.org.

What are the possible side effects?

As with most medical treatments, there are side effects associated with the process of stem cell transplantation. Everyone is different and the type and severity of side effects vary for each individual.

Some of the side effects that are associated with the process are described below.

**Stem Cell Collection**
In the majority of cases, the only side effect of the collection procedure when bone marrow is taken is soreness in the hip area for a few days. Another common side effect is light 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 relieved by medication.

In addition, catheter insertion may be associated with pain or bleeding at the insertion site. Occasionally, blood clots may form around the catheter inside the vein and in rare cases there may be infection at the catheter site that can spread to the bloodstream.

**Chemotherapy**
Most of the significant potential side effects of stem cell transplantation are a result of the high-dose chemotherapy.
Shortly before starting chemotherapy, patients usually are given large amounts of fluid to prevent dehydration and kidney damage. Medication designed to prevent or lessen some of the expected side effects of treatment are also given. 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.

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

Because of the high doses of chemotherapy your immune system will be weakened and you will be susceptible to infection, especially in the first month after transplant. While medications are given to prevent infection, special precautions are necessary to minimize patients’ risk of infection. Anemia is also common and is treated with both blood transfusions as well as growth factors to help the body produce more red blood cells.

### Preventing infection

Antibiotics, antiviral and/or antifungal medicines are often prescribed to help prevent infection. Other precautions are also recommended including:

- Visitors and family may be asked to wash their hands and wear masks and gloves to minimize contact with the patient
- Avoid contact with anyone who has a cold or other infection
- Limited contact with children may be suggested, as they may be carriers of germs
- 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

Other common, but, temporary side effects include:

- Nausea
- Vomiting
- Diarrhea
- Stomach pain/cramps*
- Heartburn*
- Mouth sores (oral mucositis)
- Painful or difficult swallowing**
- Skin rash
- Hair loss

* Caused by an inflammation of the small intestine (enteritis)
** Caused by an irritated esophagus (tube leading from the mouth to the stomach), also known as esophagitis.
Many of these side effects can be managed with medications as well as other supportive measures. Some of the medications for side effects are described below.

- **Nausea and vomiting**: Some of the commonly used medicines to prevent and treat nausea and vomiting include: Zofran®, Kytril®, Aloxi®, Anzemet®, Emend®.
- **Diarrhea**: Imodium® (loperamide) is given along with fluids containing important minerals (electrolytes) that are lost due to diarrhea.
- **Mouth sores**:
  - Kepivance® (palifermin) is a growth factor that increases the growth of the cells lining the mouth. It helps reduce the chance of developing mouth sores and also reduces the length of time that patients may experience mouth sores.
  - Glutamine is an important amino acid (protein building block) that may help reduce the severity of mouth sores.
  - Pain medicines: Depending on the severity of the mouth sores, various pain medicines may be used including morphine.

### Tips for Managing Chemotherapy Side Effects

In addition to medication, there are other ways that can help manage side effects.

**Nausea and Vomiting**
- Small, frequent meals
- Avoid lying flat immediately after eating
- Minimize food odors; cold foods may be more appealing
- Dry crackers or toast eaten before any activity may help after periods of sleep or rest
- Limit fluids with meals; eating dry meals helps to curb nausea
- Clear cool beverages are recommended

**Diarrhea and Enteritis**
- Eating small meals often
- Avoidance of high fiber foods, milk or milk products and foods that tend to cause gas and cramps

**Mouth Sores or Esophagitis**
- Good oral hygiene and a thorough dental cleaning prior to therapy are recommended to help prevent and/or reduce the severity of mouth sores.
- Eat soft foods
- Avoid of tart, acidic or very salty foods are recommended to minimize further irritation.
- Eat a high calorie, high protein diet to help speed healing.
**Stem cell infusion (transplantation)**
The most common temporary side effects of the stem cell infusion process are caused by the preservative (called DMSO) used in the cell freezing process. Potential side effects related to this preservative include:

- Nausea and vomiting
- Abdominal cramping
- Chilling
- An unusual odor
- Taste of garlic

In rare cases, this preservative 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.

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

In **allogeneic transplants**, there may be complications because the donor stem cells are from a different individual. One potentially serious complication is graft versus host disease (GVHD), a condition where immune cells in the donor transplant attack the recipient’s cells. In some cases, the recipient may reject the graft and not allow the new stem cells to grow. Patients are given drugs to suppress the immune system in order to prevent or control GVHD.

**What is the recovery process like?**
Like anything else, recovery from transplantation is individual and varies from patient to patient.

The doctors, nurses, and other members of the healthcare team will do everything possible to ensure a successful recovery. However, patients and their family or caregivers are also active participants in the recovery process.

Patients undergoing **autologous stem cell transplants** tend to have fewer side effects and a shorter recovery period than patients undergoing **allogeneic transplants**.

Patients receiving autologous transplants can expect to stay in the hospital for about 2 weeks or less following a stem cell transplant. Blood counts begin to recover 10-14 days after chemotherapy. Fatigue may continue for 1-3 months. Patients who receive part of their transplant care on an outpatient basis need to stay near the treatment center so that they can be closely monitored. Frequent check-ups and tests are required during the early recovery period, which typically lasts about 6 weeks.
Some patients are admitted to the hospital during the recovery period. On the average, it takes about 2 to 3 months to recover normal physical performance after an autologous procedure.

Patients who have undergone allogeneic transplants can expect to stay in the hospital for about 4 to 6 weeks, with a recovery period of up to 6 months, depending on the degree and nature of any complications that may occur.

Each medical center has its own specific guidelines for patient care, during recovery. The healthcare team will explain these to the patient and family members.

It is important to remember that your immune system may be compromised for a while, so you may be more susceptible to infections. Some patients, especially those receiving allogeneic transplants, may need up to a year to return to normal functioning.

Despite the many side effects that may occur, most patients have a very good quality of life after recovery from high-dose chemotherapy and stem cell transplantation.

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**When is the best time to undergo high-dose chemotherapy and stem cell transplant?**

**Early versus Delayed Transplant**
The best time to undergo high-dose chemotherapy and stem cell transplant is an individual decision. Studies have shown that there is no difference in survival in patients who choose to undergo this procedure early – immediately following induction (initial) therapy versus patients those who delay transplant until they relapse (first relapse).

Factors that play into the decision may include:

- **Response to induction therapy**: It is unclear whether or not patients who are in complete remission after induction therapy will derive additional benefit from immediate high-dose chemotherapy and stem cell transplant

- **Quality of life**: Patients who achieve disease remission following transplant have a better quality of life. Many patients may have extended remission times – as much as five to seven years. As a result, there is a longer period without the need for myeloma treatment and the side effects associated with treatment. Thus, there is the potential for improved quality of life earlier in the course of treatment.

In addition, there is some evidence that greater benefit may be achieved when a transplant is performed when a patient has received treatment for less than one year

Many experts prefer early transplant, due to the quality of life benefits.

*You and your doctor will discuss the pros and cons of early versus delayed transplant in your case.*
Can patients with relapsed or refractory disease undergo high-dose chemotherapy and stem cell transplantation?

Patients who respond or obtain stable disease after therapy for relapsed or refractory myeloma may be eligible to receive an autologous transplant. In addition, a second autologous stem cell transplant is sometimes performed in patients who have relapsed after an initial stem cell transplant.

- In a clinical study conducted in patients with relatively good prognosis, who relapsed after high-dose chemotherapy and stem cell transplantation, patients survived over 6 years after a second transplant. This survival time is similar to that achieved with a planned tandem (double) transplant in newly diagnosed patients.

See page 25 of this brochure for more information about tandem transplants.

How are researchers trying to improve treatment with high-dose chemotherapy and stem cell transplantation?

Researchers are investigating ways to increase response rates and remission time as well as to prolong survival with high-dose chemotherapy and autologous transplants. Some approaches under investigation include:

- Use of newer therapies (e.g., Velcade, Revlimid, Thalomid) following transplantation as maintenance therapy
- Various types of high-dose chemotherapy regimens (also called conditioning regimens) are also being evaluated.
- Use of double or tandem transplants.
- Use of autologous transplants followed by mini-allogeneic transplants

Promising preliminary results have been seen when the newer agents are used as induction therapy prior to transplant. The impressive response rates seen with earlier use of these newer agents (e.g., Velcade, Revlimid, Thalomid) may necessitate a re-evaluation of the role and timing of autologous stem cell transplants in the treatment of myeloma. However, the effect of these new strategies on survival has yet to be determined.
What do the experts recommend?

Although, there is no definitive consensus among myeloma specialists, the following recommendations are generally accepted.

- Transplant-eligible patients with symptomatic myeloma should receive initial (induction) therapy followed by stem cell collection for two transplants.
- Upfront high-dose chemotherapy (with 200mg/m² melphalan) followed by autologous transplantation is generally preferred following induction therapy for patients with standard risk disease.
- Patients who do not have a significant response to a first autologous transplant (VGPR or CR) may consider a second autologous transplant.
- Other options include:
  - Continuation of induction therapy
  - Standard allogeneic (younger patients only) or mini-allogeneic transplant in a clinical trial
- Maintenance therapy may be considered following high-dose chemotherapy and stem cell transplantation, particularly in patients who do not achieve a substantial response (VGPR or CR)

What major clinical trials are ongoing?

Research is underway to determine the most effective approach. One of the major trials that is underway is the BMT CTN 0702 trial. In this study, patients will first undergo high-dose chemotherapy and autologous stem cell transplant and then will be divided into three groups for comparison of additional therapies as follows:

1) Second autologous transplant (tandem transplant) followed by maintenance therapy with Revlimid
2) Consolidation therapy with Revlimid, Velcade and Dex (RVD) followed by maintenance therapy with Revlimid
3) Maintenance therapy with Revlimid

For more information on clinical trials, visit www.myelomatrials.org
Types of Transplants

How effective are autologous transplants?

The benefit of high-dose chemotherapy followed by autologous stem cell transplant versus continued therapy with current myeloma treatments is being studied.

Historically, response rates of up to 75% to 90% have been seen, with complete response rates ranging from about 20% to 40%. In these studies, survival as well as event-free survival were significantly extended. In two large studies, patients survived approximately five years on average (13-14 months longer than patients receiving older types of chemotherapy).

Data from a European Group which tracked 15,000 autologous transplants performed in patients with myeloma indicate that survival 15 years after autologous transplant is approximately 5%. Generally, patients who tend to do better are as follows:

- Younger
- Undergo transplant early in disease
- Have lower stage myeloma (Stage I or II)
- Have lower risk disease
- Had a better response to chemotherapy

*It is important to remember that these statistics do not take the use of the newer agents into consideration.*

What is the impact of the newer agents on the outcome of high-dose chemotherapy followed by stem cell transplantation?

Several studies have evaluated the impact of induction therapy with newer agents followed by high-dose chemotherapy and transplantation.

Two large studies conducted in Europe evaluated the effectiveness of Velcade plus dexamethasone (VD) and Velcade plus Thalomid plus dexamethasone (VTD). Both of these treatments resulted in high response rates, even in patients with a type of high-risk myeloma (e.g., DNA abnormalities). It is too early to know the impact on patient survival in these studies.
What are tandem autologous transplants?

A tandem autologous transplant, also known as a double autologous transplant, requires the patient to undergo two planned autologous stem cell transplants within 6 months. Stem cells are collected once before the initial transplant and half are used for each procedure. The second transplant is performed after recovery from the first procedure.

The value of double transplantation is controversial and results from studies vary. One analysis of various studies including 1800 patients did not show any survival benefit. Further there was an increase in deaths associated with this approach.

In contrast, other studies have shown improved response rates and survival with the highly demanding tandem regimen compared with single transplantation.

A major study conducted in France demonstrated that double transplantation led to improved survival compared with single transplantation in patients with previously untreated myeloma. This study included 599 patients under the age of 60.

- The percentage of patients achieving a complete or very good partial response was similar among the single (42%) and double transplant (50%) groups.
- Survival 7 years after transplant was twice that seen with single transplants
  - 42% of patients who had double transplants were alive as compared to 21% of patients who only had a single transplant.
- Double transplantation appeared to be particularly beneficial to those patients who did not achieve a very good response following the first transplant.
- Patients who had a complete response or very good partial response after their first transplant did not gain any additional benefit from a second transplant.

It is important to note that patients in this study received an older type of chemotherapy, called VAD, as induction therapy prior to high-dose chemotherapy and stem cell transplantation. Newer therapies (such as the combination of Velcade and dexamethasone) have been proven more effective than VAD, thus, one would expect even better outcomes with the newer agents that are commonly used today.

In addition, for patients who do not achieve a good response after double transplantation (e.g., complete response or very good partial response) additional myeloma treatment has been shown to be beneficial.

- One large study showed that Thalomid increased response rates and survival after double transplantation.

It has yet to be determined which patients benefit most from a tandem transplant. In particular, it is unclear as to whether high-risk patients benefit. Research is ongoing.
What are allogeneic stem cell transplants?

Allogeneic stem cell transplants refer to transplants in which stem cells are donated from another individual who is genetically similar or matched to the patient (e.g., a close relative).

Currently, high-dose chemotherapy in conjunction with allogeneic stem cell transplant is rarely performed for treatment of myeloma in the United States outside of clinical trials, due to a high rate of death associated with the treatment itself (20-50%, depending on the patients overall health). However, slightly more of these procedures are performed in Europe. Generally, if an allogeneic transplant is selected it is usually performed following a somewhat lower dose of chemotherapy. This is called a mini or non-myeloablative allogeneic transplant.

Advantages of Allogeneic Transplants

Studies have shown that allogeneic stem cell transplants leads to prolonged survival without any evidence of myeloma in some patients. In addition, the relapse rate is lower than that seen with autologous transplants. Since allografts come from an individual other than the patient, they have the benefit of not containing tumor cells. Another potential benefit of allogeneic transplants is their ability to help the patient fight against the myeloma tumor. The donor’s immune cells can help attack the tumor; a phenomenon referred to as a graft-versus-myeloma effect. This effect may account in part for the lower relapse rates seen following allogeneic transplants compared to autologous transplants.

Researchers are working to harness the anti-tumor effect of allogeneic transplants while making them safer.

Disadvantages

Allogeneic transplants are associated with a greater mortality and complications than autologous transplants, including infections and graft-versus-host disease (GVHD). In graft versus host disease the donor’s immune cells attacks the patient’s body including the skin, liver, or gastrointestinal tract and in some cases severe organ failure can occur. This is due to the fact that cells from the donor and the patient, although matched for tissue type, are still considered foreign to each other. GVHD is the primary reason that allografts are associated with significant mortality. Drugs that suppress the immune system are given to try to prevent or control GVHD.

GVHD is typically referred to as acute when it occurs within the first 3 months after transplantation and chronic when it occurs after 3 months.
**Who is a candidate for an allogeneic transplant?**
Because the conditions required for allogeneic transplants are rigorous and the potential for severe side effects is higher, these types of transplants are generally conducted within a clinical trial and limited to younger patients (under 55 years old) in good health. Candidates for allogeneic transplants include patients who:
- Progress following an autologous transplant
- Have disease that responded or is stable after initial therapy (induction therapy)
- Have relapsed or refractory disease after several prior treatments

**What are mini-allogeneic transplants?**
Another approach being investigated in myeloma is the use of a mini (or non-myeloablative) allogeneic transplant. Mini-allogeneic transplants involve the use of somewhat lower dose of chemotherapy (as compared to the typical high-dose chemotherapy) in combination with an allogeneic stem cell transplant. This dose of chemotherapy does not destroy the bone marrow completely, hence the term “mini” or non-myeloablative. For this reason, this type of transplant appears to be a safer alternative to conventional allogeneic transplants.

Typical mortality rates associated with mini-transplants are 10-20% as compared to mortality rates of 20-50% with high-dose allogeneic transplants.

In addition to using a more moderate dose of chemotherapy to kill myeloma cells, this type of transplant aims to use the immune system to further eliminate myeloma cells, a phenomenon called the graft-versus myeloma effect.

One large study has compared the effectiveness and safety of mini-allogeneic transplants to conventional transplants. Mortality due to the procedure was significantly lower and there was no difference in survival. However, patients who received the mini-allogeneic transplant had a much higher rate of relapse.

Researchers are looking at ways to improve the results of mini-allogeneic transplants such as methods to prevent acute GVHD and use of maintenance therapy following the transplant.
What are autologous transplants followed by mini-allogeneic transplants?

Mini-transplants appear to be more effective when used in combination with an autologous stem cell transplant. In this type of planned tandem transplant, patients first undergo an autologous stem cell transplant to provide substantial tumor reduction. This is followed by a mini-allogeneic transplant from a matched donor 2 to 4 months later. The objective of using the mini-allogeneic approach is to use the immune system (i.e. graft-versus myeloma effect) to eradicate any residual disease and thereby obtain long-term disease control.

Preliminary results from several small ongoing the studies investigating autologous transplant followed by mini-allogeneic transplant (also called an auto-allo transplant) show promising results, with both improved myeloma outcomes and reduced mortality due to treatment (15%, which is still much higher than the minimal mortality rate seen with autologous transplants).

One large transplant center conducted an analysis of the transplants performed and found that patients who had autologous followed by mini-allogeneic transplants had significantly longer survival (68% at 5 years) as compared to patients only undergoing a single standard dose allogeneic transplant (31% at 5 years).

A major study has compared tandem autologous transplantation with an auto-allo transplant. For patients with standard risk disease, there no difference in outcome between these types of procedures and the mortality due to treatment was higher with the auto-allo approach. However, preliminary data in patients with high risk disease showed some evidence of improved survival with the auto-allo technique. Longer term follow-up is needed to definitively determine the benefit of auto-allo transplants in high risk patients.
Practical Considerations

How does one choose a transplant center?

A stem cell transplant is a complex medical procedure that requires an expert team of healthcare professionals who specialize in the necessary type of care. There are several medical centers that specialize in stem cell transplants for patients with myeloma. Your doctor and the MMRF will be able to direct you to a suitable facility.

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<th>Questions to Ask Your Doctor</th>
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<td>• What are the pros and cons of stem cell transplantation in my case?</td>
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<td>• When is the best time for me to undergo transplantation?</td>
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<td>• Does your center do stem cell transplants? How many transplants has your center performed in multiple myeloma in the last year?</td>
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<td>• How long will I be in the hospital?</td>
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<td>• What kind of changes in my lifestyle will I need to make?</td>
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<td>• When do I go back to you for follow-up?</td>
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What type of emotional issues can I expect?

Transplantation is a physically and psychologically demanding procedure that can be very stressful. Some patients and family members may experience a range of emotions including, anger, depression, and anxiety. Support services are available through the hospital as well as many other organizations (see resources on the next page).
Where can I get more information?

In addition to the MMRF, there are several organizations listed below that can provide you with additional information about stem cell transplants, as well as counseling, referrals, insurance information, and financial assistance. A variety of support services are also provided directly through the transplant center.

<table>
<thead>
<tr>
<th>Organization</th>
<th>Address</th>
<th>Phone Number</th>
<th>Website</th>
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<tr>
<td>Blood and Marrow Transplant Information Network</td>
<td>2310 Skokie Valley Road, Suite 104, Highland Park, IL 60035</td>
<td>1-888-597-7674</td>
<td><a href="http://www.bmtinfonet.org">www.bmtinfonet.org</a></td>
</tr>
<tr>
<td>The Marrow Foundation®</td>
<td>400 Seventh Street NW, Suite 206, Washington, DC 20004</td>
<td>1-800-507-5427</td>
<td><a href="http://www.themarrowfoundation.org">www.themarrowfoundation.org</a></td>
</tr>
<tr>
<td>CancerCare®</td>
<td>275 Seventh Ave, 22nd Floor, New York, NY 10001</td>
<td>1-800-813-HOPE (4673)</td>
<td><a href="http://www.cancercare.org">www.cancercare.org</a></td>
</tr>
<tr>
<td>Patient Advocate Foundation</td>
<td>700 Thimble Shoals Blvd, Suite 200, Newport News, VA 23606</td>
<td>1-800-532-5274</td>
<td><a href="http://www.patientadvocate.org">www.patientadvocate.org</a></td>
</tr>
<tr>
<td>The Bone Marrow Foundation</td>
<td>337 E 88th Street, Suite 1B, New York, NY 10128</td>
<td>1-800-365-1336</td>
<td><a href="http://www.bonemarrow.org">www.bonemarrow.org</a></td>
</tr>
<tr>
<td>National Marrow Donor Program®</td>
<td>3001 Broadway Street NE, Suite 500, Minneapolis, MN 55413</td>
<td>1-800-MARROW2 (627-7692)</td>
<td><a href="http://www.marrow.org">www.marrow.org</a></td>
</tr>
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We would like to thank William Bensinger, MD for his contributions to this brochure.
Glossary

Anemia
Decrease in the number of red blood cells in the blood. Anemia can cause fatigue.

**Allogeneic stem cell transplant**
A procedure in which stem cells from the bone marrow or blood from a donor (usually a relative) are collected, stored, and infused into a patient following high-dose chemotherapy. Stem cells are responsible from the production of blood cells.

Allograft
See allogeneic stem cell transplant.

**Apheresis**
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.

**Autologous stem cell transplant**
A commonly used type of stem cell transplantation where the patient serves as their own donor.

**Autologous peripheral blood stem cell transplant**
A type of stem cell transplantation where the patient’s own stem cells are used. In this type of transplant stem cells are collected from the circulating blood (peripheral blood). Autologous peripheral blood stem cell transplants are the most common type of stem cell transplants performed today.

**Bone marrow**
Soft, spongy tissue found in the center of many bones where blood cells are produced.

**Bone marrow transplant**
A type of stem cell transplant where the stem cells are removed from the bone marrow. It is infrequently used today.

**Catheter**
A thin flexible tube that is inserted into the body. For example it may be inserted into a vein in order to give drugs, blood or nutrients. Catheters are also used to take blood or to empty the bladder.

**Chemotherapy**
The use of drugs to treat cancer.
**Chromosome 13, 14 or 17 deletions**
In some individuals with multiple myeloma, a piece of one or more of certain chromosomes may be missing (or deleted). Deletions in chromosome 13, 14 or 17 may result in a more aggressive form of myeloma.

**Colony-stimulating factor (CSF)**
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 move stem cells from the bone marrow into the bloodstream.

**Complete remission**
See complete response.

**Complete response (CR)**
A treatment outcome where there are no detectable myeloma cells and all laboratory tests are normal.

**Consolidation therapy**
Anti-myeloma treatment given after the initial therapy in order to further reduce the number of cancer cells.

**Conditioning regimen**
Combination of chemotherapy and/or radiation treatments administered over a period of several days prior to stem cell transplantation in order to kill cancer cells.

**CR**
See complete response.

**Cryopreservation**
A method of freezing cells that permits storage over an extended period of time. For example, stem cells may be removed and cryopreserved for use at a later date.

**Cytoxan®**
Type of chemotherapy. Also known as cyclophosphamide.

**Dex**
See dexamethasone.

**Dexamethasone (dex)**
Type of steroid used in the treatment of myeloma. It is taken orally. Dexamethasone is often used in combination with other anti-myeloma drugs. The brand name for dexamethasone is Decadron®.

**Doxil®**
A type of chemotherapy.
Electrolytes
Electrolytes are minerals that are present in the body such as sodium, potassium, chloride, and bicarbonate. The balance of electrolytes is essential for the normal function of organs. Diarrhea may cause electrolyte depletion.

Engraftment
Process in which stem cells in transplanted bone marrow or blood migrate to the bone marrow and begin to grow and produce new white blood cells, red blood cells, and platelets.

Enteritis
Stomach pain or cramps caused by an inflammation of the small intestine.

Esophagitis
Heartburn caused by an irritated esophagus (tube leading from the mouth to the stomach).

Event-free survival
Term used in cancer clinical trials to indicate the length of time that a patient remains free of certain negative events, such as cancer recurrence or progression, complications from the disease, or death from any cause.

Graft versus host disease
Complication of allogeneic transplants resulting from donor immune cells recognizing the recipient's cells as foreign and mounting an attack against them.

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

Growth factors
Drugs that are used to stimulate the production of certain types of cells. The most commonly used growth factors are red blood cell growth factors (also known as erythropoietin) and white blood cell growth factors (also known as colony stimulating factors or CSFs).

Hematopoietic stem cells
Cells found in the bone marrow or the circulating bone that are responsible for the production of red blood cells.

High-dose chemotherapy
Administration of very high doses of chemotherapy that may be more effective in eliminating myeloma cells than standard treatments. High-dose chemotherapy destroys the bone marrow, which is responsible for the production of blood cells. Therefore, stem cell transplant is required to replenish blood-forming bone marrow cells.
High risk myeloma
A type of myeloma where there is some feature that indicates a worse prognosis. For example, certain types of abnormalities in the DNA are associated with more aggressive disease. In addition, elevated blood levels of a protein called beta 2-microglobulin is also associated with worse prognosis.

Induction therapy
Initial therapy for myeloma. This term often refers to the use of anti-myeloma drugs prior to high-dose chemotherapy and stem cell transplant in order to reduce the amount of cancer in the body.

M protein
See monoclonal protein.

Maintenance therapy
Additional myeloma treatment that may be given to further reduce the chance of a relapse. For example, maintenance therapy may be given following stem cell transplantation.

Melphalan
Type of chemotherapy often used in the treatment of myeloma (also known as Alkeran®). It is given orally.

Mini-allogeneic transplant
Type of allogeneic stem cell transplant that uses lower doses of chemotherapy and thus does not completely destroy the bone marrow; also known as mini-transplant or non-myeloablative transplant.

Mini-transplant
See mini-allogeneic transplant.

Monoclonal (M) protein
A type of protein made by myeloma cells, used to estimate the extent of myeloma disease. It is an abnormal type of antibody (or immunoglobulin) and is found in the blood or urine to estimate. M protein levels are used to determine the effectiveness of myeloma treatments.

Non-myeloablative allogeneic transplant
See mini-allogeneic transplant.
Peripheral blood
The blood that circulates throughout the body.

Peripheral blood stem cell transplant (PBSC)
A type of stem cell transplant that uses stem cells collected from the blood instead of the bone marrow. In many cases, the stem cells will be collected from the patient’s own blood rather than from a donor. This is called an autologous peripheral blood cell transplant.

Refractory myeloma
Myeloma that does not respond to the first therapy given and the number of myeloma cells continues to increase in spite of treatment.

Relapsed myeloma
Myeloma disease that initially responded to therapy but then begins to progress again.

Response
A decrease in the amount of myeloma cells as a result of treatment. Response is measured by the amount of M protein in the blood or urine.

Revlimid® (lenalidomide)
Oral drug with multiple anti-myeloma effects. Revlimid has been shown to be effective in newly-diagnosed and relapsed or refractory myeloma alone and in combination with other drugs. It is chemically similar to another myeloma drug called Thalomid®.

Standard risk myeloma
Indicates myeloma with an average prognosis.

Tandem transplant
Type of transplantation technique where a patient receives two planned transplants within a short period of time. Patients may receive 2 autologous transplants or an autologous stem cell transplant followed by a mini-transplant two to four months afterward.

Thalomid® (thalidomide)
Oral drug with multiple anti-myeloma effects. Thalomid has been shown to be effective in newly-diagnosed and relapsed or refractory myeloma alone and in combination with agents such as dexamethasone. It is chemically similar to a newer drug called Revlimid®.
**VAD**
An older type of chemotherapy treatment. It consists of the combination of two chemotherapy drugs (Vincristine, Adriamycin) plus dexamethasone, a steroid.

**Velcade® (bortezomib)**
A highly effective myeloma drug, known as a proteasome inhibitor. It is given intravenously either alone or in combination with other myeloma drugs.

**Very Good Partial Response (VGPR)**
Treatment outcome where there is a greater than 90% decrease in M protein; also known as near complete response or very good partial remission.