Hi. My name is Megan Cornelison. I'm a physician’s assistant at The University of Texas MD Anderson Cancer Center in the Department of Stem Cell Transplant and Cellular Therapy. Today we will be discussing the Treatment Modality of Stem Cell Transplantation.

Upon completion of this lesson participants will be able to: describe the purpose and methods of stem cell transplant; define HLA typing and identify the differences between various kinds of matches and donor sources; and identify possible complications of stem cell transplantation.

Hematopoietic stem cells are progenitor cells found in the bone marrow. They have the capacity for self-renewal and the ability to proliferate and differentiate. These cells are identified by flow cytometry, by the presence of a cell surface marker known as CD34.

This is a diagram of normal hematopoiesis. At the top, you will see a pluripotent stem cell that differentiates into both myeloid and lymphoid cell lines. The myeloid phenotype gives rise to red blood cells, platelets, macrophages, eosinophils, and basophils. The lymphoid cell line gives rise to T and B cells responsible for immune function.

Stem cell transplantation provides several benefits. In all types of transplants, we gain the ability to give high doses of chemotherapy because we follow it with a stem cell rescue. In the case of allogeneic stem cell transplantation, we then transfer immune competent cells known as the graft from a normal donor to an immune incompetent recipient known as the host. These are derived from either the peripheral blood or the bone marrow. Stem cell transplantation relies heavily on a donor’s immune system to produce the second and most important benefit, a heavy graft versus tumor effect rather than relying solely on the chemotherapy.

There are several types of transplants. The first is autologous in which the recipient’s own cells are used. In this setting, there is a lower incidence of treatment-related mortality. Therefore, this treatment can be given in patients who are older or who have other comorbidities. The drawback is that there is a higher rate of relapse. However, there is a relatively low late --- rate of long-term complications. In the allogeneic setting, we use donor-derived stem cells. In these cases, there is a higher rate of treatment-related mortality as well as a higher rate of short and long-term complications. However, a lower risk of relapse. Increasingly, we are using alternative donor sources, such as umbilical cord blood units which are easily accessible but have the potential to cause more infectious complications and a higher incidence of graft failure.

The timing of transplant is critical. Transplant must be done at the point of maximal tumor response. Hence, patients who should really --- patients should really be in a complete remission or at least a partial remission which generally means a greater than 50% reduction in disease burden. The patient can have no active infections at the time of transplant, no evidence of CNS or leptomeningeal disease, and no uncontrolled chronic illnesses. They must have adequate organ function and have a preserved
performance status. Additionally, in the allogeneic setting we must have an identified donor source and in the autologous setting we must have been able to collect an adequate number of stem cells.

There are many indications for stem cell transplant. Most commonly, transplants are performed for patients with high-risk hematologic malignancies. These include high-risk leukemias such as those with primary induction failure, poor risk cytogenetics, or relapsed disease after standard chemotherapy as well as those with myelodysplastic syndrome, high-risk ALL patients with the MLL gene mutation or the Philadelphia chromosome, patients with CML who are either resistant or intolerant to tyrosine-kinase inhibitors or who are in accelerated or blast phase, or refractory CLL that has transformed to large cell lymphomas.

In addition to the high-risk leukemias, transplants are also performed for lymphomatous disorders including refractory or relapsed Hodgkin’s lymphoma, relapsed non-Hodgkin’s lymphoma, and chemo-sensitive multiple myeloma.

Preparative regimens or the chemotherapy a patient receives prior to transplant can be classified as either myeloablative or reduced intensity or non-myeloablative. Myeloablative means that the bone marrow’s regenerative capacity is completely destroyed by the chemotherapy. This is typically reserved for younger and healthier patients because the treatment is much stronger with a much higher toxicity and puts the patient at increased risk for infectious complications due to prolonged immunosuppression. The benefit of myeloablative regimens is that there is less risk of relapse post-transplant.

The reduced intensity or non-myeloablative regimens are typically reserved for patients with lymphomas, myelomas, and in older patients with leukemia. Most of these patients are heavily pretreated or have had a prior transplant. These regimens also cause myelosuppression, and there is still a risk for infectious complications. However, generally, there is less toxicity when compared to the myeloablative regimens. The drawback to non-myeloablative regimens is that there is an increased risk for potential rejection.

Let’s first talk about autologous transplant in detail.

In the autologous setting, we use the patient’s own stem cells collected either via the peripheral blood or by bone marrow harvest prior to chemotherapy. This type of transplant is indicated in chemosensitive diseases, including recurrent Hodgkin’s lymphoma, low-grade or intermediate-grade lymphomas, and multiple myeloma.

As previously mentioned the stem cell collection occurs prior to the administration of the preparative chemotherapy and is performed via either peripheral blood or a procedure called pheresis or by bone marrow harvest. If the cells are collected via peripheral blood, they need to be stimulated by a growth factor known as Neupogen®. In some cases, we also give chemotherapy in addition to the growth factor. By combining the
two, particularly in patients with lymphoma who have been heavily pretreated, we can simultaneously treat bulky disease and increase the yield of CD34 cells mobilized into the peripheral blood. Once the cells are collected, they are cryopreserved until the time of transplant. An adequate stem cell dose in the autologous setting is greater than two million CD34 cells per kilogram of recipient’s body weight. In the allogeneic setting, the optimal cell dose is greater than four million CD34 cells per kilogram of the recipient’s weight.

After stem cell collection, the high dose chemotherapy is given over approximately one week’s time. Within 24 to 48 hours of the completion of chemotherapy, the stem cells are infused like a blood transfusion via central venous catheter. It takes about two to three weeks for the peripheral blood counts to recover. During this time, patients are susceptible to infection and, therefore, prophylactic antibiotics and growth factor support is given on an as needed basis.

In contrast to autologous transplant, allogeneic transplant relies heavily on stem cells donated from an HLA compatible source.

These cells can be derived from a related donor, usually a sibling, or from an unrelated donor identified through the National Marrow Donor Program. These cells also can be collected via peripheral blood or bone marrow. Just as in the autologous transplant setting, chemotherapy is given to the recipient approximately one week’s time before the stem cell infusion. In this setting, however, patients are given anti-rejection or immunosuppressive medication prior to the stem cell infusion and maintained on this medicine for at least six months post-transplantation.

There are many benefits to doing an allogeneic transplant. The greatest is that it provides a graft versus tumor effect. This occurs via an immunogenic response in which the host’s immune cells identify abnormal cells, such as tumor cells as foreign and target and destroy them prior to their ability to form a clonal population, which would result in eventual relapse, thereby, exerting a continuous effective anti-tumor activity and lowering the rate of relapse increasing overall survival. However, there are many complications that can be fatal in the post-transplant setting. These include graft versus host disease which occurs when these immune cells become overactive and identify the host’s healthy functional cells as foreign and produce a widespread autoimmune response. This can cause significant morbidity and even mortality. There are also numerous infectious complications and a risk of graft rejection or graft failure.

Donor identification begins with stringent HLA typing. HLA stands for Human Leukocyte Antigen. It is a DNA-based typing of a gene found on chromosome 6. We look at the major histocompatibility class I and class II. Class I is denoted by the loci A, B, and C. Class II by DR, DQ, and DP. Each individual inherits one set from each parent for a total of 12 loci. In order to mitigate risk of graft rejection or graft versus host disease, we try to find donors who match our recipients at all 12 loci. If we look at the primary three loci that confer the most HLA compatibility, A, B, and DR, we consider 6 loci. We will accept a donor with up to one mismatched locus so we would have to have a
minimum match of 5 out of 6. If we look out further and increase our HLA compatibility requirements to include loci --- loci C and DQ, we would increase our number of considered loci to 10. And the minimum match we would consider would be 9 out of 10. If we consider the locus DP we would further increase our donor compatibility to include 12 loci.

In addition to HLA compatibility we also assess donor health status. Younger donors are generally preferred over older ones. Past medical history, infectious disease status including hepatitis, CMV, and HIV serologies and pregnancy history in females are also considered. And finally, we perform a very thorough physical examination.

There are several types of stem cell sources: Peripheral blood, bone marrow, and alternative donor sources, which include umbilical cord blood each with their own unique set of risks and benefits.

Peripheral blood-derived stem cells are easily collected via a central venous catheter after stimulation by Neupogen®. Because these cells are found in the peripheral blood and have been exposed to various antigens they have become more immune competent. And once infused into our patient they tend to engraft more quickly which means the patient’s peripheral blood counts tend to recover more quickly. However, there is an increased risk for the development of graft versus host disease. Unlike peripheral blood, bone marrow derived stem cells are collected via manual collection under general anesthesia in the operating room. These cells are more naïve. They have not been circulating in the peripheral blood and, therefore, have not seen antigen. Once given to the patient their counts are slow to recover. This increases the risk of infection and bleeding complications post-transplant. However, because these cells are more naïve, the patient’s risk for graft versus host disease is reduced.

A third type of stem cell source is umbilical cord blood. There are many advantages to using umbilical cord blood. First, cord blood uses --- units are found in multiple banks throughout the United States and internationally. These cells are collected non-invasively after birth. Cord blood is minority targeted, generally selected for patients of African American or Asian origin which becomes important when one considers that the National Marrow Donor Program registry is heavily weighted towards Caucasians. Because these cells are naïve, there is less stringent donor HLA typing and they tend to cause less graft versus host disease. The disadvantage to umbilical cord blood is that the cell doses are small and, therefore, there is much slower engraftment. Recipients of these cells take many more weeks to recover their counts and are at significantly increased risk for infectious complications and graft failure.

In the post-transplant setting…

there are many complications. Most notably, these include infections due to the severe immunocompromise, graft versus host disease, organ damage from the chemotherapeutic preparative regimen, potential risk of graft failure or rejection, and not inconsequential is the risk of relapse.
The high rate of infectious complications is due in part to the ablative nature of the preparative regimen as well as the protracted course of immunosuppressive medications given to the patient to prophylax against graft versus host disease. In the early post-transplant period, meaning within the first 100 days, we are vigilant in our surveillance of viruses including common ones, such as herpes simplex virus, cytomegalovirus, and varicella zoster. Bacterial infections remain our most common cause of mortality in this early post-transplant period. In the late post-transplant period, after day 100, Epstein-Barr virus is common as well as various fungal infections, particularly aspergillosis.

To prevent these problems our patients are given prophylactic antibiotics for up to six months post-transplant and as long as they are on immunosuppressive medications to cover both viral, specifically herpetic, bacterial and fungal infections. In addition, we also prophylax against pneumocystis infection. There is stringent surveillance for CMV reactivation and treatment depends on the patient’s past infectious history.

Graft versus host disease or GVHD as discussed before is a major complication post-transplant. It is best described as an inflammatory response mediated by the graft or donor cells hyperreactivity to the recipient’s own host cells. It begins with a strong cytokine release from the patient’s own tissues due to damage sustained from the chemotherapeutic preparative regimen. This cytokine release leads to an inflammatory response that causes increased tissue damage. GVHD is highly linked to HLA compatibility. Hence, the more incompatible the donor and the recipient are or the higher the degree of HLA mismatch, the greater the risk of graft versus host disease.

GVHD occurs in approximately 50% of patients despite adequate prophylaxis and can be described as either acute or chronic depending on the time at which it occurs post-transplant. Acute GVHD occurs within the first 100 days and chronic GVHD occurs after the day 100 milestone. If GVHD is not controlled and treated aggressively, it can be life-threatening.

We attempt to identify patients who are at greater risk of developing GVHD early --- early on in order to maximize prophylaxis and start first line treatment at our earliest opportunity. There are several factors that we use to identify those with higher risk. These include the age of the recipient, the older the patient the higher the risk of developing GVHD. We also evaluate the degree of HLA mismatch and the stem cell source. As previously mentioned, stem cells derived from the peripheral blood cause more graft versus host disease than the --- a bone marrow derived product. Again, this is due to the fact the peripheral blood cells are more immune competent than those obtained from the bone marrow.

Gender mismatching can also increase our risk of GVHD especially when using female donors. Females who have had children produce more antibodies and this produces more risk of graft versus host disease when infused into a male patient. The intensity of the preparative regimen affects the amount of pre-existing host tissue damage and
increases cytokine response, which in turn incites GVHD. This occurs with a higher frequency with myeloablative regimens than with the non-myeloablative regimens. Lastly, it is very important to maintain adequate GVHD prophylaxis evaluated by serial trough levels of the immunosuppressive medications.

GVHD can manifest in several ways. The skin is a common organ system that is affected. In the acute setting, the typical presentation can be a fine erythematous, maculopapular rash that may or may not be pruritic. In the chronic setting we see more hyperpigmentation and scleroderma, much like an autoimmune scleroderma. GVHD can also affect the mucosa of the gut anywhere along the GI tract from the mouth to the rectum. Oral symptoms can include sensitivity, poor appetite, and decreased saliva. We also see abdominal cramping, nausea, vomiting, diarrhea, weight loss, and malabsorption syndrome.

GVHD also affects other organ systems including the liver resulting in hepatitis and jaundice; the pulmonary system causing shortness of breath; the ocular surface causing a dry eye syndrome, conjunctival inflammation and injection; and connective tissue including the fascia leading to joint stiffness, pain, and swelling.

This is a picture of acute cutaneous graft versus host disease. You can see the erythematous, macular rash that may or may not be pruritic.

In contrast, this is a picture of hyperacute cutaneous GVHD occurring within the first 30 days after stem cell infusion. It’s manifested itself in this case as a very angry, red, painful rash.

This is an example of ocular graft versus host disease. You can see the eye is very red, irritated, and has a great deal of conjunctival inflammation and injection.

Oral graft versus host disease is manifested by pain and redness in the oral mucosa along with white cicatricial changes. There can also be changes in the hard palate and tongue.

The diagnosis of GVHD is a clinical one made by history and physical exam although tissue biopsy for a pathological diagnosis can be helpful in confirming tissue involvement. Often times, as is the case in many instances of chronic graft versus host disease, there are several potential causal factors for the clinical manifestations like skin rash, shortness of breath, nausea, etc. that make it hard to make a definitive diagnosis. To aid in our diagnosis we can easily do skin, liver, and bowel biopsies. For the lung we typically rely on pulmonary function testing which will demonstrate a restrictive pattern. We also use high resolution CT scanning to assess any abnormalities within the lung parenchyma.

Treatment for GVHD can either be systemic or localized depending on the extent of involvement. If there is more than one organ system involved, high dose steroids are given at a dose of 1-2 mg per kilogram of the patient’s weight. Once the patient starts
to respond, the steroid is tapered. Frontline treatment with high dose steroids induces about a 50% response rate. We rely heavily on prophylaxis with immunosuppressive medications, most commonly tacrolimus. Serum trough levels of tacrolimus must be monitored very closely as many medications, especially azoles, can affect its metabolism. Super therapeutic levels can cause both neuro- and renal toxicity while subtherapeutic levels can cause suboptimal response of clinical symptoms. In addition to oral medications a procedure called photopheresis can also be used for both skin and GI symptoms. In this setting, a patient’s stem cells are isolated by a pheresis machine which is similar in concept to a dialysis machine. These cells are injected with psoralen making them sensitive to UV light. There’s an --- They are then zapped with UV light and re-injected into the patient. In this setting our goal is to get the patient off of steroids as soon as possible. Photopheresis is given over several months, two to three times per week, until the symptoms have resolved. For localized treatment particularly of the eyes, mouth, and skin, it is easy to use topical treatments such as eye drops, mouthwashes, or topical creams. In the event that steroids are not successful, there are second line agents that can be used. These include mycophenolate mofetil, infliximab, which is most used for the GI tract, cyclosporine, and anti-thymoglobulin. All these regimens are successful as second line agents, but if patients do not respond to these second line agents there is about a 10% long term survival.

The goal of GVHD treatment is to suppress the hyperactivity of the donor immune system to mitigate end organ tissue damage without suppressing the graft. In order to strike this balance, we follow trough levels of the immunosuppressive agents, such as tacrolimus or cyclosporine to ensure we are maintaining therapeutic doses. The goal in the treatment of GVHD is to --- in some cases patients have severe nausea, vomiting, weight loss, cachexia, skin rash, extreme mouth pain, and other uncomfortable symptoms. We want to control these symptoms and improve patient’s quality of life. Effective treatment of GVHD can preserve and even improve this. However, there are many complications that arise --- arise from long term use of steroid therapy. Effective prophylaxis of GVHD with nonsteroidal immunosuppressive agents helps us to mitigate these complications to improve our patients’ lives. Long term steroid therapy often causes superimposed infections as well as induces hyperglycemia and diabetes, avascular necrosis, and osteopenia.

Another complication of stem cell transplant is graft failure or graft rejection. There are two types of graft failure. The first is primary graft failure which is characterized by the recipient’s inability to recover their cell counts after the administration of stem cells. Hence, the patients remain pancytopenic for several weeks. On pathologic review of the bone marrow, the marrow itself would be aplastic. Secondary graft failure is characterized by initial engraftment meaning the patient’s counts do recover after stem cell infusion; however, over subsequent weeks, they slowly decline. When assessing the patient’s bone marrow or peripheral blood, you notice a gradual decline in the percentage of donor cells in the patient’s total cell count. In contrast to graft failure, graft rejection occurs when the patient’s counts recover but when assessing the bone marrow or peripheral blood the recovered counts are the patient’s and not the donor cells.
The final and most feared complication is unfortunately relapsed disease. In this setting, there are several treatment options. They include supportive care alone which is typically reserved for older, debilitated patients with multiple comorbidities preventing or limiting further treatment. The first therapeutic intervention is a reduction or discontinuation of immunosuppression. For example, we begin to taper the tacrolimus to try to incite a graft versus leukemia effect. However, this does increase the patient’s risk of developing graft versus host disease. If the patient has a good performance status and is physically capable of withstanding further therapy, a course of salvage chemotherapy can also be given to put the patient back in a remission with consideration for a second transplant. An alternative to this approach is to perform a donor lymphocyte infusion.

A donor lymphocyte infusion or DLI is when donor T-cells are given to the patient without any prior conditioning chemotherapy or post-infusion immunosuppression. In this setting T-cells are collected from the donor without any growth factor or other stimulation. By doing this we hope to incite a strong graft versus tumor effect but can also increase or produce fatal graft versus host disease.

This type of treatment is indicated in the setting of relapse or progressive disease as well as in those who have residual disease post-transplant. A DLI is absolutely contraindicated if the patient has active graft versus host disease. By giving a DLI to a patient with active GVHD, again, you can incite a fatal inflammatory response.

Late complications post-transplant can include secondary malignancies including skin cancers, hematologic malignancies, and head and neck cancers. Tissue damage sustained as a result of chemotherapy can cause end organ damage that can manifest itself years later including cirrhosis of the liver. This can be multifactorial and occur as a result of prior chemotherapy, multiple transfusions, drug-induced hepatitis, or GVHD. Again, late infections are critical and often we see CMV reactivation as well as fungal, encapsulated bacterial, and Epstein-Barr virus infections. Additionally, post-transplant lymphoproliferative disease has been seen.

Care in the post-transplant period differs from the more acute nature of the care provided in the peri-transplant period but is no less important. In the post-transplant setting, it is important to remember that the patient has lost all previously acquired immunity. Beginning approximately six months post-transplant when the patient is tapering immunosuppression, we undertake a regimented revaccination program. This includes pneumococcal, influenza, polio, hepatitis B, and tetanus inoculations. The patient should be free from active infections and have no graft versus host disease at the time of vaccination. Chimerism studies are obtained on serial intervals to assess the stability of the graft. These are quantitative analyses of donor cells that can be assessed either via peripheral blood or bone marrow and can definitively delineate donor from host cell lines.
Staging is largely based on the underlying disease. However, as a general rule it’s performed every three months post-transplant in the first year, every six months in the second and third years, and annually thereafter. Health maintenance studies for long term transplant survivors include bone density and pulmonary function testing assessed at six months and then as clinically indicated thereafter.

To summarize a relatively complicated process, this is a diagram of the allogeneic transplantation in detail. In the first figure, the patient’s blood cells are denoted by the letter “A”. The cells denoted by “A” with the subscript 1 are leukemia cells. This same patient is given an ablative hematopoietic regimen. The donor cells are infused after the conditioning regimen and are denoted by the letter “B”. On serial evaluation, we see that the patient may not fully convert to express only donor cells or in some cases the patient may be fully donor but with low counts. In these cases, withdrawal of immunosuppression followed by a DLI may be required to incite complete donor chimera as evidenced by the last figure.

In conclusion, stem cell transplant is a treatment modality for various hematologic diseases. Stem cells can be collected from donors, umbilical cord blood, or from the recipient depending on the underlying disease and various patient and donor factors. Myeloablative or non-myeloablative reduced intensity chemotherapy is given prior to the stem cell transplant. In the end, the main focus of an allogeneic transplant is the promotion of a graft versus tumor effect to exert an immunologic effect and produce a long term remission. However, there are very serious complications that occur in the post-transplant setting including GVHD, organ damage, and graft failure. With all this in mind allogeneic transplants are used successfully to improve overall survival and induce long-term durable remissions in select patients with relapsed or refractory hematologic malignancies when standard chemotherapy has failed or in diseases with high rates of relapse. Thank you very much for your time and attention. Please let us know if this presentation has been helpful to you.