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## **Recent advances in the treatment of Bone Marrow Disorder**

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### **Abstract**

Bone marrow is the spongy tissue inside some of your bones, such as your hip and thigh bones. It contains immature cells, called stem cells. The stem cells can develop into the red blood cells that carry oxygen through your body, the white blood cells that fight infections, and the platelets that help with blood clotting. If you have a bone marrow disease, there are problems with the stem cells or how they develop. Leukemia is a cancer in which the bone marrow produces abnormal white blood cells. With aplastic anemia, the bone marrow doesn't make red blood cells. Other diseases, such as lymphoma, can spread into the bone marrow and affect the production of blood cells. Other causes of bone marrow disorders include your genetic makeup and environmental factors. The cell compression caused by an overgrowth of the supporting fibrous tissue network, resulting in abnormally shaped cells and decreased numbers of cells. One cell line that becomes predominant because the cells don't die at a normal rate. Diseases that may spread to the bone marrow, affecting cell production and maturation. Symptoms of bone marrow diseases vary. Treatments depend on the disorder and how severe it is. They might involve medicines, blood transfusions or a bone marrow transplant.

**Key words:** Stem cells, R.B.C., Cancer.

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### **Introduction**

Bone marrow is a special, spongy, fatty tissue that houses stem cells, located inside a few large bones. These stem cells transform themselves into white and red blood cells and platelets, essential for immunity and circulation. Anemia, leukemia, and other lymphoma cancers can

compromise the resilience of bone marrow. Bone marrow transplants are a growing treatment for these conditions of the lymphatic system that can't be otherwise cured. Our skull, sternum, ribs, pelvis, and femur bones all contain bone marrow, but other smaller bones do not. Inside this special tissue, immature stem cells reside, along with extra iron. While they are undifferentiated, the stem cells wait until unhealthy, weakened, or damaged cells need to be replaced. A stem cell can turn itself into a platelet, a white blood cell like a T-cell, or a red blood cell. This is the only way such cells get replaced to keep our body healthy. Platelets always circulate in our bloodstream, looking for tiny tears in blood vessels where blood might leak out, like a paper cut. They accumulate in such cuts during clotting. Red blood cells carry fresh oxygen from the lungs to all the cells that need it, and then carry away the unneeded carbon dioxide. White blood cells are immune responders that combat foreign microorganisms. Those invaders might cause infection, so white blood cells help produce antibodies that keep the invaders from causing damage. These three types of cells, and their associated functions, are obviously incredibly important to our entire body. That's why bone marrow tissue, as part of the lymphatic system, fights pathogens like fungi, bacteria, and viruses. Other diseases, often incurable, pose threats to bone marrow, incapacitating its ability to turn stem cells into essential cells. Leukemia, Hodgkin's Disease, and other lymphoma cancers and tumors damage bone marrow and destroy stem cells. Bone marrow examination refers to the pathologic analysis of samples of bone marrow obtained by bone marrow biopsy (often called a trephine biopsy) and bone marrow aspiration. Bone marrow examination is used in the diagnosis of a number of conditions, including leukemia, multiple myeloma, anemia, and pancytopenia. The bone marrow produces the cellular elements of the blood, including platelets, red blood cells and white blood cells. While much information can be gleaned by testing the blood itself (drawn from a vein by phlebotomy), it is sometimes necessary to examine the source of the blood cells in the bone marrow to obtain more information on hematopoiesis; this is the role of bone marrow aspiration and biopsy. The bone marrow biopsy may be done in the health care provider's office or in a hospital. The sample is usually taken from the hip bone. The skin is cleansed, and a local anesthetic is injected to numb the skin. The biopsy needle is then inserted into the bone. The center of the needle is removed and the needle is moved deeper into the bone. This creates a tiny sample, or core, of bone marrow within the needle. The needle is then removed, along with the bone marrow sample. Pressure is applied to the biopsy site to stop bleeding, and a bandage is applied. An aspirate may also be performed, usually before the biopsy is taken. After the skin is numbed, the aspirate needle is inserted into the bone, and a syringe is used to withdraw the liquid bone marrow. If this is done, the needle will be removed and either repositioned, or another needle may be used for the biopsy.

### **Diagnosis Test**

Bone marrow aspiration and trephine biopsy are usually performed on the back of the hipbone, or posterior iliac crest. However, an *aspirate* can also be obtained from the sternum (breastbone). A trephine biopsy should never be performed on the sternum, due to the risk of injury to blood vessels, lungs or the heart. A bone marrow biopsy may be done in a health care provider's office or in a hospital. Informed consent for the procedure is typically required. The patient is asked to lie on his or her abdomen (prone position) or on his/her side (lateral decubitus position). The skin is cleansed, and a local anesthetic such as lidocaine is injected to numb the area. Patients may also be pretreated with analgesics and/or anti-anxiety medications, although this is not a routine

practice. Typically, the aspirate is performed first. An aspirate needle is inserted through the skin until it abuts the bone. Then, with a twisting motion, the needle is advanced through the bony cortex (the hard outer layer of the bone) and into the marrow cavity. Once the needle is in the marrow cavity, a syringe is attached and used to aspirate ("suck out") liquid bone marrow. A twisting motion is performed during the aspiration to avoid excess content of blood in the sample, which might be the case if an excessively large sample from one single point is taken. Subsequently; the biopsy is performed if indicated. A different, larger trephine needle is inserted and anchored in the bony cortex. The needle is then advanced with a twisting motion and rotated to obtain a solid piece of bone marrow. This piece is then removed along with the needle. The entire procedure, once preparation is complete, typically takes 10-15 minutes. If several samples are taken, the needle is removed between the samples to avoid blood coagulation. After the procedure is complete, the patient is typically asked to lie flat for 5-10 minutes to provide pressure over the procedure site. After that, assuming no bleeding is observed, the patient can get up and go about their normal activities. Paracetamol (acetaminophen) or other simple analgesics can be used to ease soreness, which is common for 2-3 days after the procedure. Any worsening pain, redness, fever, bleeding or swelling may suggest a complication. Patients are also advised to avoid washing the procedure site for at least 24 hours after the procedure is completed.

### **Bone Marrow Transplantation**

The most important cell needed for successful transplantation is the hematopoietic stem cell. Currently, the major sources of stem cells for transplantation include bone marrow, peripheral blood, and cord blood. These can be obtained from various donors. When they are obtained from the recipient, they are called autologous. When they come from someone other than the recipient, they are termed allogeneic. The transplant process generally is divided into the following 5 phases: (1) conditioning, (2) stem cell infusion, (3) neutropenic phase, (4) engraftment phase, and (5) postengraftment period.

### **Conditioning**

The conditioning period typically lasts 7-10 days. The purpose is to deliver chemotherapy, radiation, or both to eliminate malignancy, prevent rejection of new stem cells, and create space for the new cells. The most common conditioning regimens include total body irradiation (TBI) and cyclophosphamide or busulfan (Myleran, Busulflex) and cyclophosphamide. Numerous other combinations are also used and commonly include drugs such as fludarabine, etoposide, melphalan, cytarabine, and thiotepa in addition to the above-mentioned agents. Also, anti-T-cell agents, such as antithymocyte globulin (ATG), may be added to the regimen in certain cases to prevent rejection of the graft. Patients generally tolerate conditioning well, although antiemetic therapy is used to prevent the significant nausea that can occur.

### **Stem cell processing and infusion**

The stem cell infusion is usually performed over about an hour, but this period varies depending on the volume infused. The stem cells may be processed before infusion, if indicated. Depletion of T cells can be performed to decrease GVHD. This is often performed before haplotype-matched transplants or other transplants that may have a significant degree of mismatch. Stem

cell CD34<sup>+</sup> selection may be performed, either for depletion of T cells or for tumor-purging purposes. In addition, many centers are investigating ex vivo expansion of a portion of the cells before transplant in order to improve engraftment. Before infusion, the patient is premedicated with acetaminophen and diphenhydramine to prevent reaction. The cells then are infused through a central venous catheter, much like a blood transfusion. Anaphylaxis, volume overload, and a transient GVHD are the major potential complications involved. Also, stem cell products that have been cryopreserved contain dimethyl sulfoxide (DMSO), a preservative, and can potentially cause renal failure in addition to the unpleasant smell and taste.

### **Neutropenic phase**

During this period (2-4 wk), the patient essentially has no effective immune system. Healing is poor, and the patient is susceptible to infection. Supportive care and empiric antibiotic therapy are the mainstays of successful passage through this phase. Early in this period, herpes simplex virus (HSV) is an important potential pathogen. Usually, this is acquired from reactivation of a previous infection. Also during this period, endogenous flora, such as skin and gut organisms, are the most frequently encountered organisms. Hospital-acquired nosocomial infections perhaps pose the biggest risk because they are frequently more resistant to the standard antibiotic regimens used. During initiation of widespread antibacterial therapy, fungal selection can occur. Typically, fever manifests 5-7 days following the start of broad-spectrum antibiotic therapy and is treated empirically with antifungal agents; amphotericin is the mainstay. The use of gut sterilizers (oral antibiotics to reduce gut flora) is controversial. They have been shown to reduce the number of positive blood cultures obtained but have had no significant impact on outcomes. In addition to infection risks, nutrition is also a key problem. Oral intake is usually severely reduced because of the severe mucositis that most patients develop. Total parenteral nutrition is provided and is usually quite necessary, especially for children.

### **Engraftment phase**

During this period (several weeks), the healing process begins with resolution of mucositis and other acquired lesions. In addition, fever begins to subside, and infections often begin to clear. The greatest challenges at this time include management of GVHD and prevention of viral infections (especially CMV). In solid organ transplants, rejection of the organ is the major hurdle. However, in hematopoietic cell transplantation, the immune system is part of the transplanted organ; therefore, the new immune system can attack the entire body. When this occurs, it is termed GVHD. GVHD generally involves the skin, GI tract, and the liver, causing a rash and blistering, diarrhea, and hyperbilirubinemia, respectively. This is discussed in detail in another article. Patients receiving allogeneic hematopoietic stem cell transplants are typically placed on one or more immunosuppressive medications to protect against the development of GVHD. The good side of GVHD is the graft versus leukemic (GVL) effect that may also be present. In addition, patients can develop an entity called venoocclusive disease (VOD). The etiology and the most effective management of VOD are unclear. VOD consists of the triad of weight gain, platelet transfusion refractoriness, and hyperbilirubinemia. The process includes damage to the liver with the deposition of thrombotic elements throughout the liver microcirculation. Supportive care and careful fluid management are essential. Antifibrinolytic therapy has unproven benefit.

### Post engraftment phase

This period lasts for months to years. Hallmarks of this phase include the gradual development of tolerance, weaning off of immunosuppression, management of chronic GVHD, and documentation of immune reconstitution. Transplants using T-cell depletion or from mismatched or haplotypic sources often have delayed or incomplete immune reconstitution. Patients who received TBI as part of their conditioning regimen often have significant splenic dysfunction. Most patients need reimmunization, usually beginning one year posttransplantation. Typically, this is begun using tetanus (DT), with titers obtained before and at least one month following to document a response. The use of the DT immunization is age dependent. In addition to the DT, immunization also can be given with the inactivated poliovirus vaccine (IPV). Oral polio vaccine should not be administered. Influenza vaccination should be administered to all patients every year. If a protective titer is obtained from the tetanus vaccine, proceed with the *Haemophilus influenzae*, pneumococcal, and hepatitis B series. Typically, after 2 years, immunization may be given with the measles, mumps, and rubella (MMR) vaccine only if the patient is successfully immunized with the above vaccines, the patient is off immunosuppressants for more than 6 months, and the patient does not have chronic GVHD. If the patient has adequate rubella titers, immunization may be withheld. All other live virus vaccines should be avoided if at all possible. Please refer to the American Academy of Pediatrics' *Red Book Report of the Committee on Infectious Diseases* for further information regarding immunizations in the posttransplant patient. Improvements in supportive care, antibiotic regimens, and DNA-HLA typing have had significant impact on improving survival and quality of life following transplant. In general, patients with stable disease or disease in remission have better outcomes than those transplanted during a later disease phase or with relapsed disease. Young age at time of transplant also leads to more favorable outcomes. CMV-negative status of recipient and donor enhance the likelihood of survival. A larger hematopoietic cell dose given at time of transplant may hasten engraftment and improve outcome but may also increase the risk of GVHD. Transplants for nonmalignant diseases generally have more favorable outcomes, with survival rate of 70-90% if the donor is a matched sibling and 36-65% if the donor is unrelated. Transplants for acute leukemias (eg, ALL, AML) in remission at the time of transplant have survival rates of 55-68% if the donor is related and 26-50% if the donor is unrelated. The outcome statistics of autologous transplant for solid tumors are somewhat disappointing for the pediatric malignancies, except for relapsed lymphomas and certain brain tumors. Autologous transplant may offer some advantage over chemotherapy alone in patients with relapsed germ cell tumors, Wilms tumor, or Ewing sarcoma. Autologous transplant provides superior results than chemotherapy alone in the 3-year disease-free survival rate for stage IV neuroblastoma, although the survival rate does not exceed 35%. In patients in first remission for metastatic alveolar rhabdomyosarcoma or metastatic Ewing sarcoma, no significant advantage has been demonstrated to date for autologous transplant over chemotherapy alone. Some recent transplant regimens use strategies designed to induce autologous GVHD in order to elicit a graft-versus-tumor effect in hopes of improving outcomes. Various regimens have been explored in an attempt to improve survival rates in these diseases, including the use of novel conditioning regimens, the use of several courses of high-dose therapy with stem-cell support, and the use of donor-lymphocyte infusions. Likewise, treatment of brain tumors has yielded similarly disappointing results, with the exception of medulloblastoma. Current transplant regimens for treatment of solid tumors emphasize introduction of promising new agents into the regimen or the use of sequential rounds of high-

dose therapy followed by stem cell support. The emphasis of current research is primarily directed at decreasing toxicity and GVHD while increasing the pool of potential donors by developing techniques to cross the traditional HLA histocompatibility barriers more successfully. Transplants are performed with increasing degrees of mismatch. Efforts to reduce the toxicity and transplant-related mortality are being made using strategies such as nonmyeloablative therapy with increased peritransplant immune suppression and posttransplant immune suppression to obtain a partial graft. This is then followed with donor leukocyte infusions to achieve complete chimerism. In addition, donor leukocyte infusions are used with increasing frequency for the treatment of patients with leukemia that relapses following transplant. Cord blood remains a promising source of hematopoietic stem cells. The use of multiple cord blood units for the transplant of larger individuals continues to be explored in the context of a nationwide Bone Marrow Transplant-Clinical Trials Network (BMT-CTN) study exploring the efficacy of double cord transplants. The potential plasticity of stem cells in cord blood hold promise for regeneration of various cell types such as cardiac, endocrine, and neuro tissue without the ethical controversies that surround embryonic stem cells.

Expanded indications for transplant continue to be explored. Preliminary data suggest a possible role for transplant in the treatment of autoimmune diseases such as lupus, multiple sclerosis, systemic sclerosis, and juvenile rheumatoid arthritis. In addition, in utero transplant holds promise for early correction of genetic disease, with some success already demonstrated with the immunodeficiency syndromes. The use of gene therapy with the targeting of cord blood may also hold promise for the correction of genetic disease. Recently, hematopoietic stem cells and other primitive cell types have been shown to retain the ability to differentiate into various mature cells when they receive the proper cytokine cues. This may hold potential for use in restoring function to ailing hearts or regenerating damaged nervous tissue. The transplant of hematopoietic stem cells continues to be an advancing field in the treatment of human disease.

### **Types of Bone Marrow Transplant**

A bone marrow transplant delivers healthy bone marrow stem cells into the patient. It replaces bone marrow that is either not working properly or has been destroyed (ablated) by chemotherapy or radiation.

Bone marrow is the soft, fatty tissue inside your bones. Stem cells are immature cells in the bone marrow. Some stem cells grow into different parts of your blood. These parts are:

- Red blood cells (which carry oxygen to your tissues)
- White blood cells (which fight infection)
- Platelets (which help your blood clot)

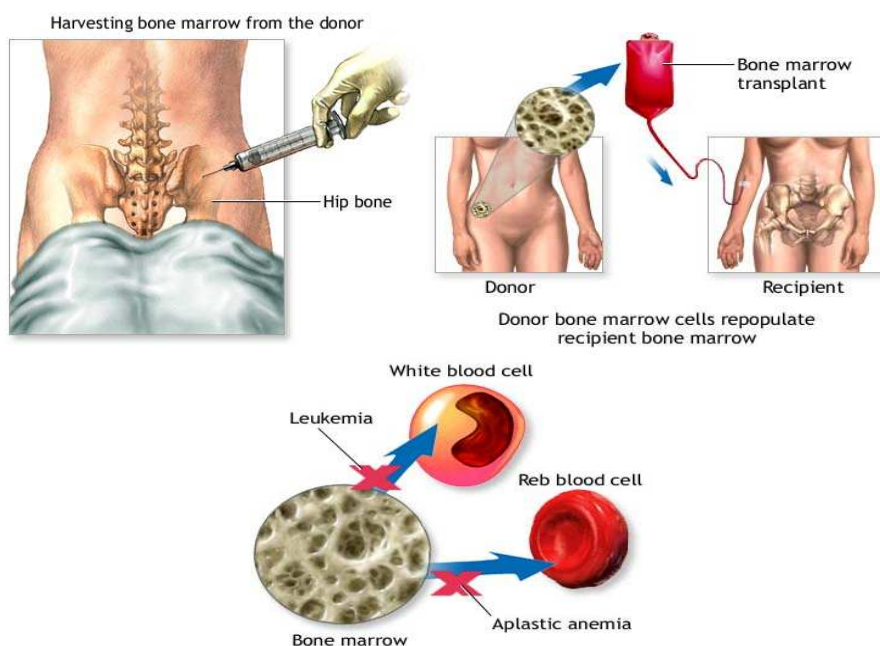
In a bone marrow transplant, you will receive healthy stem cells after your own bone marrow has been destroyed.

There are three kinds of bone marrow transplants:

- ❖ Autologous bone marrow transplant. "Auto" means "self." Stem cells are taken from the patient before the patient gets chemotherapy or radiation treatment. When chemotherapy or radiation is done, the patient gets their stem cells back. This is called a "rescue" transplant.
- ❖ Allogeneic bone marrow transplant. "Allo" means "other." Stem cells come from another person, who is called a donor. Donor stem cells come from the donor's bone marrow or their

blood. Most times, a donor must have the same genetic typing as the patient, so that their blood "matches" the patient's. Special blood tests will tell whether a possible donor is a good match for the patient. A patient's brothers and sisters have the highest chance of being a good match. But, sometimes parents and children of the patient and other relatives may be matches. Donors who are not related to the patient may be found through national bone marrow registries. These are lists of people who have offered to be donors.

- ❖ Umbilical cord blood transplant. Stem cells are taken from an umbilical cord right after delivery of an infant. The stem cells are tested, typed, counted, and frozen until they are needed for a transplant.



**Figure-1 Bone marrow Transplantation**

Most patients get high doses of chemotherapy, radiation, or both, before the bone marrow transplant. This is called ablative (or myeloablative) treatment. It kills any cancer cells that might remain, and it makes room in the bone marrow for the new stem cells to grow. Today, some patients are getting less chemotherapy and radiation before their transplant. This is called a reduced intensity (non-myeloablative) or "mini" transplant. After the patient gets chemotherapy and radiation, a doctor will do the stem cell transplant. The patient gets the stem cells through a tube called a central venous catheter. The cells go right into the bloodstream. This delivery of cells is called an infusion. It may take up to several hours. It is not surgery. It is similar to a blood transfusion. The stem cells find their way into the bone marrow, where they may begin reproducing and making healthy new blood cells. Donors must have minor surgery to collect their bone marrow and stem cells. They will be unconscious and pain-free (under general anesthesia) while their bone marrow is removed from their hip bone.

When receiving stem cells, a patient may have these symptoms:

- Pain
- Chills

- Fever
- Hives
- Chest pain
- Drop in blood pressure
- Shortness of breath
- Nausea
- Flushing
- Headache
- Funny taste in the mouth

## Conclusion

Bone marrow grows inside some of the larger bones in the body. It produces platelets and red and white blood cells. Bone marrow is the spongy tissue inside some of your bones, such as your hip and thigh bones. It contains immature cells, called stem cells. The stem cells can develop into the red blood cells that carry oxygen through your body, the white blood cells that fight infections, and the platelets help with blood clotting. If there is a problem with your bone marrow, a transplant can give you healthy new marrow. You could need a transplant because of a disease, such as bone marrow diseases or cancers like leukemia or lymphoma. Or you might need one if a strong cancer treatment kills your healthy blood cells. People with cancer sometimes donate bone marrow before treatment to be transplanted later. But often the new marrow comes from a donor, either a close family member or someone unrelated. A bone marrow transplant is when special cells (called stem cells) that are normally found in the bone marrow are taken out, filtered, and given back either to the same person or to another person. Bone marrow produces stem cells. These stem cells eventually develop into blood cells. Bone marrow is a critical part of the body because it is the body's main blood cell "factory." If something is wrong with the marrow, a person can become very ill, even die. In diseases such as leukemia and aplastic anemia, the bone marrow is unhealthy. The purpose of a bone marrow transplant is to put healthy stem cells in place of the unhealthy ones. This can treat or even cure the disease.

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