Donor Consent Form

Title: Multiple Myeloma Protocol

TITLE

High Dose Intravenous Melphalan with Autologous Peripheral Stem Cell or Bone Marrow Transplantation for Patients with High Risk Multiple Myeloma

CONSENT TO TREATMENT

You are invited to receive very high doses of chemotherapy and autologous bone marrow cell rescue because you have multiple myeloma that has a low likelihood of cure or prolonged survival free of disease with less aggressive therapy. Your doctors have recommended that you be treated with high dose chemotherapy with autologous bone marrow cell rescue.

EXPLANATION OF PROCEDURES

Obtain and Store Bone Marrow and/or Peripheral Blood Stem Cells

The high doses of chemotherapy used in this treatment require the collection of bone marrow cells (stem cells) from the bone marrow or bloodstream. These cells are preserved and later reinfused, after the high dose chemotherapy has been administered, to rescue the bone marrow.

This therapy involves one cycle of a single chemotherapy drug in high dose with stem cell (bone marrow) transplantation. Sufficient stem cells must be collected in advance to perform the transplant procedure. This will provide for rescue of the bone marrow from high dose therapy. We will plan to collect cells directly from the blood prior to any high dose chemotherapy. Alternatively, cells may be obtained from the pelvis if stem cell collection from the blood is insufficient.

The first aspect of this treatment is to collect and store your bone marrow cells collected from either the blood (peripheral blood stem cells) or directly from the bone marrow. It is important that before we collect your bone marrow cells we determine as best we can with present day methods that your bone marrow does not contain an excess amount of tumor cells. To do this we will obtain a sample of your bone marrow via a bone marrow biopsy. Bone marrow biopsy involves numbing your skin with a drug like Novocaine and inserting a needle through the numb skin into your pelvic bone and taking out a piece of marrow with the needle. We will study the bone marrow samples to determine how many tumor cells are present.

Stem cells collected from the blood are called “peripheral blood stem cells.” They are collected after the administration of drug(s) to help the stem cells escape the bone marrow and circulate in the blood. In addition to the chemotherapy drug cyclophosphamide (Cytoxan), you will receive a growth factor called G-CSF (Neupogen) or (Mozibil) before beginning stem cell collection to increase the number of circulating

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stem cells and decrease the length of time it takes to collect them. A central venous catheter is placed into your vein prior to beginning peripheral blood stem cell collection. The stem cells are then collected on a machine that takes blood from the catheter, separates and removes the stem cells, and gives the remaining blood back to you. This is done in the outpatient area of the Transplant Unit prior to admission for high dose chemotherapy. Once stem cells are collected they are processed and stored in the Bone Marrow Transplant Graft Engineering Lab.

Occasionally, we may not be able to collect all of the cells needed to safely do a bone marrow transplant from the blood. In this case, we may recommend collecting additional bone marrow cells in the operating room, called a bone marrow harvest. While you are under a general anesthetic enough marrow to produce a successful transplant (less than 10% of your total marrow) will be removed from your pelvic bones through needles. The procedure would be too painful without general anesthesia. We can collect your bone marrow and store it just like the cells from the bloodstream.

Once stem cells are collected, they are processed and preserved in the Bone Marrow Processing Facility.

**Giving High Dose Chemotherapy**

The second aspect of the treatment involves giving you chemotherapy in high doses. High doses of the chemotherapy drug melphalan will be used. This drug is a standard chemotherapy agent and not investigational in autologous bone marrow transplant treatments for multiple myeloma. The treatment as planned has perhaps the highest reported effectiveness of any bone marrow transplant treatment to date for multiple myeloma.

The chemotherapy will begin a few days to a week after your peripheral blood stem cell collection and/or marrow harvest unless delayed for medical reasons. All chemotherapy drugs will be given in your vein (through your central venous catheter).

High dose chemotherapy consists of the chemotherapy drug melphalan. On the second day, melphalan will be given over approximately 15 minutes, given with vigorous intravenous fluids. Twenty-four hours later, your stem cells are reinfused (transplant day).

You must have adequate major organ system function in order to proceed to transplant. You will undergo restaging of all sites of measurable and/or evaluable disease to confirm that your disease is responding to therapy. If there is evidence of progressive disease you may be offered alternative therapy. Such alternative options include other low dose chemotherapy, investigational drug studies, or other salvage therapies.

**Bone Marrow Transplant**

You will receive your bone marrow transplant approximately 24 hours after the chemotherapy is completed. Giving back your bone marrow involves the thawing out

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of your previously stored bone marrow and giving it back by vein. The freezing and storage process is done using methods commonly used by bone marrow transplant programs for bone marrow cells. A substance known as DMSO is used to protect the bone marrow cells from the freezing process. This compound has been used frequently in bone marrow transplantation and has been found to be entirely safe in bone marrow transplants. However, the compound has quite an unpleasant odor and when you receive your marrow transplant you will be aware of this odor for several hours. You may have chills or fever when you get your bone marrow; however, we will give you some medicines that should make these side effects less severe. You may require hospitalization until your blood counts return to normal, usually 2 to 4 weeks after your transplant, or may be offered much of the therapy as an outpatient.

POTENTIAL RISKS AND DISCOMFORTS

The following are the risks and discomforts you could potentially experience during this treatment:

Bone Marrow Stem Cell Collection Process:
Every effort will be made to collect sufficient peripheral blood stem cells to be able to safely do the transplant. The growth factor given to increase the number of circulating stem cells (G-CSF or Neupogen®) may be associated with mild side effects. You may have some irritation in the area of the skin where you receive your daily subcutaneous shots of G-CSF. You may also develop a rash. You may experience some pain in your bones and muscles, as well as fatigue and fevers. Your spleen may also become enlarged, but will return to a normal size after you stop using the medicine. There are rare reports of rupture of the spleen due to G-CSF. G-CSF will cause your white blood cell count to rise above a normal level, and some of those white blood cells are stem cells. The white blood cell count will return to a normal level once G-CSF is discontinued, upon satisfactory stem cell collection. Rarely, G-CSF can lower platelets, resulting in easy bruising or bleeding. G-CSF can cause elevation of your blood uric acid. In persons with hemoglobin disorders such as sickle cell disease, a severe crisis can be triggered by G-CSF. You will be screened if you are felt to be at risk for a hemoglobin disorder. If you test positive for a hemoglobin disorder, we will discuss the option of performing a red blood cell exchange before you start G-CSF to prevent complications. You will be closely followed for these problems.

The peripheral blood stem cells are separated on a cell separator device designed to collect only the cells we need to rescue the bone marrow and return the remainder to you. However, the separation of cells is not complete and some platelets and/or red blood cells may be removed in the process. This may on rare occasion require transfusion support after the procedure. The collection of peripheral blood stem cells on the cell separator machine requires the use of an anticoagulant (blood thinner) to prevent any clotting of blood in the tubing of the machine. The body rapidly breaks down this anticoagulant; thus, anticoagulation only occurs in the machine. The anticoagulant used can cause changes in the blood chemistry, resulting in temporary tingling of the mouth or hands, nausea, or weakness. These side effects are improved by the administration of calcium during the procedure.
There is an extremely small risk of irregular heartbeats as a result of the altered blood chemistry during the collection process. The process of peripheral blood stem cell collection is very similar to that used when donating platelets and has been applied safely thousands of times in that setting.

If direct bone marrow collection (bone marrow harvest) is required, a very small but definite risk is associated with general anesthesia. We do not expect any increased risk for patients undergoing anesthesia for bone marrow collection. We are depending on bone marrow biopsies prior to transplantation to tell us how much myeloma involvement of the bone marrow remains after your previous treatment. Studies have shown that up to 30% of the bone marrow cells can be malignant and yet you can still derive benefit from high dose therapy and bone marrow cell transplantation. You will have received chemotherapy prior to consideration of bone marrow transplantation to reduce the amount of the disease in the bone marrow prior to stem cell collection.

Central Venous Catheters: You will have a central venous catheter placed in the operating room or in the outpatient area of the transplant unit prior to peripheral blood stem cell collection. Coumadin (an anticoagulant pill) will be given in extremely low doses to help prevent a blood clot around the catheters. Although the dose of coumadin used is safe and effective, there is a theoretical risk that even this low dose of coumadin can increase your risk of bleeding. For that reason, the drug is discontinued after high dose therapy when your platelet count starts to drop.

High Dose Chemotherapy: The side effects of the chemotherapy are many but tolerable in most patients. A dangerous and troublesome side effect involves low white blood cell counts and low platelet counts which are expected to develop about one week after treatment is complete and recover about 3 to 4 weeks after treatment. The exact time low white counts and platelet counts occur and recover will vary from patient to patient. The low counts will expose you to dangerous and potentially fatal forms of infections, as well as increased risk from serious bleeding. These two events (low white cell count and low platelet count) are seen quite often in treating cancer patients and the entire bone marrow transplant team is skilled at watching for and treating these difficulties.

Nausea and vomiting will occur on the days of treatment and may be troublesome off and on until and even after the white count and platelet count recovers. A sore mouth is very likely that may extend into the throat and esophagus and may be so severe as to impair your ability to talk or swallow. A number of medications are used to relieve this pain. You need not be concerned about the lack of food intake because during the pre and post transplant period, you can receive nutrition therapy through your intravenous catheter if necessary. This will disappear as time passes, and generally begins to disappear when the white count becomes normal. Diarrhea may occur due to damage to the lining of the intestinal tract and may be severe. Hair loss will occur about 3 weeks after you receive high dose chemotherapy and is not permanent.

You will lose the ability to make sperm cells or egg cells thereby making you unable to become a natural parent (you will become sterile). The sterility may or may not be permanent. Loss of sexual drive may be experienced. Women may have irregular menstrual cycles or permanent loss of menstruation may occur, resulting in menopause.

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**Cyclophosphamide:** This drug may cause irritation to the lining of the urinary bladder, which may result in hemorrhage and scarring of the bladder. This side effect usually does not occur and preventative measures will be used to reduce the risk. Limited damage to the liver may occur, and is generally reversible. Abnormalities of the blood water balance may occur. Heart damage may occur and may lead to irreversible heart failure. Long term effects include sterility and a small (1-3%) risk of producing other types of cancer.

**Melphalan:** There is a risk of secondary malignancy, primarily acute leukemia or myelodysplasia. There is a 1 to 2% yearly incidence of secondary hematologic malignancy in patients treated with chronic low dose melphalan, but this is rarely reported after high dose melphalan alone. Uncommon toxicities include scarring of the lungs and worsening of liver or kidney function.

**Laboratory/Radiological Studies**

Repeated blood tests and X-rays will be required to monitor any toxicities or infections encountered during therapy. No tests are planned in addition to those ordinarily encountered in the course of high dose therapy and bone marrow transplantation. Bone marrow biopsies are required at the start of therapy and may be required thereafter. There is a risk of discomfort at the biopsy site, bruising, bleeding, and infection. Discomfort is usually mild, bruising and bleeding at the site is usually minimal, and infection is rare.

**Blood Product Transfusion**

During the high dose chemotherapy cycle you will almost certainly require the transfusion of blood or blood components. Transfusion is associated with risks such as transfusion reactions and the possible transmission of viral infections such as hepatitis or AIDS.

**GENERAL STATEMENT REGARDING RISKS**

While the autologous bone marrow transplantation process is associated with considerable risk, the goal of the treatment is to bring about a cure when this would not be possible with easier therapy. However, the side effects, as noted above, are considerable and can lead to death. It is important for you to understand every aspect of the risks involved and to question your doctors closely about this treatment program.

It may be that other side effects will occur that at present are not recognized as possible or worse toxicities may be encountered than that expected. That is the nature of high dose chemotherapy.

**POTENTIAL BENEFITS**

This therapy does not promise cure of your disease. It does offer a chance of slowing down the progression of your multiple myeloma. It is also possible the myeloma will

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continue to grow despite this treatment. There may be other high dose chemotherapy options available to you.

PERIPHERAL STEM CELL/BONE MARROW STORAGE

The stem cells collected from the peripheral blood and/or bone marrow are specifically collected as a rescue from the bone marrow damage that may be encountered in the course of the therapy outlined in this consent. The cells will be processed and stored in the Roper Bone Marrow Processing Facility for that purpose only. If the cells remain stored for a period of two years or longer without being used, there is an extremely low likelihood that they will be needed for transplantation. Furthermore, it is very expensive to maintain these cells in long-term storage. Therefore, stem cells will be stored for a maximum of two (2) years from the date of collection and/or harvest. Thereafter, the stored cells will be used for research purposes or otherwise destroyed and will not be available for use in transplantation. Longer-term storage is possible for unusual circumstances, and will be performed by prior arrangement only.
EFFECTS ON UNBORN CHILDREN

Exposure to the drugs used in this treatment will be extremely harmful and probably fatal to an unborn child carried by a mother who is receiving these drugs. You cannot participate in this treatment if you are pregnant. Also, if a man fathers a child, there may be potential risk to the unborn baby; therefore, female sexual partners of men on treatment as well as women of childbearing age on treatment must use an adequate form of birth control while on treatment and until instructed otherwise. Reliable methods of birth control are considered to be abstinence (not having sex), oral contraceptives, intrauterine device (IUD), DepoProvera, Norplant, tubal ligation or hysterectomy. An acceptable, although less reliable method involves careful use of condoms and spermicidal foam or gel and/or cervical cap or sponge. If you think you might be pregnant anytime during the treatment, you agree to tell your doctor immediately. Since most methods of birth control are not 100% reliable, if you are a woman of childbearing potential, a pregnancy test is required. We encourage you to discuss this issue further with your doctors if you have any questions.

ALTERNATIVES TO THIS THERAPY

Other treatment for your cancer is available including drugs in lower doses and possibly radiation therapy and/or investigational therapy, depending on your particular condition.

If you choose not to participate in this treatment and do not wish to seek alternate forms of anti-cancer therapy this does not preclude your receipt of treatment for any pain or other effects of your disease.

FINANCIAL OBLIGATION

You will receive a hospital charge for all pharmaceutical services that are used in the conduct of this treatment. You will be responsible for all lab tests, x-rays, or any other tests that are deemed necessary in the conduct of this treatment. You are also financially responsible for the hospital, physician, and clinic charges generated by your participation in this treatment program.

EMERGENCY MEDICAL TREATMENT

In the event of a treatment related injury or if you experience an adverse reaction, please immediately contact your physician at the number listed below.
COMPENSATION IN CASE OF INJURY

Because you have a serious disease requiring therapeutic procedures that have associated risks and/or side effects, no compensation will be provided by Roper CareAlliance or the physicians involved in your care for any injury that you may suffer as a direct consequence of the procedures described above. However, in the event that any injury should occur, the emergency medical care required to treat the injury will be provided at Roper Hospital. You will be responsible for the cost of such medical care not reimbursable through our own health insurance. None of the above shall be construed as a waiver of any legal rights or redress you may have.

ASSURANCE OF CONFIDENTIALITY

Your desire for privacy is understood and we will use standard, accepted methods to protect this right. Any information obtained during this treatment that could identify you will be kept strictly confidential to the extent permitted by law. Your records related to this treatment will be made available to government agencies or other governing bodies upon appropriate request. Information obtained during the course of this treatment may be reported to the Autologous Blood and Marrow Transplant Registry, published in scientific journals or presented at scientific meetings, but your identity will be kept strictly confidential.

RIGHT TO WITHDRAW/TERMINATION

Participation is voluntary. You decision whether or not to participate will not affect your present or future medical care by your doctor or Roper CareAlliance. If you decide to participate you are free to withdraw your consent and to discontinue participation at any time. You will be informed of any significant new findings, beneficial or otherwise, during the course of this treatment which might affect your decision to participate. Your participation in this treatment may be terminated by your doctor without your consent if you are not benefiting from the treatment or for any other reason at his/her discretion.

If any new information develops during the course of this treatment that may affect your willingness to continue, you will be informed immediately.

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OFFER TO ANSWER QUESTIONS

If you have any questions please do not hesitate to ask and they will be answered at this time. If you think of any additional questions later, please feel free to contact the Bone Marrow Transplant Attending Physician listed below.

*You are voluntarily making a decision whether or not to participate in this treatment. Your signature certifies that you have decided to participate having read and understood the information presented. Your signature also certifies that you have had an adequate opportunity to discuss this treatment with the Bone Marrow Transplant Attending Physician and you have had all your questions answered to your satisfaction. You will be given a copy of this consent form to keep.*

Signature of Patient or Legal Guardian

____________________________  ______________________________
Patient                           Legal Guardian
Date: __________              Date: __________

My signature as witness certifies that the patient or legal guardian signed this consent form in my presence as his/her voluntary act and deed.

____________________________
Signature of Witness
Date: __________

In my judgement the patient or legal guardian is voluntarily and knowingly giving informed consent and possesses the legal capacity to give the informed consent to participate in this treatment.

____________________________
Signature of Physician
Date: __________

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