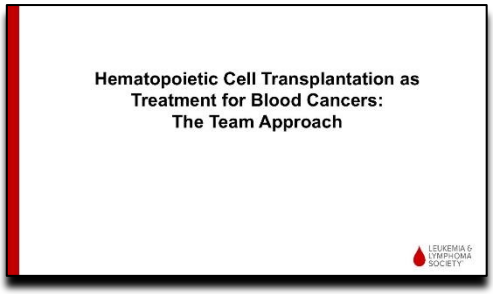
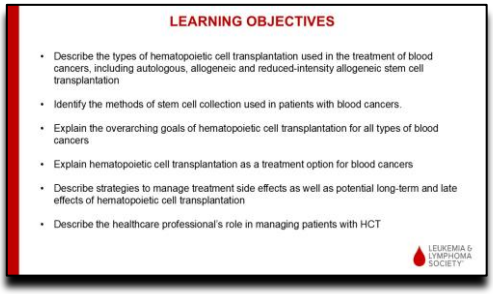


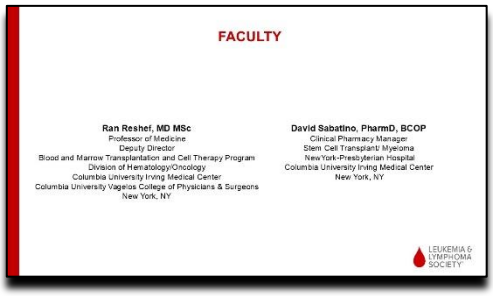
Slide 1: Hematopoietic Cell Transplantation as Treatment for Blood Cancers: The Team Approach

Lauren Berger, MPH: Hello everyone. On behalf of The Leukemia & Lymphoma Society thank you for sharing your time with us for this continuing education program on Hematopoietic Cell Transplantation as Treatment for Blood Cancers.



Slide 2: Learning Objectives

The learning objectives are listed on this slide.



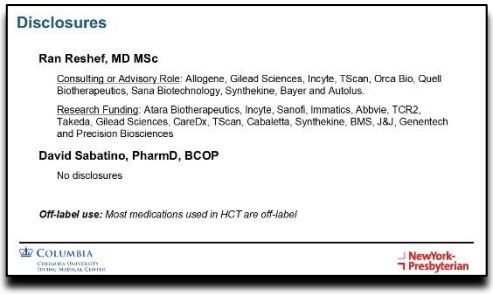
Slide 3: Faculty

We're fortunate to have as our presenters Dr. Ran Reshef, a leading expert in Hematopoietic Cell Transplantation, and his colleague, Dr. David Sabatino, a clinical pharmacy specialist. We appreciate their dedication and their commitment to caring for patients living with blood cancers.

Dr. Reshef is Professor of Medicine; Deputy Director, Blood & Marrow Transplantation & Cell Therapy Program; Division of Hematology/Oncology, at Columbia Univ Irving Medical Center, Columbia University Vagelos College of Physicians & Surgeons, in New York City. Dr. Sabatino is Clinical Pharmacy Manager, Stem Cell Transplant/Myeloma, at New York Presbyterian Hospital, Columbia Univ Irving Medical Center, in New York City.

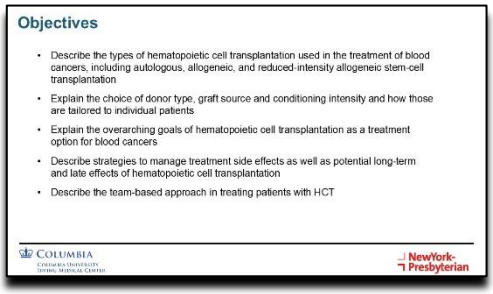
Dr. Reshef and Dr. Sabatino, I am now privileged to turn the program over to you.

Ran Reshef, MD, MSc: Hello and welcome to our webinar, *Hematopoietic Cell Transplantation as Treatment for Blood Cancers: f*ocusing on *The Team Approach*. Thank you so much, Lauren, for the introduction and for the opportunity to present here. As you mentioned, my name is Ran Reshef, and I'm here with David Sabatino; and we're both from the Blood and Marrow Transplantation and Cell Therapy Program at New York-Presbyterian Hospital, Columbia University Irving Medical Center. We're extremely pleased to be here and share our experience and knowledge in this area.



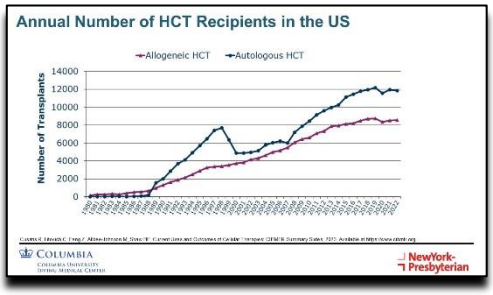
Slide 4: Disclosures

These are our disclosures, and I would just want to point out that most medications used in hematopoietic cell transplantation are off label, although there's been a number of medications approved in the past few years; and we will review those.



Slide 5: Objectives

So, our objectives are pretty straightforward. We will describe the types of hematopoietic cell transplantation in the treatment of blood cancers, focusing on the differences between autologous, allogeneic, reduced intensity, and myeloablative transplantation, which are the most common types and forms of transplant that we use in blood cancers. We will talk about the choice of donor type, graft source, which are important parameter as well as conditioning intensity; and we will talk about the overarching goal of hematopoietic cell transplantation and why we think it's either a curative approach in some cancer and can certainly prolong survival in many other cancers. We will talk about strategies to manage the various side effects that occur after transplantation, and we'll talk about the team approach in managing transplantations.



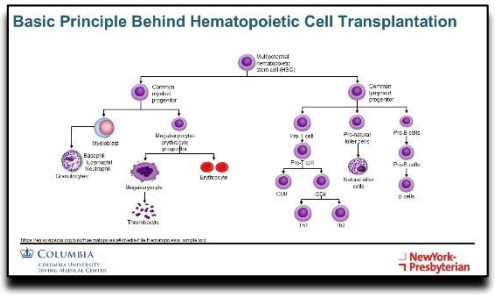
Slide 6: Annual Number of HCT Recipients in the US

Many of the slides that I'm going to show you come from the Center for International Blood and Marrow Transplant Research or CIBMTR, so I wanted to give them credit for collecting data for several decades, both in the US and internationally, on all hematopoietic cell transplants and recently also on cell therapy approaches. These data are tremendously useful for our research into advanced field.

And you can see on this slide an overview of the number of transplants that take place in the United States. You can see that there's been a steady increase in the numbers; and at this point, or in 2022, which is where we have our most recent data for, there have been roughly 8,000 allogeneic transplants each year and approximately 12,000 autologous transplants each year.

This translates to nearly a total of 100,000 transplants worldwide performed each year, which is quite a striking number. You will also note on this interesting plot some of the trends over the years. Primarily, you would see the dramatic dip in the numbers of

autologous transplants around the years 1999 or 2000. The reason for that is that some of you may recall in the 1990s, most autologous transplants were performed for metastatic breast cancer. And then following publication of randomized data that showed and questioned the benefit of this approach, there's been a major drop in the number of transplants which was then replaced by, and picked up quite quickly, with the demonstration of efficacy of autologous transplants in myeloma, non-Hodgkin, and Hodgkin lymphoma where the procedure was then they had become very standard.

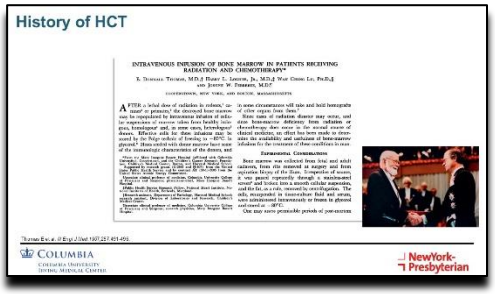


Slide 7: Basic Principle Behind Hematopoietic Cell Transplantation

So, what is the basic principle behind hematopoietic cell transplantation? It's a very basic biology behind this. Similar to many other tissues in our body, our entire blood system and immune system can be generated from a small number of what we call multipotential stem cells. And in this case, we call them hematopoietic stem cells, and they usually live in the bone marrow.

These unique cells that have tremendous regenerative potential and can live for many, many years mature and differentiate into common progenitors of the lymphoid lineage and the myeloid lineage. And these common lymphoid and myeloid progenitors mature and differentiate into the various types of cells that we have circulating in our blood and are part of our immune system. Mature B-cells, T-cells, natural killer cells, and on the myeloid side, neutrophils, various granulocytes, megakaryocytes that generate platelets, and, of course, red blood cells.

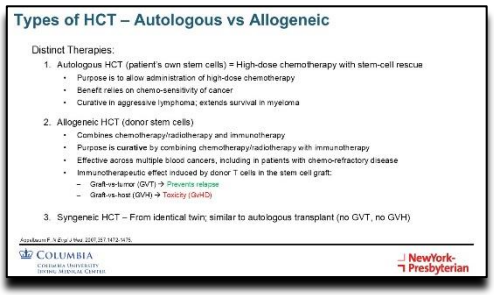
So, the principle behind this. That if you take hematopoietic stem cells, you can generate an entire blood system and an entire immune system from a very small number of cells. So, that's basically what we do in a hematopoietic cell transplant. We eliminate the existing blood system in the marrow, in the blood, and in the lymph nodes; and we generate an entirely new one from a small number of hematopoietic stem cells, either taken ahead of time from the patient themselves or taken from a donor.



Slide 8: History of HCT

Just one piece of interesting history, on a more personal note for our group, this is the original paper published by E. Donnall Thomas in *The New England Journal of Medicine* in 1957 describing the first few patients who underwent repopulation of their bone marrow using donor stem cells. And what's interesting is that this first bone marrow transplant in humans took place in Cooperstown, New York, which

was then, and is still today, the hospital that is affiliated with Columbia University Vagelos College of Physicians and Scientists. So, there's certainly a personal touch to this webinar. E. Donnall Thomas then moved on and received the Nobel Prize ultimately for his work in developing hematopoietic cell transplants.



Slide 9: Types of HCT – Autologous vs Allogeneic

So, first of all, it's important to distinguish the types of transplant because they are very much distinct. We talk about autologous transplants and allogeneic transplants as two very, very distinct and unique entities.

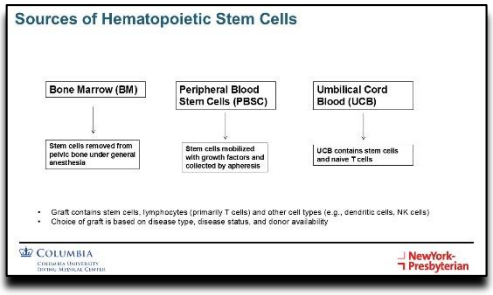
Autologous transplants, as you see here, rely on the chemosensitivity of the cancer. And the role of the stem cells is really to act as a rescue from high doses of chemotherapy that we administer to these chemosensitive tumors. So, the purpose of an autologous transplant is really as a salvage therapy because administration of high doses of chemotherapy would, invariably, be associated with bone marrow aplasia and may lead to the patient's mortality if we don't administer stem cells which we harvested and kept in the freezer in advance.

So, high doses of chemotherapy work better in specific cancers where standard doses of chemotherapy already work but are not sufficient to completely eliminate the cancer. This is why an autologous transplant really relies on chemosensitivity of the cancer. Autologous transplants are considered curative in many types of lymphoma and has become a standard of care in myeloma where it is a major contributor for the prolonged survival that we now see in this disease compared to decades previously where we were not using transplant.

An allogeneic transplant combines the potential effect of chemotherapy and radiation on the tumor with immunotherapy that is driven primarily by the fact that we're transplanting the donor's immune system into the recipient with cancer. The purpose here is always curative, and it's usually used in cases where standard chemotherapy or radiation are unable to cure the cancer; and it relies heavily on this donor immune systems' response and its ability to reject any residual recipient cells, whether they're malignant or healthy in order to generate complete engraftment and complete remission with sufficient depth.

So, this can be used not just in patients with chemotherapy-sensitive disease. It is commonly used in situations where the tumor is refractory to standard therapies. The therapeutic effect relies heavily on T-cells that come along with the donor graft. And these T-cells generate what we call a graft-versus-tumor immune response in which these T-cells eradicate residual cancer cells but comes along with a potential risk, which we call graft-versus-host response, in which case the same donor T-cells can also attack normal healthy tissues in the recipient; and we're going to talk more about that.

Just to mention one additional type of transplant, which is not used frequently, and that's a syngeneic transplant, which we use in the case that the recipient has an identical twin. So, in that case, the transplant works quite well because there is no genetic disparity between the donor and the recipient. There is no risk for rejection of the transplant, and there is no risk for graft-versus-host disease. But on the other hand, there is also no benefit as an immunotherapy because the lack of genetic mismatch means that there will be also no graft-versus-tumor response.

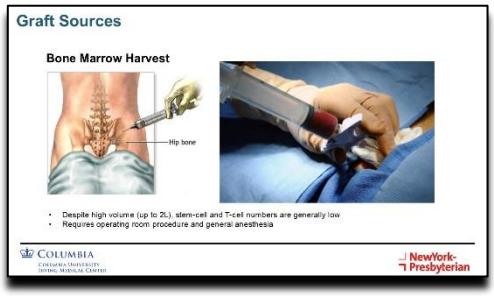


Slide 10: Sources of Hematopoietic Stem Cells

So, one more thing to consider is that the stem cells can come in a variety of forms and shapes. And when we collect them from either the patient or from a donor, we could collect them in various ways and from various locations. Originally, it was thought that hematopoietic stem cells can only be found in the bone marrow and that we should harvest them from the bone marrow where they sit at their physiologic niches. That means that stem cells would need to be removed directly from a bone, most likely the pelvic bone; and that's quite an aggressive procedure requiring general anesthesia and removal of large amounts of bone marrow in order to collect sufficient numbers of stem cells that would be good enough for engraftment.

So, this is a bit aggressive; but that's, in fact, the way bone marrow transplants were done from the late '50s all through the '90s. In the late '90s, the ability to mobilize stem cells from the marrow into the peripheral blood led to the development of a different harvest method called peripheral blood stem cell mobilization and collection. By mobilizing the stem cells out of the bone marrow niche using growth factors such as G-CSF and other mobilizing agents which we will talk about, we can collect them from the peripheral blood by a simple apheresis procedure. This makes it a lot easier for the donor and does not require an operating room procedure and does not require general anesthesia.

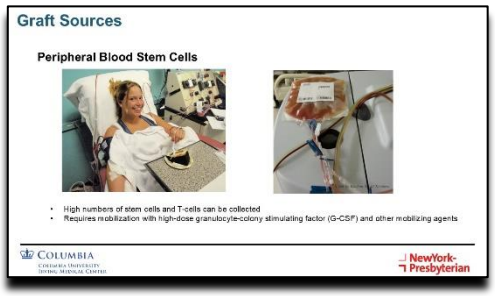
Another source of stem cells that has been developed in the last few decades is using umbilical cord blood, which is enriched with stem cells and also the types of immune cells in umbilical cord blood are quite different from what we would see in an adult because they're more likely to be naïve, less experienced, and maybe less violent T-cells. Therefore, people who donate the umbilical cord blood into either public banks or private banks, those could be used as a source of stem cells for transplant; and it certainly has different characteristics. And we're going to talk a little bit about the differences between them in the next few slides.



Slide 11: Graft Sources

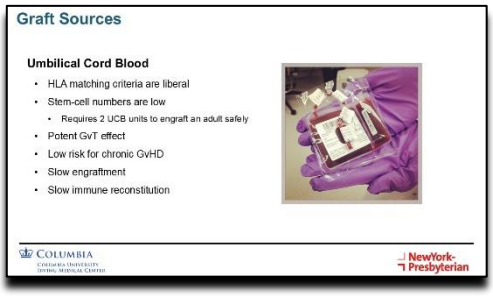
So, just to illustrate how these graft sources are generated and how they're used, a bone marrow harvest, as I mentioned, is done in the operating room. And despite the fact that we sometimes harvest a very high volume of bone marrow, in fact, up to 2 liters of bone marrow aspirate can be removed in one procedure from an adult, then the stem cell numbers and the T-cell numbers in that graft will still generally be on the lower side.

And that's one of the reasons why this method is associated with, perhaps, slower engraftment of the transplant, some risk for rejection, just because of low numbers of the stem cells and the T-cells which are required for engraftment. And along with that, some differences in the graft-versus-tumor and graft-versus-host responses because the lower number of T-cells would mean that the patient would be less likely to develop severe graft-versus-host disease, primarily chronic graft-versus-host disease, but also is somewhat likely to have a less potent graft-versus-tumor response. As a result of those various issues, there is much less use of bone marrow grafts nowadays, at least in adults, while it remains the predominate graft source in pediatrics. And we're going to talk about the reasons for that a little bit later.



Slide 12: Graft Sources

So, as you can see here, peripheral blood stem harvest is a somewhat more elegant procedure. The donor can sit happily connected to an apheresis machine, having a cake or reading a book, and is also generally able to collect a very high number of stem cells and a very high number of T-cells into a fairly small bag, as you can see on the right side of this slide. The only downside, which is no longer considered a real downside, is that these stem cells will need to be mobilized, either with high doses of granulocyte-colony stimulating factor, or G-CSF, or other mobilizing agents with, which have been introduced in the past couple of decades. And now there is a long track record of safety using these agents, so this is really no longer considered a major safety issue; and this has become the most commonly used graft source in the United States and all over the world.

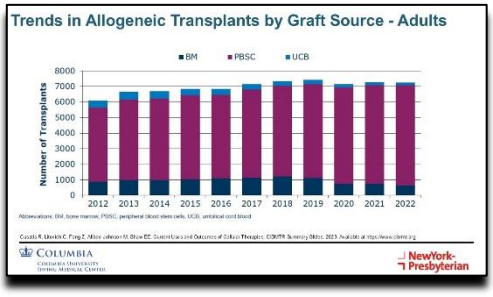


Slide 13: Graft Sources

So, the umbilical cord blood, as you can see, this picture was chosen on purpose to demonstrate how small each unit is. And it's not just the size of the bag, but the major advantage of umbilical cord blood is that it would do, it would offer us a much more liberal criteria when it comes to HLA matching. You don't need to undergo very careful HLA matching in order for cord blood to engraft because of its various properties of the cells in it.

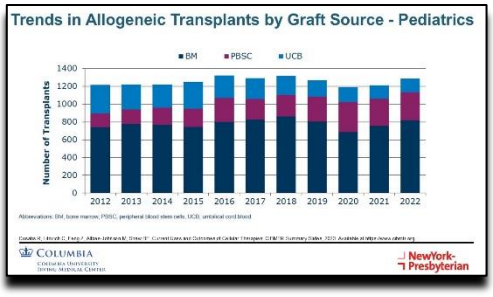
However, the stem cell numbers that we can get from a single unit of umbilical cord blood is relatively low; and that might be sufficient to engraft a baby or a small child. But to safely engraft an adult, we would generally require two separate umbilical cord blood units which would usually not even match each other when it comes to their HLA typing and are also fairly expensive to retrieve and somewhat slow to retrieve from various banks.

So, this graft source does have some unique properties. It has a very potent graft-versus-tumor effect because of how effective the naïve T-cells in a baby's blood are against cancer. But that also is associated with a pretty slow immune reconstitution, so their ability to fight infections is similar to a newborn baby who's at risk for quite significant infections once exposed to the outside world. Those are the reasons that this, umbilical cord blood as a graft source has become less and less commonly used, definitely in adults, but also in children.



Slide 14: Trends in Allogeneic Transplants by Graft Source - Adults

So, the pros and cons that I just illustrated for the various graft sources help explain this plot, which show you that in the contemporary era, over 90% of the transplants in adults, allogeneic transplants, and certainly nearly 100% of autologous transplants, are using G-CSF mobilized peripheral blood stem cells.



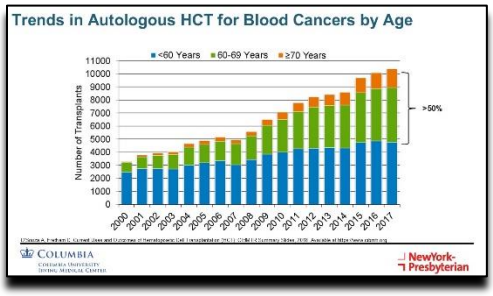
Slide 15: Trends in Allogeneic Transplants by Graft Source - Pediatrics

As opposed to that, in children, bone marrow does remain a predominant graft source that is still in use; and that is driven by two major factors. First of all, for the most part, when children get transplanted, the donor is an adult. And just because of the size differences, you could harvest sufficient numbers of

stem cells and T-cells, immune cells from an adult to adequately engraft a child.

In addition to that, in children, a much higher proportion of the transplants are done for nonmalignant disorders such as congenital immunodeficiencies or hemoglobinopathies where we don't need a graft-versus-tumor response. We just need to replace the marrow with healthy stem cells that do not carry a certain genetic aberration. And for that purpose, a bone marrow graft is perfect and remains the predominant source.

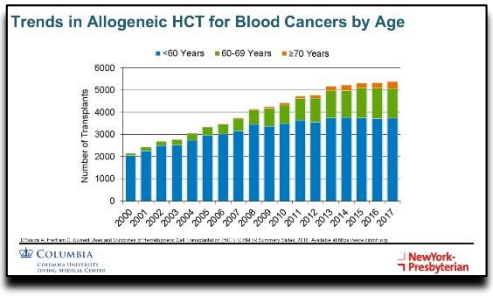
What you can see on this plot is still that there has been a growth in use of peripheral blood stem cells, even in children, and a significant decrease in use of the umbilical cord blood, which at this point primarily have a few disadvantages that make them somewhat difficult to work with.



Slide 16: Trends in Autologous HCT for Blood Cancers by Age

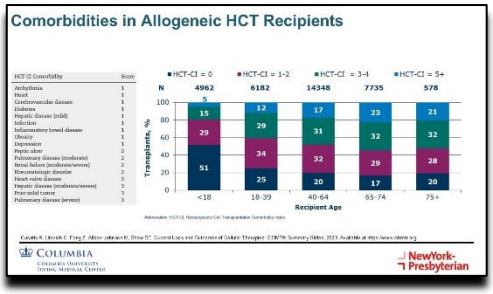
Another issue that's important to emphasize is that the age range in which we would like to apply transplants is the same age range where blood cancers are common. So, we know that blood cancers are common, primarily in older individuals. And the reason for that is that most blood cancers are driven by naturally occurring genetic abnormalities or naturally occurring mutations that simply accumulate over time, which makes blood cancers peak incidence occur in individuals in their 60s and 70s. But the procedure when it was first done and the way it was designed and how aggressive it was, it was really appropriate for patients under age 50; and that has been one of the major issues in development of transplant over the years. How do we apply it to older individuals where blood cancers are, in fact, common?

And, as you can see on this plot, we have largely overcome that barrier; and at least for autologous transplants, more than 50% of transplants over the past few years are done in patients over the age of 60, which is where most of these blood cancers occurred.



Slide 17: Trends in Allogeneic HCT for Blood Cancers by Age

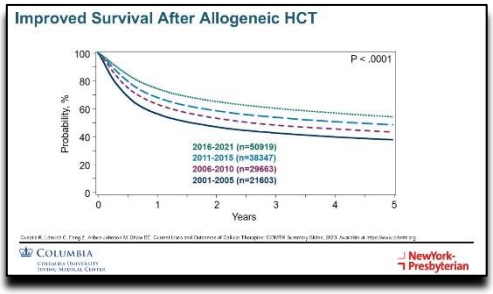
We see a similar trend, maybe a little bit slower, with allogeneic transplants where we have found ways to introduce allogeneic transplants into older individuals, primarily through advances in reduced intensity conditioning, which we will talk a little bit about later. And as you can see here, there are plenty of patients over age 60 and even some patients over age 70 that can safely undergo an allogeneic transplant in the contemporary era.



Slide 18: Comorbidities in Allogeneic HCT Recipients

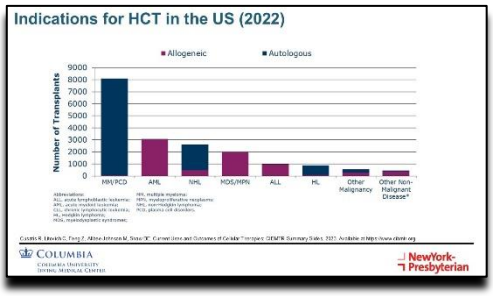
Age is not the only important parameter when deciding if a patient would benefit from a transplant; and along with age, come significant comorbidities, as you can see on this slide. And this slide is a good opportunity to introduce this grading system called the hematopoietic cell transplant comorbidity index, which was developed quite a while ago in Seattle and has been refined and validated over the years. As you can see here, we basically apply a certain scoring system to patients who have comorbidities in their heart, lung, kidney, liver, and even issues like obesity, diabetes, or depression have entered into the scoring system. The more comorbidities a patient accumulates, the higher the risk for treatment-related morbidity and mortality is; and that is linked directly with the overall survival.

And as you could see, as the age range goes up, certainly the number of comorbidities goes along with that. And that's important to keep in mind when selecting appropriate patients for transplant.



Slide 19: Improved Survival After Allogeneic HCT

These slides help put into context the improvement in overall survival that we've seen over the past few decades with transplant. And this slide specifically depicts the survival outcomes over the years for allogeneic transplants. And as you can see, despite the fact that we're transplanting older individuals and much sicker individuals nowadays, there has been a dramatic and gradual and ongoing improvement in the outcomes; and probably the contemporary outcomes beyond 2021 will continue to improve over the years with advances in patient selection, advances in our ability to detect minimal residual disease, and prevent disease relapse better, and dramatic advances in supportive care and ways to prevent graft-versus-host disease, which we're going to talk about later.

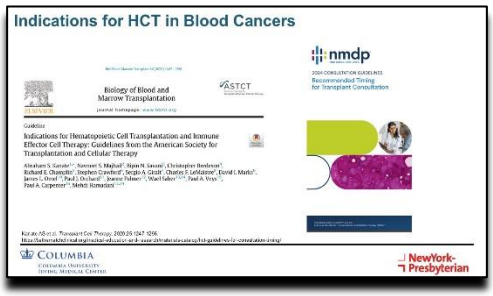


Slide 20: Indications for HCT in the US (2022)

So, what are the common indications for transplant in the United States? As you can see here, this is, again, from the CIBMTR data. Autologous transplants are primarily done in myeloma and still done very frequently in non-Hodgkin and Hodgkin lymphoma, although in some types of non-Hodgkin lymphoma, transplants are now being replaced quite effectively by cell therapy approaches such as CAR T-cells. And CAR T-cells are also

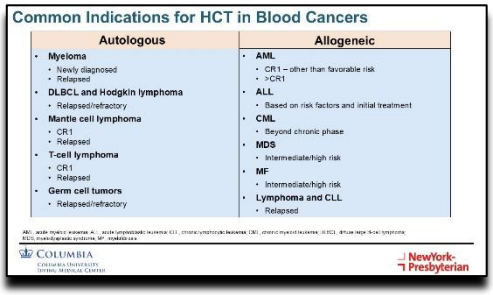
done generally by transplanters in most centers, but we will not focus on this in this webinar. And there's plenty of material on The Leukemia & Lymphoma Society website to discuss CAR T-cells as one of the next approaches or upcoming approaches in treatment of these cancers.

As you can see, allogeneic transplants are primarily performed in acute leukemias in a growing number in myelodysplastic syndromes and myeloproliferative neoplasms. There are also some additional malignancies that I'm not going to go too much in depth to discuss them and some nonmalignant diseases which will not be the topic of this webinar.



Slide 21: Indications for HCT in Blood Cancers

We are not going to review the indications for the various blood cancers one by one, but just as one place where you could find resources that discusses what type of patients should be referred to transplant, then the National Marrow Donor Program has guidance for referring physicians, which you can see on the right side of this slide. And if you want to go more into the details of what level of evidence exists for each type of cancer in each type of disease state, such as first remission, second remission, relapsed or refractory disease, you can find guidance that gets updated every few years by the American Society of Transplant and Cell Therapy, which was last updated in 2020, as you can see on the left side of this slide.



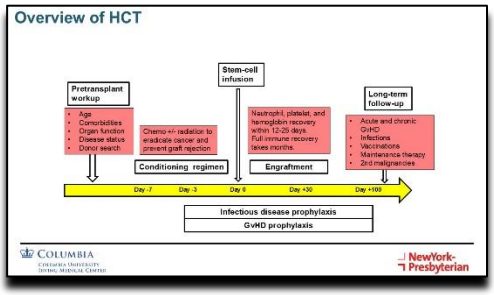
Slide 22: Common Indications for HCT in Blood Cancers

So, just to review this very briefly, without going too much in-depth into the literature, the common indications as you can see for autologous and allogeneic transplants are displayed on this slide. Autologous transplants are standard of care in newly diagnosed myeloma patients after initial induction therapy and certainly in relapsed myeloma in patients who have not had a chance to undergo transplant as part of their first line of therapy. In other diseases, we primarily use autologous transplant in their relapsed or refractory setting, although in some types of lymphoma such as mantle cell lymphoma or peripheral T-cell lymphoma, there is a standard of using transplant, even in patients in first remission.

On the allogeneic side of things, in acute leukemia, transplant is now standard in first remission in AML in anyone who does not have favorable-risk AML. And again, this needs to be personalized; and the risk-benefit of transplants needs to be assessed and individualized in each patient. But largely speaking, most patients with acute leukemia are

eligible and may benefit from a transplant; and it's worth at least having that discussion with them.

In non-Hodgkin lymphoma and Hodgkin lymphoma, we primarily use allogeneic transplants only in heavily refractory patients; and in CML, myelodysplastic syndrome, and myeloproliferative neoplasms, patients with certain risk criteria are eligible and will benefit from a transplant.



Slide 23: Overview of HCT

So, to set the stage for the rest of our webinar, let's just review what the patient journey looks like when they are a candidate for a hematopoietic stem cell transplant. And let's get familiarized with the terminology that we commonly use.

So, when patients get referred to transplant, they undergo a pretransplant workup that includes review of their comorbidities, age, performance status, as we've discussed, are important parameters in prognosticating patients and predicting what their chance of developing significant toxicity from transplant would be. We look at various risk factors for complications. We look at organ function in quite significant detail. We look at disease status as, to figure out whether a transplant is indicated. And sometimes it would even impact the way we would do the transplant because we would not do the transplant exactly the same way in a patient with refractory leukemia as opposed to a patient who is first remission.

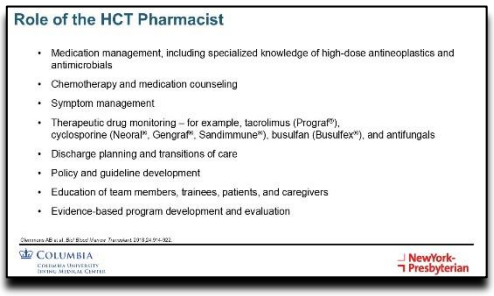
Following this assessment, which David will talk about a little bit in greater detail, we also have our patients undergo quite a fair amount of education from our transplant coordinators, from our physicians and nurse practitioners. Patients learn about the process. Their caregivers are educated, and they meet several members of our team, including a liaison psychiatrist that in our program meets with all of the allogeneic transplant candidates, a social worker to discuss some of the psychosocial support and, and get acquainted with their individual issues, and even a registered dietitian, which is an essential part of both the workup for transplant and also an essential part of accompanying the patient through the transplant process.

It is quite critical to identify patients who are at a high nutrition risk and provide nutrition education to all patients. Our nutritionists are heavily involved through the transplant process, both if the transplant goes perfectly well without complications, and their role is especially essential if patients do develop complications such as graft-versus-host disease or significant conditioning related GI toxicity which may affect their nutritional status dramatically. So, following these pretransplant workup and education part, patients would receive a conditioning regimen which has a dual role of both eradicating cancer cells and,

in the case of an allogeneic transplant, helps with the engraftment and prevents rejection and helps prevent graft-versus-host disease.

The stem cell infusion, the terminology we use for that day is day 0; and David will talk about that a little bit more. And then there's an initial period of engraftment where patient's blood counts recover as their stem cells differentiate and form new blood cells. This can be done either inpatient, but if it's done outpatient, it requires nearly daily monitoring of these patients during this high-risk period where significant toxicities may happen.

And then we go into long-term follow-ups that, where these patients may encounter complications such as acute or chronic GVHD, disease relapse, infections, we need to follow their immune reconstitution and see if we need to revaccinate them. And issues such as second primary malignancies, which we will mention later on, and there's quite a bit of supportive care that goes along with that such as infectious disease prophylaxis and graft-versus-host disease prophylaxis that we will talk about in detail.



Slide 24: Role of the HCT Pharmacist

So, this was a broad overview of the transplant process and how it's done and what is the purpose. I'm going to hand this over to my colleague, David, who is the PharmD of our program here at Columbia. He will explain more about the role of the pharmacist in the HCT program and their role in the patient's overall journey and then discuss autologous hematopoietic cell transplantation specifically in greater detail. David, take it away.

David Sabatino, PharmD, BCOP: Thank you, Dr. Reshef. So, like Dr. Reshef said, we'll start with the role of the stem cell transplant pharmacist, which is a quite diverse role and revolves primarily around patient-centered care.

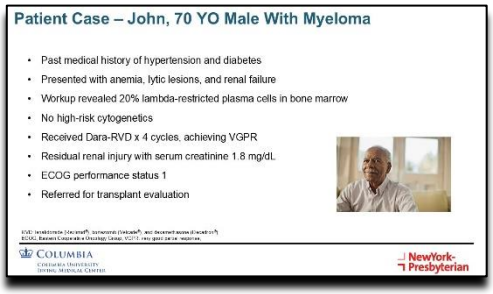
First and foremost, we oversee medication management, which can include, but not limited to, chemotherapy conditioning regimens, graft-versus-host disease prophylaxis, and supportive care measures. Part of this process includes evaluating drug levels of antineoplastics, immunosuppressants, and antimicrobials to make dose adjustments and recommendations if necessary. We also assure patients are fully educated on their chemotherapy regimens, as well as make sure the patient has a firm understanding of the medications they will continue taking as an outpatient.

Furthermore, we play a role in quality and safety. We have the ability to evaluate policies and guidelines to assure we're adhering to them and suggest ways to improve current processes. Lastly, we tie all these pieces together by educating other team members,

trainees, patients, and caregivers to make sure everyone is on the same page when a patient is undergoing a transplant.

Slide 25: Autologous Stem Cell Transplant

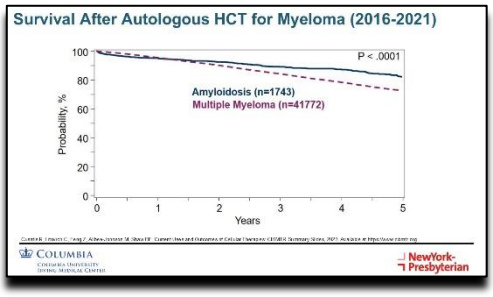
Now, we'll take a deeper dive into autologous stem cell transplants.



Slide 26: Patient Case – John, 70 YO Male with Myeloma

Before we go more into detail, we'll first introduce a patient case. This is patient John. He's a 70-year-old male with myeloma. He has a past medical history significant for hypertension and diabetes. He presented with anemia, lytic lesions, and renal failure. His workup revealed 20% lambda-restricted plasma cells in the bone marrow and has no high-risk cytogenetics.

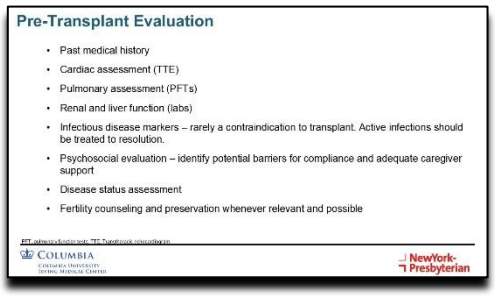
For induction chemotherapy, he received dara-RVD, a regimen that contains daratumumab (Darzalex®), lenalidomide (Revlimid®), bortezomib (Velcade®), and dexamethasone (Decadron®) for a total of four cycles and achieved a very big partial response. Residual renal injury was significant for a serum creatinine up to 1.8. His performance status at the time is 1, and then he was referred to, for a transplant evaluation at this time. So, we'll revisit this case throughout the presentation to help kind of guide our treatment decisions that we've decided for this patient, John.



Slide 27: Survival After Autologous HCT for Myeloma (2016-2021)

Before we do go more into depth on our patient, first I would like to talk about the survival of autologous stem cell transplants for patients with myeloma. This graph represents overall survival over the last five years for myeloma patients, as well as amyloid patients. I would like to focus your attention on the dotted purple line. This line indicates that myeloma patients that undergo an autologous transplant that roughly 75% of them will still be alive in five years.

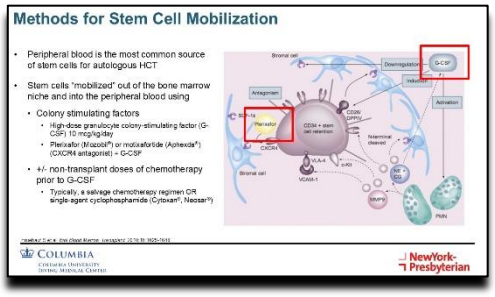
This is encouraging data as Dr. Reshef mentioned earlier as overall survival in years past was probably closer to only 60% in this patient population.



Slide 28: Pre-Transplant Evaluation

Before a patient can proceed with an autologous stem cell transplant, they must go through a thorough pretransplant evaluation. Important things to consider in this process is past medical history and what comorbidities are present as well as organ function assessment, which includes cardiac, pulmonary, renal, and hepatic.

We also must assure that patients have no active infections and they are treated prior to undergoing a transplant. Psychosocial evaluation allows us to identify any barriers for compliance and ensure patient had an adequate caregiver at home. Lastly, we must assess the patient's disease status at the time of transplant, as well as consider fertility preservation and counseling if appropriate in certain patients.

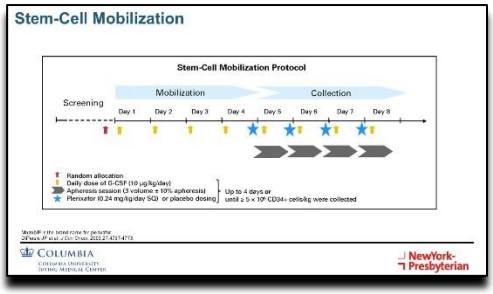


Slide 29: Methods for Stem Cell Mobilization

Once the patient clears the pretransplant evaluation process, the patient will need to undergo stem cell mobilization. Peripheral blood remains the most common source of stem cells. Chemotherapeutic agents, such as cyclophosphamide (Cytoxan®), have been used in conjunction to growth factors to mobilize the stem cells from the bone marrow to the peripheral blood.

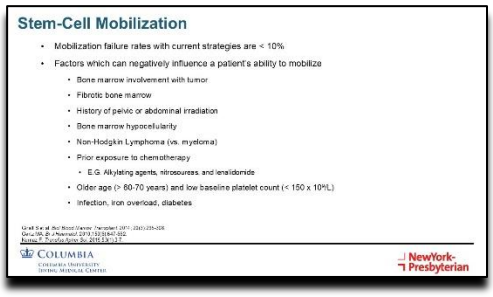
There are low concentrations of stem cells in the peripheral blood, and they are typically tethered to the bone marrow via adhesion molecules and receptor interactions within the bone marrow stromal cells. One of these receptors is chemokine receptor type 4 which is also known as CXCR4. We are able to increase the quantity of these stem cells in peripheral blood by disrupting the bone marrow microenvironment.

Our first step is using granulocyte colony-stimulating factor, also known as G-CSF. This is given prior to apheresis sessions; and then we also have the ability to add additional growth factor support such as CXC4 inhibitors if patients do not have an adequate initial response to just G-CSF.



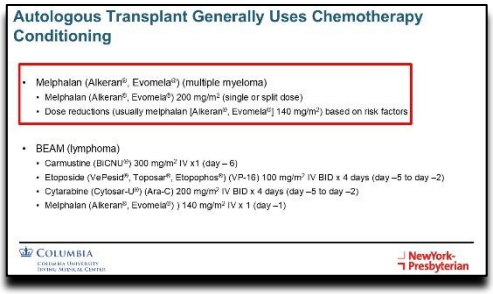
Slide 30: Stem-Cell Mobilization

Here's the timeline of what a typical stem cell mobilization looks like. We start with high-dose G-CSF on days 1-4 with plan for apheresis to start on day 4. By day 5, we expect the CD34+ stem cells to peak in peripheral circulation. If the CD34 concentration is lower than expected or patient has suboptimal collection, we will add a CXCR4 inhibitor to allow for further mobilization of the stem cells for subsequent apheresis days.



Slide 31: Stem-Cell Mobilization

There are other factors to consider when a patient is undergoing mobilization, including factors that may negatively affect the ability to mobilize. Although mobilization failure is rare, it's important to consider if patients have bone marrow involvement of their disease, fibrotic marrow, history of pelvic or abdominal radiation, and what prior chemotherapies they have received as these all may affect patient's ability to have a successful collection. It is important to note if the patient has been on lenalidomide (Revlimid®) therapy prior as this is not a contraindication to mobilization, but it may suggest that a patient may need more strategies to help them mobilize their stem cells adequately with the addition of CXC4 inhibitors specifically. Other things to consider is the patient's age, the patient's baseline platelet count, infection, iron overload, and the patient's past medical history.

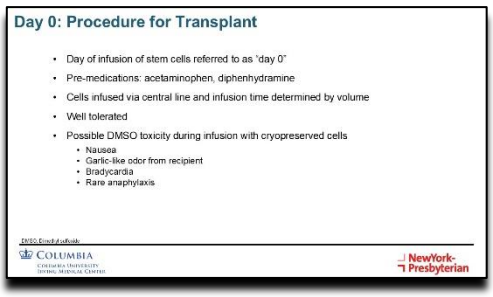


Slide 32: Autologous Transplant Generally Uses Chemotherapy Conditioning

The conditioning chemotherapy for autologous stem cell transplants will vary based on malignancy. Melphalan (Alkeran®) is typically, we use for multiple myeloma and amyloidosis; and BEAM regimen, which we'll talk more about, includes carmustine (BiCNU®), etoposide (Vepesid®), cytarabine (Cytosar-U®), and melphalan (Alkeran®) is the standard of care for lymphoma patients.

If we think about to our patient case, John has multiple myeloma so would probably benefit most from using regimens that just use melphalan (Alkeran®) as a conditioning regimen. One thing we do need to consider is the dose of melphalan (Alkeran®) that we could potentially use. The standard dose is 200 milligrams per meter squared, but we need to factor in things such as age and performance status when considering dose reductions. Most likely patient John will undergo an autologous stem cell transplant with melphalan

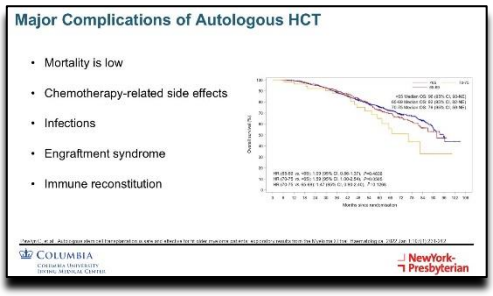
(Alkeran®) dose reduced to 140 milligrams per meter squared, based on his performance status of 1 and his old, older age of 70-year-old.



Slide 33: Day 0: Procedure for Transplant

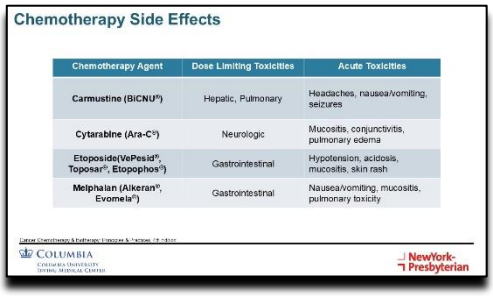
After conditioning chemotherapy is complete, we've reached day 0, which is the day of stem cell infusion. Premedications are given prior to the infusion and typically include acetaminophen (Tylenol®), diphenhydramine (Benadryl®), and sometimes hydrocortisone (Hydrocort®). Afterwards, the stem cells are infused via a dedicated central line.

The actual stem cells are very well-tolerated. But in cases of cryo-preserved stem cells, DMSO preservative is also infused into the patient and can cause some toxicity. Some signs and symptoms we observe is nausea, bradycardia, and even in some patients a garlic-like odor from the recipient. In very rare cases, anaphylaxis is possible.



Slide 34: Major Complications of Autologous HCT

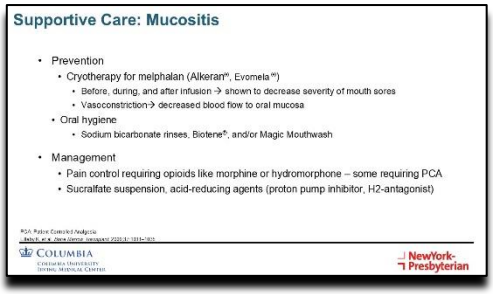
The major complications of autologous stem cell transplants are typically related to the chemotherapy side effects. Mortality related to the transplant itself is relatively low, which is depicted in the graph on the right. Mortality within the first few months ranges from only 1% to 5%. Other possible complications over the first week or two after stem cell infusion includes infections, engraftment syndrome, immune reconstitution. Over the next few slides we'll go into more detail on each of these.



Slide 35: Chemotherapy Side Effects

We'll start with chemotherapy side effects. So, the chemotherapy side effects are dependent on the agent being used as each has its own dose-limiting toxicity. For most of the common chemotherapies used for autologous transplants can be found on this slide. We will focus on melphalan (Alkeran®) as we can relate this back to our patient case.

For melphalan (Alkeran®) specifically, the dose limiting toxicity is gastrointestinal. So, we would expect side effects that primarily include nausea/vomiting, mucositis, and pulmonary toxicity when counseling John and educating him on his chemotherapy regimen.

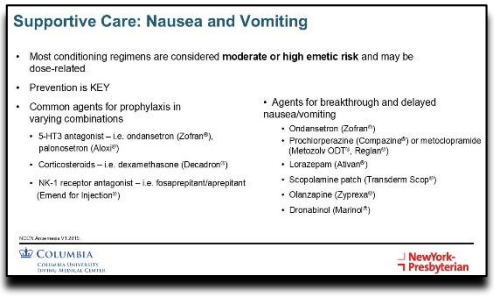


Slide 36: Supportive Care: Mucositis

Given mucositis is a common side effect of many chemotherapy agents, we want to provide the best care for patients and prevent and treat this toxicity if possible. Mucositis caused by melphalan (Alkeran®) can be mitigated through the use of cryotherapy. Studies have shown that when patients suck on ice chips before, during, and after melphalan (Alkeran®) infusions, the severity of mouth sores are significantly less.

This works specifically with melphalan (Alkeran®) due to the short half-life of melphalan (Alkeran®) and is cleared quickly through the body. In addition to the ice chips where it's able to vasoconstrict the oral mucosa and prevent drug delivery to this area, prevent damage to the oral mucosa. When the oral mucosa is damaged and patients have developed mucositis, we provide patients with mouthwashes to keep the mouth clean, to prevent infections, and also numb the pain topically.

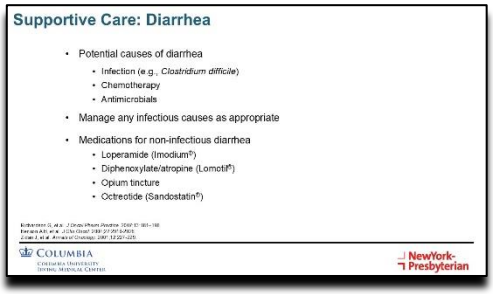
For severe pain, patients are often started on opioids; and if they are unable to tolerate oral medications, they are frequently started on IV pain medications, and even in the most severe cases, sometimes a PCA. Lastly, we provide acid suppressants to increase the pH of the stomach to not further irritate potential stomach ulcers that are caused by mucositis.



Slide 37: Supportive Care: Nausea and Vomiting

Next, we'll discuss nausea and vomiting. Most conditioning regimens are associated with a moderate- to high-risk of emesis. Common prophylaxis agents are typically given in combination, such as ondansetron (Zofran®), a serotonin antagonist; dexamethasone (Decadron®), a steroid; aprepitant (Emend®), an NK-1 receptor antagonist; and olanzapine (Zyprexa®), which is able to inhibit multiple receptors, including dopamine. In total, patients receive typically three to four of these different classes of medications to optimally prevent nausea and vomiting from occurring. Some patients still may develop breakthrough nausea and vomiting, in which prochlorperazine (Compazine®) is usually given as needed in these patients.

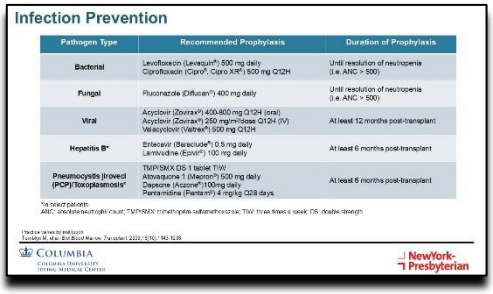
Patients that have experienced nausea and vomiting in the past due to chemotherapy may have a component of anticipatory nausea and vomiting. In these cases, an anxiolytic such as lorazepam (Ativan®) can be used before chemotherapy to prevent nausea and vomiting in developing in these patients.



Slide 38: Supportive Care: Diarrhea

Next, we'll go into detail on diarrhea. There are several reasons why patients could develop diarrhea in the transplant process. Some reasons could be, include infectious causes such as *C. diff* or chemotherapy related, or even antibiotic related.

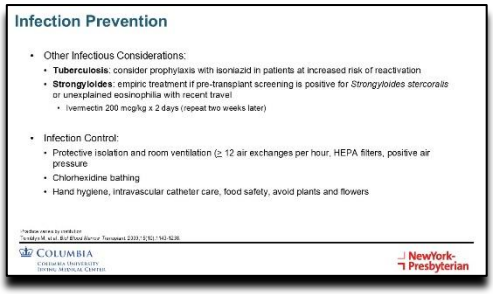
First, reassure the patient is not infected; but if they are, our management will be directed at the infection itself. Once an infection is ruled out, we're able to use antimotility agents such as loperamide (Imodium®); diphenoxylate/atropine (Lomotil®); opium tincture (Laudanum); and very refractory cases even octreotide (Sandostatin®), which can work as an antisecretory agent as well.



Slide 39: Infection Prevention

Now we'll go a bit into detail for infection prevention. Patients undergoing autologous transplant are at risk for bacterial, fungal, and viral infections for different lengths of time. Bacterial and fungal infections are most common during times of neutropenia, so we start prophylaxis medications typically on Day 1 and continue these agents through the duration of their neutropenia.

Antiviral prophylaxis is extended usually past the duration of neutropenia as viral infections can happen even past the time of neutropenia. Some patients often require prophylaxis for hepatitis B or *Pneumocystis* and even toxoplasmosis. These prophylaxis agents will be administered, depending on patients' underlying disease state, as well as their infectious serologies prior to transplant. The most common agents utilized in dosing are listed on this slide for your reference.

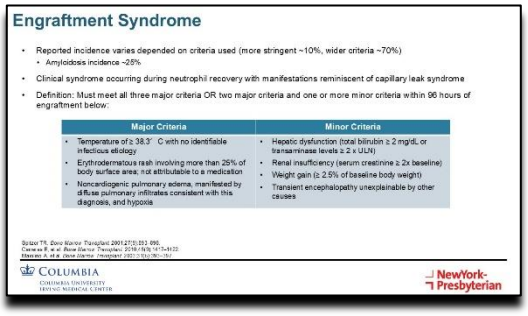


Slide 40: Infection Prevention

There are some other infection prevention considerations that we should take into account, one being tuberculosis. Patients have a risk of reactivating tuberculosis if they are considered high-risk for reactivation. In patients that are considered high-risk for reactivation, you should start prophylaxis with isoniazid (Nydrazid®).

Another potential complication is *Strongyloides*. Empiric treatment if, is warranted if the pretransplant screen process is positive for *Strongyloides* or if they have unexplained eosinophilia with recent travel.

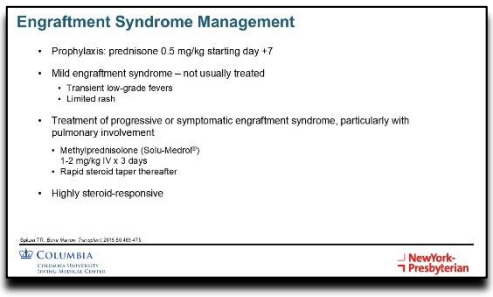
The empiric treatment for *Strongyloides* is ivermectin (Stromectol®), 200 micrograms per kilogram for two doses; and then you repeat these two doses two weeks later.
Other infection control precautions should include patients being placed in an isolation room with appropriate ventilation. Chlorhexidine (Betasept®) baths, hand hygiene, intravascular catheter care, food safety, including patients being educated on only eating cooked food, and the avoidance of plants and flowers as source of potential infections should be avoided in these patients.



Slide 41: Engraftment Syndrome

Another potential complication of autologous transplant is engraftment syndrome. This is a febrile syndrome that occurs in the early phase of neutrophil recovery. Incidents in the literature may vary, depending on the criteria used and can range anywhere from 10% to 70%. We see in the literature that it's probably most common in patients with amyloidosis where the incidence is about 25%. Clinical features include combinations of noninfectious fever, skin rash, pulmonary infiltrates, hypoxia, diarrhea, and manifestations of capillary leak syndrome such as weight gain, edema, and ascites.

There is no uniform definition, but the table provided here gives an outline for diagnostic criteria. The patients must meet all three major criteria or two major criteria and at least one minor criteria within four days of engraftment to be considered, have a diagnosis of engraftment syndrome.



Slide 42: Engraftment Syndrome Management

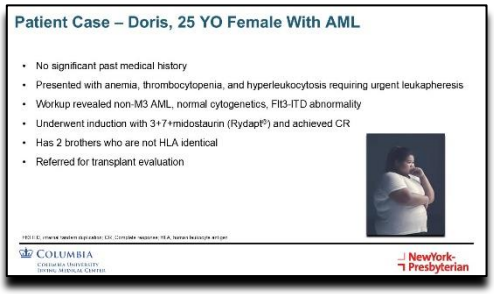
Engraftment syndrome prophylaxis can be provided for our high-risk patients; and typically, we do so in our amyloid patients in which we start prednisone (Deltasone®), 0.5 milligrams per kilogram on day +7 through the time that the patients engraft their neutrophils.

In patients that develop engraftment syndrome, management is usually dependent on the severity. In patients with mild engraftment syndrome, that's transient low-grade fevers and a minor rash, sometimes we don't need to treat these patients is [at] all. If patients have worsening or severe engraftment syndrome, particularly with pulmonary involvement, we will start treatment with steroids. Typical dosing is methylprednisolone (Solu-Medrol®), 1 to 2 mgs/kg for 3 days, followed by a rapid taper. Most patients will respond to therapy within a few days of initiating steroids and can be promptly tapered off steroids in the subsequent days.

Slide 43: Allogeneic Stem Cell Transplant

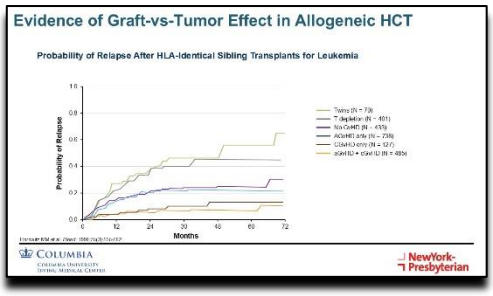
I will now pass it over, back to Dr. Reshef, to go more into detail on allogeneic stem transplants.

Dr. Reshef: Thank you very much, David. So, I'm going to discuss allogeneic hematopoietic cell transplant in further detail. There are going to be a lot of things that overlap with what you just heard from David, and I'm not going to review them a second time. And I'm going to try and focus on things that are unique to the allogeneic setting.



Slide 44: Patient Case – Doris, 25 YO Female With AML

So again here, I will use a patient case. And this is Doris, a 25-year-old female with no past medical history who presented with acute myelogenous leukemia. She presented with cytopenias and hyperleukocytosis that required urgent treatment in the form of leukapheresis, and her workup revealed that she had a non-M3 AML with normal cytogenetics in one of the more common abnormalities that we see in AML – FLT3-ITD, which is a high-risk feature which usually drives hyperleukocytosis. This is considered a fairly clear indication for an allogeneic transplant in first remission. So once the patient underwent successful induction with a regimen called 3+7, in addition to midostaurin (Rydapt®), which is a FLT3 inhibitor, she was referred to an allogeneic transplant in first remission. She has two brothers, but these brothers are not HLA identical; and we are ready to evaluate her.



Slide 45: Evidence of Graft-vs-Tumor Effect in Allogeneic HCT

So, as I mentioned earlier, the purpose of an allogeneic transplant is always a cure. And the way to achieve that is by the dual effect of the chemotherapy and radiation which eliminate most likely most of the residual cancer cells. But then also an immunotherapeutic effect driven by the donor's immune system, something that is called the graft-versus-tumor response.

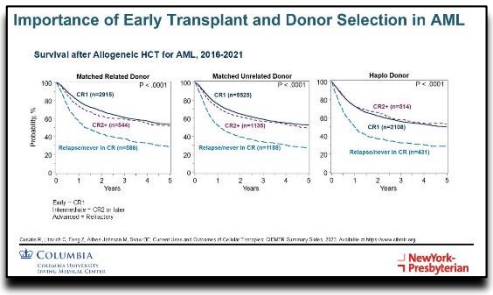
How do we know that that exists? So, there's plenty of evidence in mice, which I'm not going to go over. The donor T-cells can eradicate a tumor in a mouse. But there's also very good epidemiologic evidence in humans. This is one of the first papers that had

shown this by Mary Horowitz in 1990 looking at a large data set of patients undergoing HLA-identical sibling allogeneic transplant for acute leukemia.

And as you can see here, the probability of relapse is quite different, depending on several factors. The patients who may have the highest chance of relapse are actually the ones getting a syngeneic transplant where there is no genetic disparity between the donor and the recipient; and therefore, no immunotherapeutic response, no graft versus tumor. They also have no risk for graft-versus-host disease. But as you can see, there is a major downside to that by just having a very high relapse risk.

The rest of the group seemed to be distinguished by whether they developed acute or chronic graft-versus-host disease. And in fact, the lowest chance of leukemic relapse is seen in those individuals who develop both acute and chronic graft-versus-host disease. This is a clear demonstration that this is, there is an immunologic effect driven by the donor cells that is driving down the rates of disease relapse but, at the same time, drives up the chance of developing both acute and chronic graft-versus-host disease.

This study also shows us that this is largely dependent on T-cells because if you can see one of the highest relapse risks is seen in individuals who underwent T-cell depletion where the T-cells were simply removed from the graft and the graft contained primarily hematopoietic stem cells. In that case, there is very little graft-versus-tumor effect that's left; and these patients have a very high risk of relapse.



Slide 46: Importance of Early Transplant and Donor Selection in AML

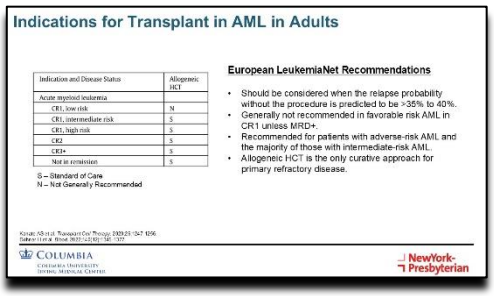
So, why does Doris need a transplant in first remission? And I'm not going to show all of the data that supports using transplant in first remission but just show you one nugget to illustrate what would happen if Doris wouldn't get a transplant in first remission and waits until she has progressed and developed relapse disease.

So, you can see in relapsed or refractory disease, patients who either never achieved a complete remission or are just transplant at the time of relapse without any treatment, the outcome of transplant is very poor. And, in fact, it's also inferior for patients getting transplanted in second remission as opposed to first remission. So, this is one indication why a transplant in AML might be best done when the patient is in the first remission.

If we look at the other two plots on this slide, you can see another important point, which helps us determine what would be the optimal donor. And you can see here on the left the outcomes of transplant in AML with a matched related donor in the middle with a matched

unrelated donor where there is some degree of genetic disparity that's greater just because of minor antigens that we don't really type for.

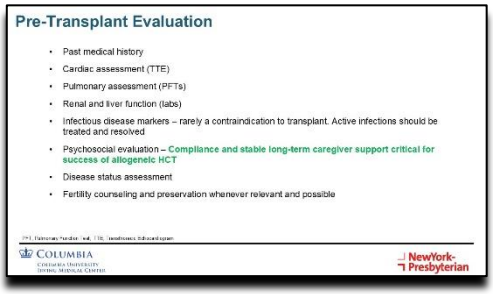
And on the right side, the use of half-matched donor or a haploidentical donor, and the message that I really want to show here is that in the contemporary era, these three plots actually don't look very different from one another. And historically, we would always consider the matched related donor to be the top priority, and the donor we should always go along with. But with the methods we have to do transplants today, these donor types don't appear to be very different in their outcome any longer. So, certain additional variables to their relatedness in HLA, variables such as age and the availability of a donor, whether it's someone who's available immediately or would take three or four months to collect in, in the case of an unrelated donor, those variables become a lot more important today in, in a situation where HLA may not be the top priority for us anymore.



Slide 47: Indications for Transplant in AML in Adults

So, again, without showing all of the data that supports transplant in AML in first remission, there is one resource that we can use. There are several actually. One of them are already shown, which is the ASTCT recommendation which clearly show that patients with AML in first remission, unless they have favorable-risk AML, which is not super common but those patients do quite well with chemotherapy alone, pretty much everyone else should at least be referred to consider transplant. And there's quite good evidence to support transplant in both intermediate-risk and adverse-risk cytogenetics and certainly in relapse, in refractory AML or any situation beyond first remission where transplant is considered the only curative approach.

This is also supported by the more recent European LeukemiaNet recommendations which would recommend a transplant in any situation where the probability of relapse exceeds 35% or 40% or situations where there is MRD positivity, a point which is a little bit problematic because we don't yet have established MRD testing for all types of AML and all of its subtypes.

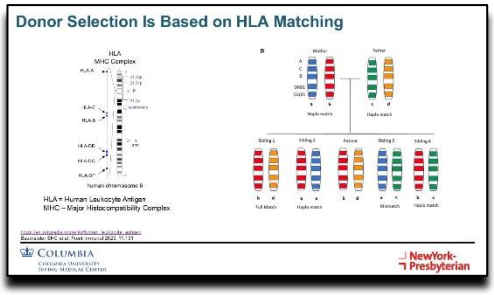


Slide 48: Pre-Transplant Evaluation

So David has, has already discussed the pretransplant evaluation in the context of autologous transplant. Some of it is extremely similar. We put a lot of heavy weight in the allogeneic transplant setting on the patients' understanding of the risk and benefit, the level of caregiver support, and the psychosocial support that patients would need. We try to make

sure that those are rarely a contraindication for transplant. We have teams of social workers, and we try to recruit family support and sometimes other caregivers outside the family to remove such barriers.

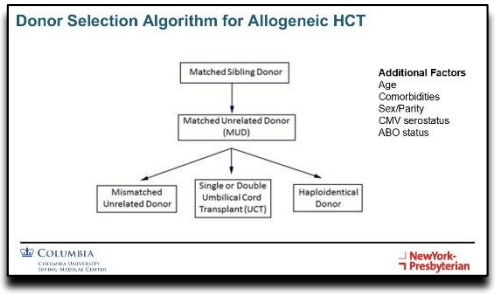
But compliance is a major issue in allogeneic transplant because of the complexity of the complications, the complexity of the drug regimen that these patients need to be on, and how important it is for them to be compliant, both with their medications and with the post-transplant monitoring and follow-up. So, lack of appropriate compliance, or lack of good caregiver support, or lack of good understanding of the transplant process can sometimes be barriers and are important to evaluate in the pretransplant workup.



Slide 49: Donor Selection Is Based on HLA Matching

So, we talked about the donor selection process; and it is still largely based on HLA matching as the first criterion we look at. But other criteria have gone up in their degree of priority in how we take them into account. So, HLA's the human leukocyte antigen. It is a set of genes that generate proteins on the surface of each and every cell of our body. And we have Class I antigens, which are A, B, and C. We have Class II antigens, which are DR, DQ, and nowadays we also consider DP as important. And we look at all of them when we look for HLA matching. They're all encoded by one chromosome, chromosome 6. So, patients will generally inherit a full haplotype of all of these HLA loci from both of their parents, their mother and their father. And as you can see in this illustration here, because of how the genetics work.

Each one of the patients' siblings has a one-in-four chance of being a full match, because they would inherit both haplotypes from both their parents; about a two-to-four chance of being half-match because they inherit only one haplotype, same as the patient. But there's also a one-in-four chance that a sibling would share none of the haplotypes and will have absolutely no matching with the patient. An HLA-matched donor is still considered somewhat superior to the other options, but we now have methods to cross HLA barriers, so haploidentical donors are more and more commonly used; and we're going to talk about this in one of the next few slides.



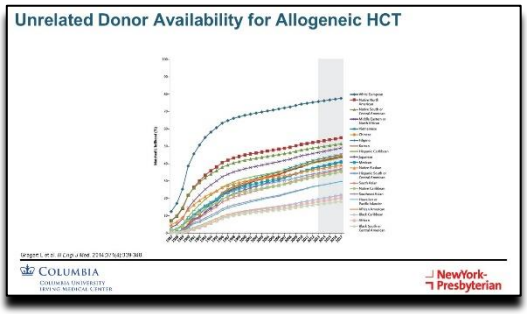
Slide 50: Donor Selection Algorithm for Allogeneic HCT

So, this is a bit historical; and it's certainly being revisited today. We still think about a full HLA match as, as the first criterion to look at; and that's usually been prioritized to be a matched or sibling donor or an HLA-identical sibling. And the next donor option we would go after is a matched unrelated donor, followed by these sets of alternative donor options, which are either haploidentical, mismatched unrelated, or even a single or double umbilical cord blood unit.

We know nowadays, as I've shown you in one of the previous slides, that the outcomes of transplant do not depend solely on the level of HLA matching. And some of the regimens that have been developed in the recent couple of decades, for example, post-transplant cyclophosphamide (Cytoxan®), which we're going to talk about, allow us to cross HLA barriers quite safely and allow us to increase the importance of some other variable.

For example, now that we do transplants in much older individuals then we did historically, then very frequently a matched, related donor would be a brother or a sister who are also quite old. It might be people in their 60s and 70s if the recipient is in that age range. And it turns out that age is a very important parameter, and that the use of an unrelated donor who's very young, might be beneficial and might be a better option than using a fully matched related donor who's on the older side.

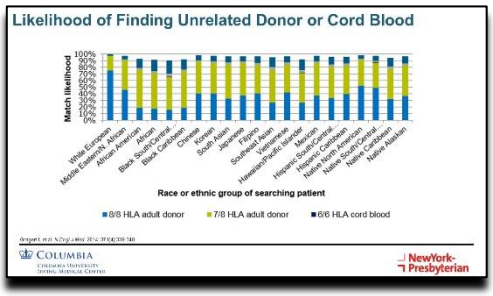
Similarly, donor availability is becoming very important because a related donor, whether that's a matched related or a haplo donor are usually very available, immediately available. We can sometimes do a transplant from a haploidentical or matched related donor within a couple of weeks from the patients being referred to us. Unrelated donors will take time, on average, two to four months to get through donor identifications, screening, and scheduling the donor collection; and that precious time may be disadvantageous to the recipient. It may turn us to a less well-matched but a more available donor.



Slide 51: Unrelated Donor Availability for Allogeneic HCT

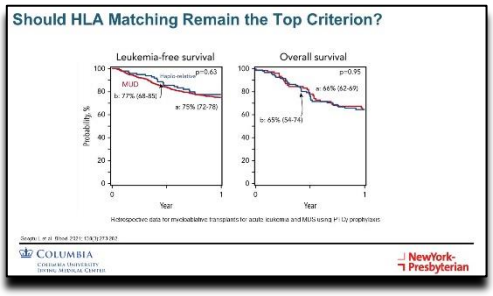
So, here to show again why we sometimes have an interest in using donors that are not fully matched, this is the unrelated donor availability for allogeneic transplant. And although the availability of unrelated donors has grown dramatically over the years with the growth of the registries, there is still significant disparity between racial and ethnic groups that is important to point out.

The chances of identifying a matched unrelated donor for a Caucasian European patient are quite high – the range of 80% or even higher than that nowadays. But as we go to other racial groups, at the bottom of the list you can see Africans, African Americans, and several Asian groups that have a much lower likelihood of identifying an unrelated donor. They may not have the matched-related donor because the chance for that is only one in four in full siblings. So, considering the size of the registry and the HLA diversity of certain ethnicities and races, we sometimes have challenges finding fully matched donors.



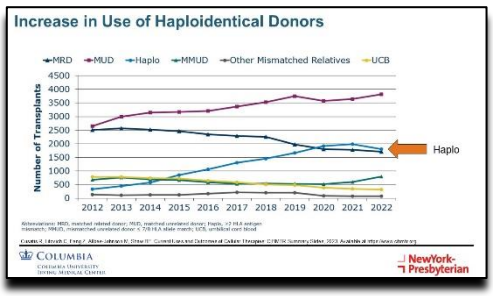
Slide 52: Likelihood of Finding Unrelated Donor or Cord Blood

And that is really where both cord blood and haploidentical donors have given us a lot of assistance, and in the early 2000s when the umbilical cord blood became a more relevant donor source with growing experience using it has become more and more standard to use umbilical cord blood. You could see that with that. You can find an 80% or 90% likelihood of a reasonable match if you include cord blood units for these racial groups that have this significant degree of disparity in finding unrelated donors.



Slide 53: Should HLA Matching Remain the Top Criterion?

And this is one piece of evidence that we now use to explain why we think that haploidentical donors are actually as good as matched-related or matched-unrelated donors. This is one example from a study that was done by CIBMTR and published a number of years ago looking at all matched, unrelated donor transplants versus haploidentical transplants for acute leukemia or MDS. And you could see here that at least in the myeloablative setting, the leukemia-free survival and overall survival for these two donor sources has become quite similar or maybe even very much identical. So, that's the driver for what I'm going to show you in the next slide, which is a dramatic increase in the use of haploidentical donors over time.

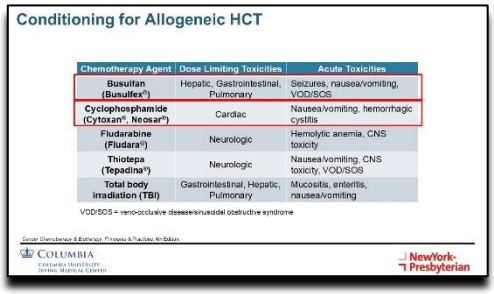


Slide 54: Increase in Use of Haploidentical Donors

So, as you can see here, haploidentical donors, which were considered in the past very high risk and associated with very high risk of both rejection and graft-versus-host disease, have become very standard; and in the past few years, they are the second most common donor source that we use.

And that is largely because of the implementation of a new method for prevention of graft-versus-host disease called post-transplant cyclophosphamide (Cytoxan®).

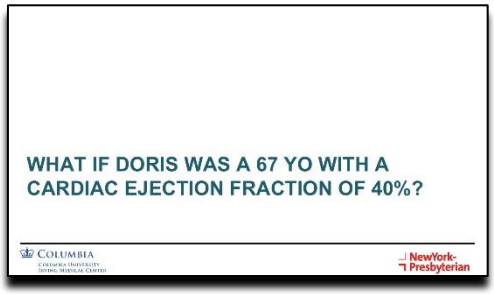
As you can see here as well, there's also been a drop over time in the use of the umbilical cord blood that I pointed earlier but also a decrease in use of matched related donors. And that is driven mostly because of that phenomena that when we use older donors for these older recipients that we now transplant, the outcomes are actually not so good. So, it might be preferable to use a young donor, whether that's a haploidentical son or daughter or a young, fully matched unrelated donor; and the outcomes of such a transplant are likely to be much better.



Slide 55: Conditioning for Allogeneic HCT

So, the next thing after donor selection is to pick a conditioning regimen; and there's quite a bit of thought invested in this decision, as David has already pointed out. Conditioning regimens are not all created equal. The various types of chemotherapies have different toxicity profile, including dose-limiting toxicities. They also have different properties in terms of pharmacokinetics, their penetration into the central nervous system, and even sensitivity of different diseases. For example, in ALL, we will favor total body irradiation where in AML we may not need radiation specifically to eliminate any residual disease.

So, some of the common ones are listed here, including alkylating agents, purine analogs, and total body irradiation. All of those are used either alone but more likely in combination. In the case of Doris, who's a young and healthy patient with a fairly high-risk disease, we decided to go with the combination of high-dose cyclophosphamide (Cytoxan®) and high-dose busulfan (Busulfex®). This combination is one of the more aggressive but also one of the more potent regimens that we have for conditioning.

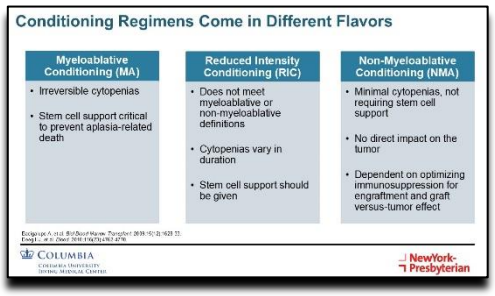


Slide 56: What if Doris was A 67 YO with a Cardiac Ejection Fraction of 40%?

So, what if Doris was not a woman in her 20s in perfect health but was a 67-year-old with some cardiac history and an ejection fraction of 40%? Would that still be the conditioning regimen that we would pick? So, let me pose this question to David, and he will take it from here.

Dr. Sabatino: Yes, that definitely makes things a bit more complex with this patient given that Doris is now an older age with a cardiac dysfunction. It makes us think on what type

of conditioning she may tolerate best. Before we pick a regimen for Doris, we'll go more into depth on the different types of conditioning regimens there are.



Slide 57: Conditioning Regimens Come in Different Flavors

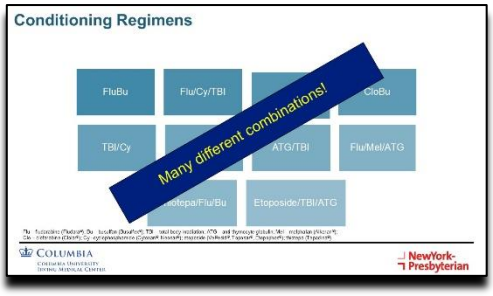
There are three categories of conditioning regimens: myeloablative conditioning, reduced intensity conditioning, and nonmyeloablative conditioning. The goal of providing patients with conditioning chemotherapy and/or radiotherapy serve multiple purposes, such as decreasing the tumor burden and to suppress the recipients' immune system to allow the new stem cells to engraft. By reducing the intensity of the conditioning, the main benefit of the transplant will come from graft-versus-tumor effect, rather than the cytoreductive properties of the chemotherapy, which we'll talk more about in an upcoming slide.

The term myeloablation refers to the administration of total body irradiation with or without alkylating agents at doses that would not allow for autologous hematologic recovery. These regimens would produce profound cytopenia within one to three weeks and would be irreversible if we did not restore the patient's hematopoiesis via a stem cell infusion. Transplant-related mortality increases with age in patients that get myeloablative chemotherapy regimens. As we mentioned earlier, 50 years old used to be the upper limit for these patients to receive a transplant. But now due to alterations of these regimens, it is possible to allow for older patients to tolerate and receive bone marrow transplants.

This is where nonmyeloablative regimens come in. They typically cause minimal cytopenias and toxicity but are immunosuppressive enough to facility stem cell engraftment. There's also this middle category of reduced intensity chemotherapy, which is a bit newer. These regimens don't meet the criteria for myeloablative but also do not meet the criteria for nonmyeloablative. They do cause prolonged cytopenias and are associated with substantial toxicity. Also, an in-between category of reduced intensity conditioning, which are regimens that do not meet the criteria of myeloablative conditioning but also do not meet the criteria for nonmyeloablative conditioning. They do cause prolonged cytopenias and are associated with substantial toxicity, but it may be possible for patients to recover their counts without stem cell support. So, now thinking to Doris, in her case, she is a bit older and the cardiac dysfunction, so we definitely want to avoid cyclophosphamide (Cytoxan®), which we saw has cardiac dysfunction as a dose-limiting toxicity.

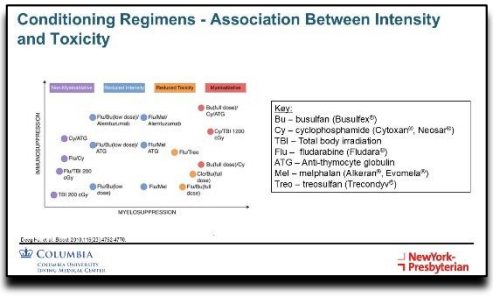
So, there's kind of two approaches here. The more aggressive approach would be do something such as a myeloablative conditioning regimen that doesn't include cyclophosphamide (Cytoxan®), such as busulfan (Busulfex®) and fludarabine (Fludara®) together. But if she, we thought that due to the older age and her performance status, she

cannot even tolerate a myeloablative regimen. Reduced intensity conditioning can also be an option for her as well, such as getting less doses of busulfan (Busulfex®) with fludarabine (Fludara®) to assure that she can tolerate it.



Slide 58: Conditioning Regimens

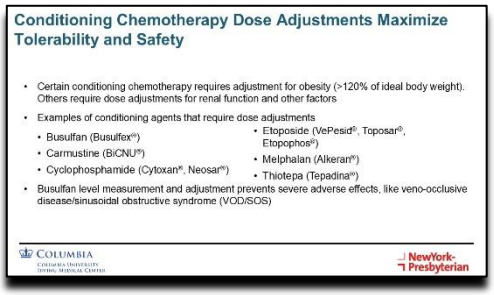
Here's an example of a handful of regimens that can be utilized from conditioning. We use many of the same agents in different combinations, depending on risk factors that we talked about and their underlying disease state, their donor status, and toxicities and comorbidities related to the patients.



Slide 59: Conditioning Regimens - Association Between Intensity and Toxicity

This graph on the left nicely depicts the association between intensity and immunosuppression. As intensity on the bottom X axis increases, we can expect that toxicity will also subsequently increase. However, as intensity of the conditioning regimen decreases, we can also expect that we need a higher requirement of graft-versus-tumor effect for the transplant to be successful in eradicating disease in the recipient.

So, this is just an outline of multiple different regimens that we kind of highlighted on the last slide and where they fall on the spectrum of myeloablation to nonmyeloablation and their effect on immunosuppression on somebody more immunosuppressive than others. And all these factors will be taken into consideration when selecting a regimen for different patients.

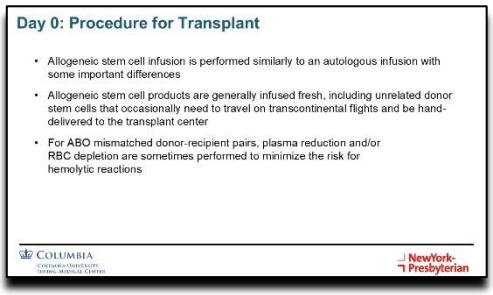


Slide 60: Conditioning Chemotherapy Dose Adjustments Maximize Tolerability and Safety

Certain conditioning regimens require dose adjustments to assure safety and tolerability. A handful of agents require dose adjustments based on obesity. The rule of thumb is that if a patient's weight is greater than 120% of their ideal body weight, the patient's dose should be adjusted to use adjusted body weight.

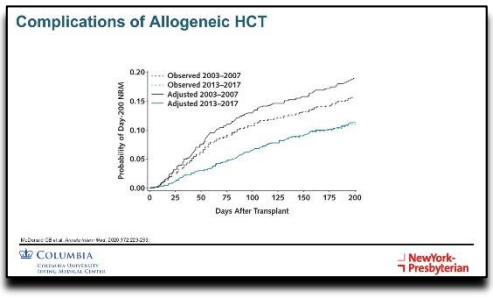
Many of the agents that require this dose adjustment for obesity are alkylating agents, which are listed on the slide here. Other factors such as renal or liver impairment may also impact dosing of some agents.

Lastly, in the case of busulfan (Busulfex®), dose adjustments are made based on pharmacokinetic analysis performed to target a certain area under the curve for conditioning. Typically, our target is about 5,000. This is done to assure the patient achieves adequate myeloablation effects but also to mitigate the risk of one of the main side effects, which is veno-occlusive disease, also known as sinusoidal obstruction syndrome.



Slide 61: Day 0: Procedure for Transplant

Similarly to autologous transplants, the day of cell infusion for allogeneic transplants is also called day 0. Some differences include that allogeneic transplants are typically infused fresh. Sometimes this is challenging if the patient has an unrelated donor as a product sometimes needs to travel on transcontinental flights and be hand-delivered to the transplant center before infusion. Also, patients may have ABO mismatched donors. Plasma reduction or red blood cell depletion sometimes needs to be performed prior to this cell infusion to minimize the risk of patient developing hemolytic reactions.

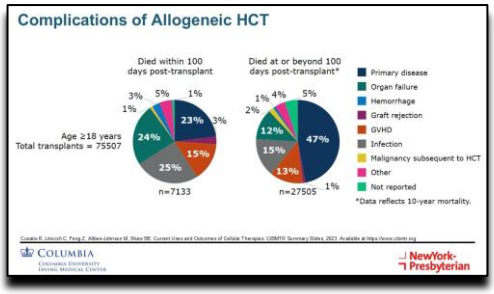


Slide 62: Complications of Allogeneic HCT

I will now give it back to Dr. Reshef to talk more in detail about some of the complications associated with allogeneic stem cell transplants.

Dr. Reshef: Thank you, David. We spend a lot of time with our patients preparing them to be educated and aware of complications of both autologous and allogeneic transplants. There's certainly a very long list of complication, and it's longer for allogeneic transplants compared to autologous, who we're going to focus on that. With that said, the probability of significant morbidity or mortality due to complications has dramatically been reduced over time. A procedure that used to be lethal to 25% or 30% of the patients by six months post-transplant in the 1990s is now, by far, safer. And this plot generated by George McDonald, based on the experience at the Fred Hutchinson Cancer Center in Seattle, illustrates that very nicely. You can see that the rates of mortality in the first 200 days, nonrelapse mortality, meaning related to the treatment and unrelated to disease relapse have dramatically gone down when you compare a previous era of 2003 to 2007 to a more contemporary era of 2013 through 2017.

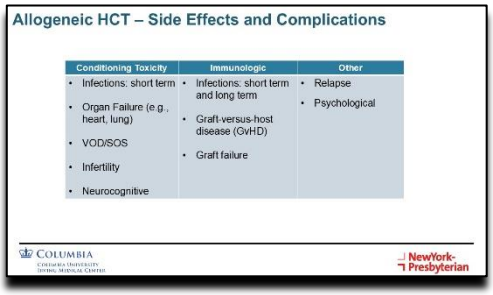
And, in fact, what you can see here, because we're treating today much sicker and older individuals with different donor sources, different graft sources, if you were to match and adjust these plots to account for these confounders, you will see that the gap is even much bigger; and we have cut down the mortality very significantly by close to 40%.



Slide 63: Complications of Allogeneic HCT

So, what are the causes of severe and lethal complications after allogeneic transplant? You can see that the causes are quite different when we compare the first 100 days and before, and beyond the first 100 days. In the first 100 days, we have a mix of damage from the conditioning regimens, some degree of potential for severe graft-versus-host disease, high risk of infections, and some risk of recurrence of the primary disease, especially in diseases that are very high risk or patients who were transplanted with completely refractory cancer.

Beyond the first 100 days, we see quite a different map. Most of the treatment-related complications are much less of a contributor to death; and the major contributor is, in fact, disease relapse. And that is one area where there's a tremendous amount of focus right now on how to simply reduce the chances of relapse after transplant and eliminate that as a cause of significant mortality. You could see that graft-versus-host disease technically in these pie charts take no more than 13% or 15% of the direct causes of death. That's a bit of an underestimate because graft-versus-host disease frequently drives some of the other causes that we see here such as infection and organ dysfunction.



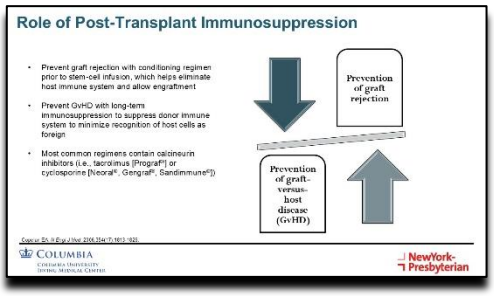
Slide 64: Allogeneic HCT – Side Effects and Complications

So, some of the complications can be attributed simply to the high-dose conditioning therapy that we use. Pancytopenia as a result of high-dose conditioning can cause infections in the short term, which we work very hard to prevent using prophylactic agents, as David has already described. You can get with some conditioning regimens acute or even more longstanding organ failure in the lung or the heart, which is really why we spend such a tremendous amount of time in evaluating the patients' baseline organ function in picking the right conditioning regimen for each individual patient.

Some of the immunologic side effects are also very important, and they also include infections on the short term and long term, mostly because patients after transplant would remain on immune suppressive therapy, and those would increase the risk of infections for as long as the patients are on them. And then there is a period of immune reconstitution until patients rebuild a fully intact immune system and will remain at risk for infections throughout that period.

Graft-versus-host disease is by far the most important immunologic complications. We did mention disease relapse. Psychological and cognitive effects, which we've seen in studies

dramatically improve after the first year post-transplant; but certainly require help and assistance to get patients to go through that tough, tough period of time. And we did mention already when discussing the conditioning agents, the risk of VOD or SOS, the risk of infertility. We universally use either alkylating agents or radiation, so there is a significant risk of either transient or more likely permanent infertility and some likelihood of neurocognitive dysfunction, especially with the use of radiation that includes CNS radiation with it.

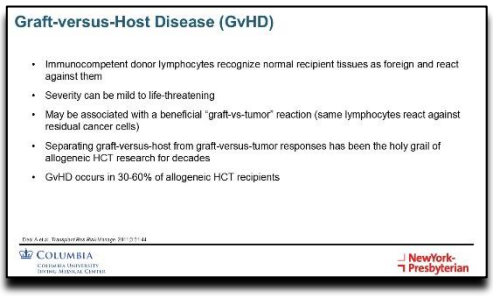


Slide 65: Role of Post-Transplant Immunosuppression

So, let's talk a little bit about the role of post-transplant immune suppression because, similar to solid organ transplants, almost all patients undergoing an allogeneic transplant will be discharged home from their transplant with a regimen that suppresses their immune system. The immune suppression is a major driver of some of the complications I just mentioned, but it is important, and it has a dual role. One role is to suppress the immune system of the recipient to make sure that it does not reject the infused stem cells.

But that is a very short-term purpose. The other goal, which may be a little bit more important in the long run, is to moderate the proliferation and activation of the donor T-cells and maybe even eliminate some of the donor T-cell clones that are capable of causing graft-versus-host disease. That would minimize the recognition of healthy host tissues and prevent this dreadful and sometimes life-threatening complication called graft-versus-host disease, which in the absence of adequate immune suppression, would likely be universal to all transplant recipients and can very well be lethal.

Most of the common regimens we use for post-transplant immune suppression are built on calcineurin inhibitors – tacrolimus (Prograf®) or cyclosporine (Neoral®), very similar to what is used in the solid organ transplant world, but we have a much greater variety of immune suppressants that are now well-established and some of them even approved by the FDA; and we will review those.

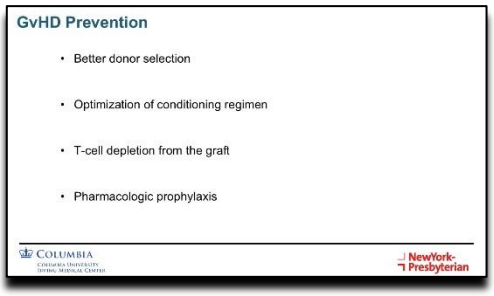


Slide 66: Graft-versus-Host Disease (GvHD)

So, what is graft-versus-host disease clinically? We've already mentioned this terminology multiple times. It is based on the immunologic principle that the immune-competent donor lymphocytes can recognize not just tumor cells but also normal healthy recipient tissues as foreign and react against them very violently. This could be extremely mild, such as a faint skin rash that can be even completely

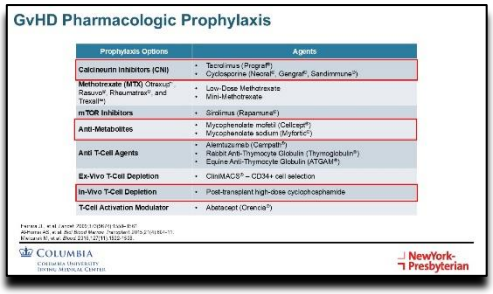
asymptomatic and unnoticed by the patient, or it can be life-threatening leading to profound levels of GI symptoms and high-volume diarrhea, liver failure, and complications that was resolved from that, as it results from translocation of bacteria, disruption of the gut barrier integrity, and various other complications, and malnutrition, of course.

I've already mentioned that there is a close association between the graft-versus-host disease and the graft-versus-tumor reactions. It is basically the same lymphocytes from the donor that may react against healthy tissue and residual cancer cells. And the holy grail of allogeneic transplant research for many, many investigators, including myself, has been how to separate effectively the graft-versus-host response from the graft-versus-tumor response. GvHD is extremely common. Thankfully, in the majority of patients nowadays it is manageable and can be controlled and does not lead to significant morbidity or mortality, but still in some case it does and can lead to those more severe complications.



Slide 67: GvHD Prevention

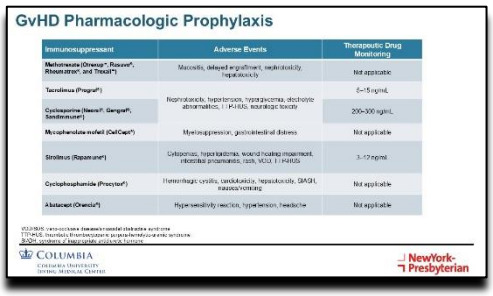
So, GvHD can either be treated when it happens but much more effectively can be prevented before it happens. There's a lot of emphasis on that prevention because we think it is a much more effective strategy. It starts with better donor selection; and as I highlighted earlier, young donors, better matched donors, and some other parameters that we look at may improve and reduce the risk of graft-versus-host disease. This is a major driver for the development of high-resolution HLA testing and was a major driver historically for why HLA typing was the number one criterion for donor selection. We can also optimize conditioning regimens to make sure that there isn't too much toxicity involved that may trigger graft-versus-host disease just by throwing a lot of damage into healthy tissue. And there are also methods that involve the depletion of T-cells from the graft. And while you lose some of the graft-versus-tumor response in certain diseases and certain situation, it can certainly help overcome the barrier of graft-versus-host disease. And we're going to talk about a pharmacologic method of depleting certain types of T-cells and maybe not all of them, and that is through the use of post-transplant cyclophosphamide (Cytoxan®). And that is one of the methods of pharmacologic prophylaxis that I'm going to have, ask David to talk about in greater detail.



Slide 68: GvHD Pharmacologic Prophylaxis

Dr. Sabatino: Thanks, Dr. Reshef. There are a handful of different graft-versus-host disease prophylaxis regimens, which can vary depending on conditioning regimens and some institutional preferences.

Based on newer data, which we will discuss in a few slides, the majority of patients will receive a regimen called post-transplant cyclophosphamide (Cytoxan®). This regimen typically contains a calcineurin inhibitor, usually tacrolimus (Prograf®), an antimetabolite mycophenolate (CellCept®), and two doses of cyclophosphamide (Cytoxan®) to achieve in vivo T-cell depletion. Other regimens and medications that have been used in the past include methotrexate (Trexall™) and tacrolimus (Prograf®), which was long considered the standard of care for many transplants. Other additional considerations to use sirolimus-based regimens; and like Dr. Reshef mentioned, T-cell depletion methods with alemtuzumab (Campath®) or antithymocyte globulin (Thymoglobulin®).



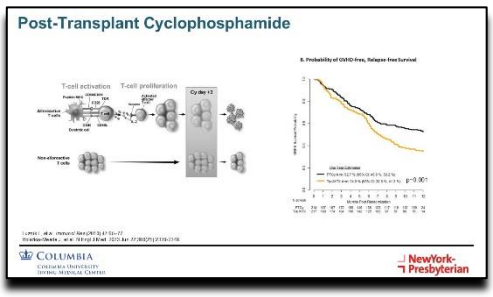
Slide 69: GvHD Pharmacologic Prophylaxis

This slide highlights the main side effects and relevant therapeutic drug monitoring of agents we discussed on the prior slide. As you can see here, the adverse events vary, depending on the agents used. For methotrexate (Trexall™), the most common adverse effect is mucositis and delayed engraftment. There's no therapeutic drug monitoring available for this agent.

For tacrolimus (Prograf®) and cyclosporine (Neoral®), these both fall into the category of calcineurin inhibitors. These agents have a lot of toxicities associated with them, and we need careful monitoring. Some of these include nephrotoxicity, hypertension, hyperglycemia, electrolyte abnormalities, a risk of developing TMA, and even neurologic toxicity. Both of these, it's very important to counsel the patients on the timing of these medications, as we need to measure the amount of medication in their blood at a given time to make sure these patients are not too high, in which they can get side effects from or too low, which may increase their risk of graft-versus-host disease. Other agents include mycophenolate (CellCept®), which we primarily watch out for myelosuppression in gastrointestinal distress such as diarrhea. Sirolimus is an alternative to calcineurin inhibitors for patients that cannot tolerate them. Some side effects we see here are cytopenias, hyperlipidemia, impaired wound healing, interstitial pneumonitis, and some risk of VOD as well. Again, similarly to the calcineurin inhibitors, therapeutic drug monitoring is warranted; and we need to counsel our patients on the timing of these medications as well.

Next is cyclophosphamide (Cytoxan®), which we'll talk more about the mechanism on the next slide; but given that we're going to be giving high doses of cyclophosphamide (Cytoxan®) in the post-transplant cyclophosphamide (Cytoxan®) regimen, patients are at risk of developing hemorrhagic cystitis, are at risk for cardiotoxicity, hepatotoxicity, and even some SIADH.

And, lastly, a newer agent called abatacept (Orencia®) is overall well-tolerated where side effects really just range from hypersensitivity reactions, which are relatively rare, hypertension and headache.

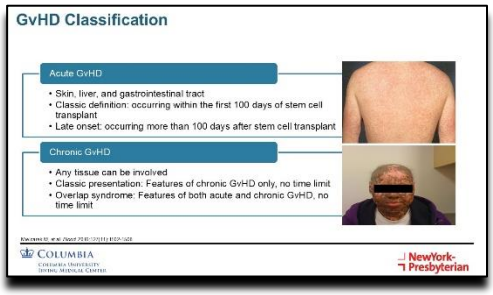


Slide 70: Post-Transplant Cyclophosphamide (Cytoxan®)

As we alluded to in this presentation in the past, post-transplant cyclophosphamide (Cytoxan®), also known as PTCy, has been used in bone marrow transplantation for over a decade. But it was primarily used in the haploidentical transplant setting to overcome HLA mismatch. The mechanism that PTCy is believed to work is described on the graphic on the left. After stem cell infusion, alloreactive T-cells are activated as early as days 1 and 2, which allow for an intentionally timed doses of cyclophosphamide (Cytoxan®) on days 3 and 4 to be able to kill off these rapidly dividing T-cells which are thought to be the driver of graft-versus-host disease.

And as we can see on the bottom of this graphic, they're able to spare the non-, alloreactive T-cells which may be protective of graft-versus-host disease and have an effect for graft-versus-tumor effect and do not limit our ability for patients to have decreases in relapse. In 2023, BMT 1703 was published. This paper evaluated PTCy in matched, reduced-intensity transplants, compared to the old standard of care, methotrexate (Trexall™) and tacrolimus (Prograf®). Figure B on the right-hand side highlights the primary outcome which we see a significant decrease in the probability of GvHD-free, relapse-free survival in patients who receive post-transplant cyclophosphamide (Cytoxan®) compared to the old standard of care methotrexate (Trexall™)/tacrolimus (Prograf®).

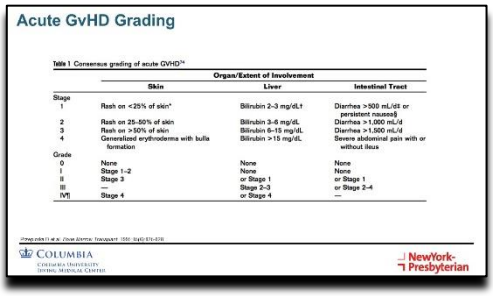
This was a landmark publication. It ultimately changed the standard of care for the majority of allogeneic transplants and the GvHD prophylaxis regimens associated with them.



Slide 71: GvHD Classification

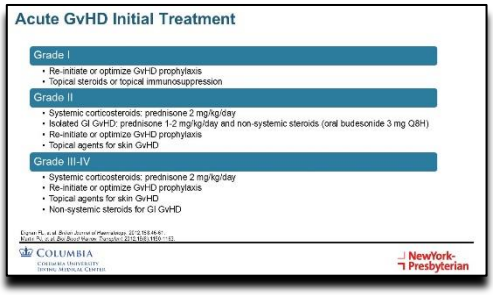
Since the widespread use of PTCy, the rates of GvHD have significantly decreased. However, we still see cases from time to time. GvHD is broken down into two general buckets, acute and chronic GvHD. Acute primarily, primarily affects the skin, liver, and GI tract, and most commonly occurs within the first 100 days post-transplant. However, there are cases that can develop after the day 100 mark.

Chronic GvHD can affect any organ in the body and can present at any time after transplant. There is also an overlap syndrome in which both features of acute and chronic GvHD may develop at the same time, in which treatment may have to be guided to treat both of these at once.



Slide 72: Acute GvHD Grading

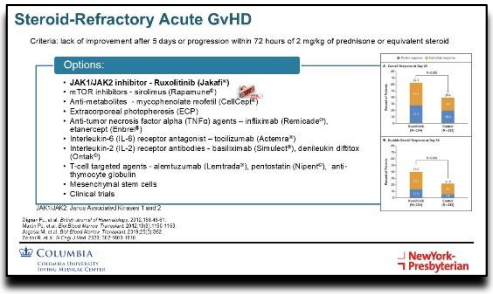
Grading acute GvHD can be complex as it requires staging of each organ to get a grade. For skin, the hallmark sign is rash; and the stage will be dependent on the percent of total body that the rash is seen on. The liver is staged based upon the patient's bilirubin, and GI is assessed by the amount of diarrhea output or, in some cases, abdominal pain with or without ileus. Once all organs have been staged, you can get your final grade of acute GvHD to help guide your management and dosing of steroids.



Slide 73: Acute GvHD Initial Treatment

When it comes to treating acute GvHD, across the board we reinitiate or optimize existing immunosuppression if the patient remains on immunosuppression. This could be increasing tacrolimus (Prograf®), through level monitoring, or reinitiating it if the patient has recently tapered off their calcineurin inhibitor. Grade I acute GvHD can usually be managed initially with topical steroids or non-absorbed steroids such as budesonide (Pulmicort®) if the patient only has gastrointestinal GvHD.

Grade II acute GvHD is when you start to consider more systemic steroids. The usual starting dose of steroids is prednisone (Deltasone®), 2 mgs/kg per day, and typically this is split into two doses. For higher grades of GvHD, we often sometimes consider additional nonsteroid agents, which we'll discuss more, so on the next slide.

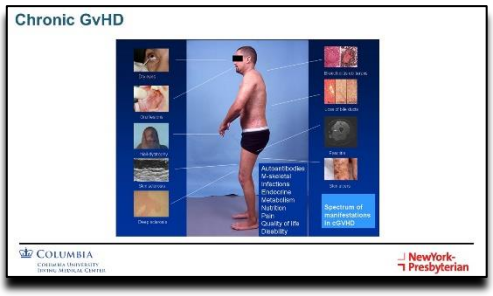


Slide 74: Steroid-Refractory Acute GvHD

In patients who do not respond promptly or have symptoms of progression while on systemic steroids are deemed to have steroid-refractory GvHD. Although there are numerous agents listed on this slide, the efficacy and response rates to these agents have been quite variable in the literature.

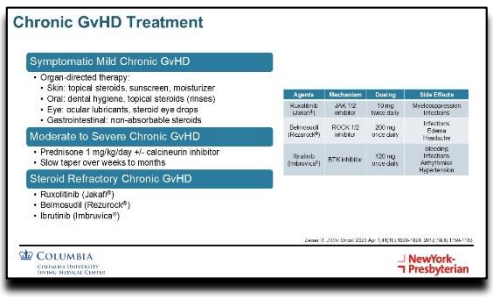
The JAK1 and 2 inhibitor, ruxolitinib, also known as Jakafi®, is the only approved agent for steroid-refractory acute GvHD. The data that led to the FDA approval of this study from Zeiser and colleagues demonstrate a 62.3% overall response rate compared to 39.4% in the control arm. Due to this data, ruxolitinib (Jakafi®) is often the first agent we'll initiate in patients that develop steroid-refractory GvHD in patients.

The data from this study is highlighted on the graphic on the right here.



Slide 75: Chronic GvHD

To take a closer look at what chronic GvHD looks like, we can see that it can affect any organ and essentially have features of autoimmune disease where the skin may become more fibrotic; and there are often sclerotic changes in the skin, liver, eyes, GI tract, and possibly even more. Patients that develop these features often have impaired quality of life due to their symptoms, but also the medications that are required to treat these symptoms.

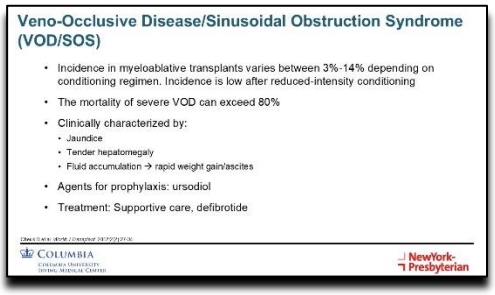


Slide 76: Chronic GvHD Treatment

The treatment of chronic graft-versus-host disease is very dependent on which organs are involved. In many mild cases, management revolves around supportive care, such as topical steroids for skin GvHD, dental hygiene and rinses for oral GvHD, eye drops for eye GvHD, and nonabsorbable steroids for GI GvHD such as budesonide (Pulmicort®).

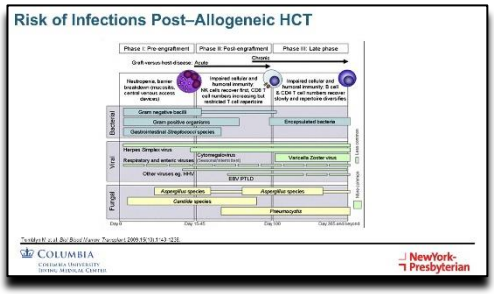
For moderate-to-severe chronic graft-versus-host disease, prednisone (Deltasone®) is typically started at 1 mg/kg per day, with or without reinitiation or optimization of their current immunosuppression. Usually, a slow steroid taper is then performed over weeks to months to make sure the patient isn't progressing and also able to tolerate doses of steroids from their side effect profile.

For patients that develop worsening chronic graft-versus-host disease, despite being on steroids, are once again deemed to have steroid-refractory disease. There are three FDA-approved agents which are listed on, on the table to the right, which include ruxolitinib (Jakafi®), belumosudil (Rezurock®), and ibrutinib (Imbruvica®). Each of them have unique side effects that are listed on the table, mainly being for ruxolitinib (Jakafi®), myelosuppression and increased risk of infection. For belumosudil (Rezurock®), it nicely does not have any myelosuppression. Could be a useful agent in patients with prolonged cytopenias, but they do develop increased risk of infection and headache. And lastly, ibrutinib (Imbruvica®), which is not commonly used for chronic GvHD, has many more side effects such as bleeding, infections, arrhythmias, and hypertension.



Slide 77: Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome (VOD/SOS)

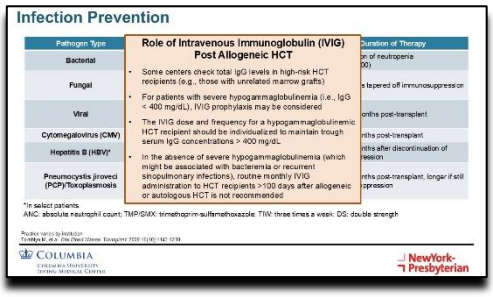
The next complication we will discuss is veno-occlusive disease or sinusoidal obstruction syndrome. In myeloablative transplants, the incidence has been reported anywhere from 3% to 14%, depending on the regimen used and the agents included in that regimen. Although rare, the mortality associated with patients that develop VOD is over 80%. Clinical features include jaundice, tender hepatomegaly, fluid accumulation leading to rapid weight gain. The only known effective prophylaxis strategy for these patients is ursodiol (Actigall®), in which we typically start ursodiol (Actigall®) on admission for their transplant and continue it through day 100. And we can usually see if we discontinue this agent if the patient has normal liver function at that time. Treatment is mainly, revolves around supportive care; and there is an agent called defibrotide (Defitelio®) that can be used only in confirmed cases of VOD.



Slide 78: Risk of Infections Post–Allogeneic HCT

Due to prolonged pancytopenias and immunosuppressive medications, patients are at high risk for various infectious at different time points after an allogeneic transplant. The duration of initial neutropenia will often play a role in their initial infectious risk. This can depend on the source of the graft and the conditioning or GvHD regimens utilized in these patients. There are generally three phases of opportunistic infections that are categorized on this slide. Each phase is dependent on the recovery of the immune system. The first is the pre-engraftment phase. So, this is typically days 15 to 45 where the patients have profound neutropenia and are at risk for a multitude of infections in the hospital. Phase II has to do with the post-engraftment phase, which typically takes place on days 30 to 100. And then the late phase is Phase III which typically happens after day 100. Other factors can play a role in infectious risk such as the

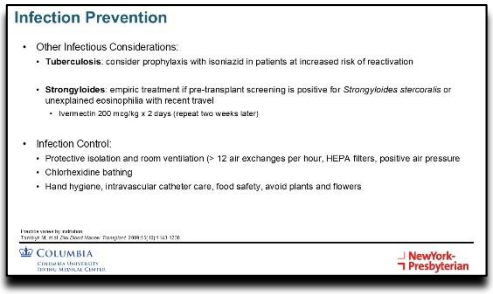
presence of graft-versus-host disease and poor graft function which may lead to prolonged cytopenias.



Slide 79: Infection Prevention

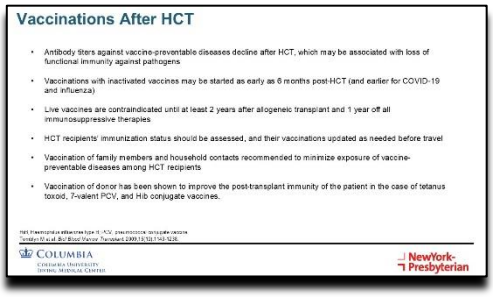
Although similar to infection prophylaxis for the autologous transplants we already discussed, there are some differences worth highlighting. These patients require longer antifungal coverage, specifically mold coverage due to the duration of immunosuppression. These patients will usually remain on antimold prophylaxis until they're off immunosuppression as their calcineurin inhibitor needs to be discontinued to safely discontinue antimold coverage. These patients are also prone to CMV reactivation, specifically the highest risk in seropositive recipients that require the term of your prophylaxis.

Lastly, there is evidence to suggest that patients with persistently low IgG levels, which we consider less than 400, and chronic or recurrent infections benefit from the use of IVIg to maintain their IgG levels above 400 after day 100 of transplant to prevent the development of recurrent infections in this patient population.



Slide 80: Infection Prevention

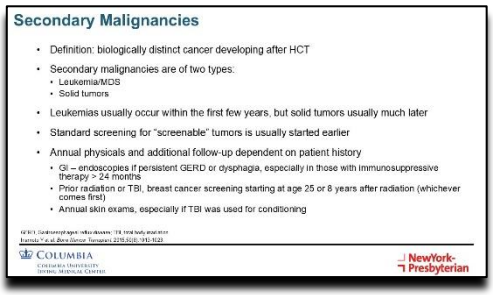
This slide may look very similar to the slide that we talked about earlier, and I just, included it here for completeness sake. But these infection prevention strategies should also be utilized in our allogeneic transplant patients as well.



Slide 81: Vaccinations After HCT

Lastly, post-transplant patients often lose their prior immunity to routine vaccines that they may have received as a child. As early as six months after transplant, patients may begin to receive inactivated vaccines such as flu vaccine and COVID-19. Live vaccines pose a risk to immunocompromised patients and should be avoided for at least two years after transplant. And to assure that patients do not have a reaction to the live vaccine, they should also be off immunosuppression for at least one year.

If these patients are planning on traveling, they should have their vaccines reviewed with their transplant team to make sure they are up to date and they can safely travel to different areas of the world. It is also recommended to vaccinate household contacts to further decrease the risk of exposure to vaccine-preventable diseases.



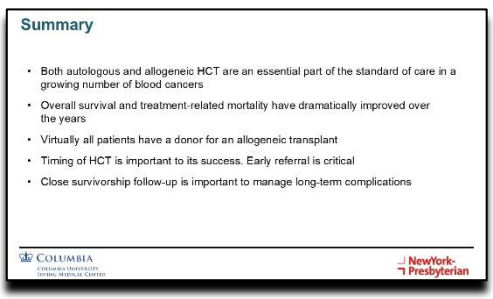
Slide 82: Secondary Malignancies

And lastly, I'll hand it back to Dr. Reshef to discuss the risk of secondary malignancies post-allogeneic transplant.

Dr. Reshef: Thank you, David, and, and thank you for this wonderful overview. So, this is the last complication we're going to talk about, but that doesn't mean that it's not important. This is certainly worth mentioning, and the issue of second primary malignancies is, is central to oncology in general because we frequently use chemotherapy agents that can dispose patients to secondary malignancies.

So, screening for secondary malignancies is important in oncology in general, not just after transplant. However, the exposure to high-dose conditioning, and in particular total body irradiation, certainly increases the risk for second malignancies. Those can be of two flavors. We see occasionally leukemia or myelodysplastic syndrome, which can generally occur within the first few years. And we see a higher incidence of solid tumors as well, without particularly noting one versus another as being particularly common. But screening and paying attention to early symptoms and adhering to screening procedures based on the general recommendations is extremely important.

So, we apply standard screening for those tumors that are screenable, but in general we would start them earlier, and we would have a lower threshold for sending a patient for an imaging study or removing skin lesion or performing endoscopies for patients with any type of symptoms related to those organs or any type of imaging finding.
Breast cancer screening should probably start earlier in patients who've had exposure to total body irradiation, and we put a lot of emphasis on gynecologic exams annually and skin exams annually, especially if radiation was used.



Slide 83: Summary

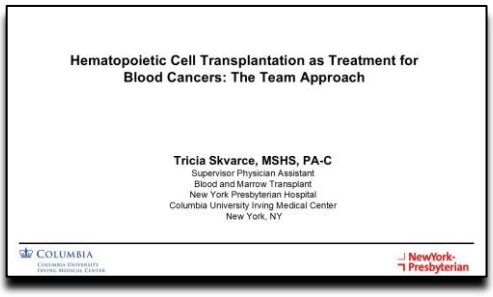
So, in summary, I hope we met the objectives of this webinar. We've talked about autologous and allogeneic transplants, which are both now standard-of-care approaches and an essential part of the treatment paradigm for a growing number of blood cancers. We have seen dramatic improvement in treatment-related mortality and overall survival. We've shown you quite a bit of that data. We also know that nowadays virtually all patients have a

donor for an allogeneic transplant. The days of struggling to find a donor are pretty much over since we've learned how to cross HLA barriers, thanks to the regimen of post-transplant cyclophosphamide (Cytoxan®) that David spoke about.

So, we have these advances, and I'm also including the availability of cord blood for those patients who are really in a, in a crunch to find a donor. We can safely engraft nearly every patient that is referred to our care. I could not have emphasized more the importance of timing of referral for transplant. The early referral is critical, because as David and I have shown you, there is significant amount of pretransplant workup; and the donor identification optimizing the donor selection may take time.

That is critical and sometimes challenging to coordinate, especially in patients who are still undergoing treatment for their underlying disease. So, getting a patient acquainted with a transplant program early in the course of their disease and getting their HLA typing and their family information is always a favorable thing. You cannot do that too early. There are various survivorship issues that we've discussed, and that includes secondary malignancies, long-term risks for infections, and chronic graft- versus-host disease that we've touched upon. I very much hope that this was informative and helpful for everyone who's within the field or is interested in the field, and I want to thank again The Leukemia & Lymphoma Society for giving us this opportunity.

Lauren Berger: Thank you Dr. Reshef and Dr. Sabatino, for your very clear & informative presentations.



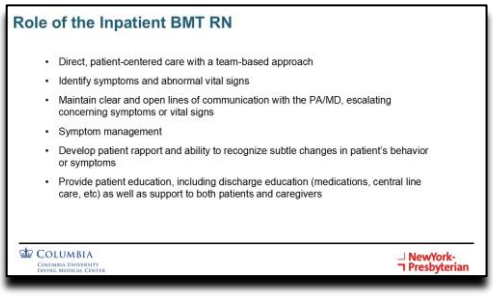
Slide 84: Hematopoietic Cell Transplantation as Treatment for Blood Cancers: The Team Approach

Lauren Berger: I am now pleased to introduce PA Tricia Skvarce and Social Worker Muyun Zhao. PA Skvarce is Supervisor Physician Assistant, Blood and Marrow Transplant, at New York Presbyterian/Columbia University Irving Medical Center in New York City. Ms. Zhao is a social worker, Outpatient Hematology/Oncology & BMT Program at New York Presbyterian Hospital, Columbia University Irving Medical Center, in New York City.

Tricia Skvarce, MSHS, PA-C: The topics for this portion of the presentation are to highlight and describe the roles that the registered nurses and PAs play in the inpatient management of hematopoietic stem cell transplant recipients. In general, teamwide collaboration between each member of the multidisciplinary team is key to sustaining good outcomes in the management of these complex bone marrow transplant patients.

During this presentation, I would like to highlight the importance of a team-based approach and maintaining open lines of communication, recognizing important lab trends and

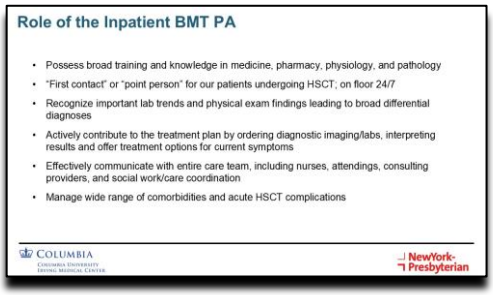
physical exam findings, and their associated differential diagnoses. We will also briefly discuss management of some common stem cell transplant-specific complications, as well as discuss two patient cases



Slide 85: Role of the Inpatient BMT RN

Our BMT nurses provide direct patient-centered care to all of our stem cell transplant recipients. The BMT RN can identify symptoms and abnormal vital signs and efficiently communicate these concerning findings to the PA or doctor. Since our stem cell transplant recipients are admitted over a long period of time, our nurses build rapport with each of our patients and are able to identify subtle changes in behavior or symptoms.

In addition, our nurses provide symptomatic management, education and support, and are skilled in managing acute complications of stem cell transplantation, alongside the PAs. We rely heavily on our nurses to recognize subtle changes and act in a timely manner, communicating their concerns.



Slide 86: Role of the Inpatient BMT PA

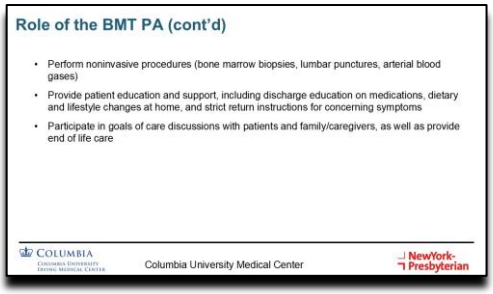
Physician assistants possess training in general medicine and have in-depth knowledge of pharmacy, physiology, and pathology.

Given the complexity of stem cell transplantation and its affect on all organ systems, bone marrow transplant PAs are expected to function at a high level of autonomy and be able to manage high acuity patients by quickly escalating any concerns to the attending and make time-sensitive interventions.

At our institution, the physician assistants are assigned as the first contact or the point person for our patients undergoing hematopoietic stem cell transplantation. We are staffed 24 hours a day, 7 days a week so that we can provide time-sensitive interventions for acute complications. We are skilled at identifying key lab trends or physical exam findings and correlating those findings with the patients' timeline during transplant to determine the appropriate differential diagnosis. We actively corroborate with our attendings to determine the appropriate treatment plan for each patient; and we communicate these plans officially with the patient, caregivers, nursing staff, and consulting services

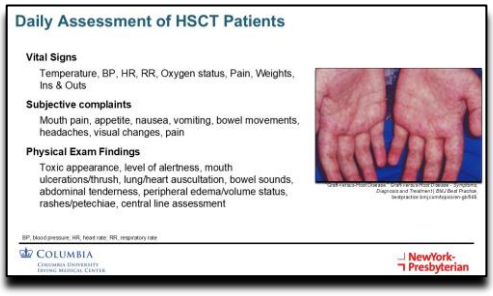
In addition, stem cell transplant recipients are often medically complicated with existing comorbidities such as heart failure, hypertension, cardiac disease, chronic kidney disease,

or prior infectious histories, though we also manage simultaneously with the complications of stem cell transplant.



Slide 87: Role of the BMT PA (cont'd)

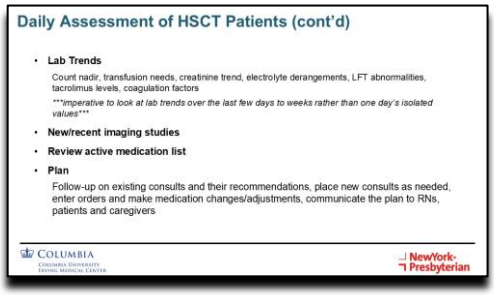
PAs also participate in some noninvasive bedside procedures such as bone marrow biopsies, lumbar punctures, arterial blood gases, and nasogastric tube insertions. We also provide medication and discharge education and support to each patient and their caregivers. In addition, the PAs are often involved in goals of care conversations in conjunction with attendings, palliative care services, and social workers.



Slide 88: Daily Assessment of HSCT Patients

Now let's talk more about the role of the nurse and the PA in the day-to-day assessment of our transplant patients. The daily assessments done by nurses and PAs include routine vital sign checks every four hours, which consists of temperature, blood pressure, heart rate, respiratory rate, oxygen status, pain level, as well as daily weights, and strict input and output measured throughout each 12-hour shift.

Both the nurse and the PA pay close attention to the subjective complaints of each patient. We perform a thorough physical exam to assess whether the patient appears toxic, their level of alertness. If there are any mouth sores, we perform lung and cardiac auscultation. We perform an abdominal exam to assess for distention or tenderness. We listen to bowel sounds, and we assess for any peripheral edema, rashes, and we take note of the central line to make sure that there's no erythema or tenderness.

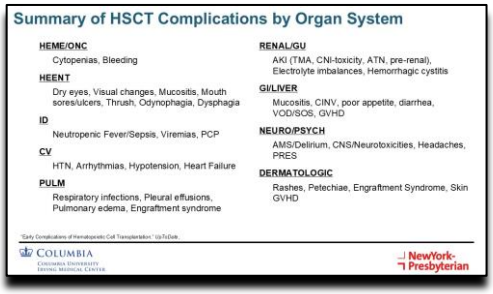


Slide 89: Daily Assessment of HSCT Patients (cont'd)

The PA then closely reviews recent lab work, paying close attention to lab trends over the last few to several days, rather than one day's isolated values. The PA also reviews recent imaging tests, current medication lists, taking note of any changes to their patients' creatinine clearance that may require any dose adjustments of medications. After this review, the PA then comes up with their preliminary plan that is then discussed with the attending

physician and the pharmacist, during rounds. In addition, the PA ensures that all medications that are ordered and accounted for that are discussed during those rounds.

For example, at our institution, pain medications and other controlled substances have an expiration date after three days. So we ensure that medication orders are not expired, or do not fall off and are reordered within that time frame. The PA is also responsible for placing orders and consults, communicating plans to the nurses and patients as well as updating caregivers of the current plan.



Slide 90: Summary of HSCT Complications by Organ System

This slide highlights the common stem cell transplant complications of each organ system. This is not a full list of complications but a highlight of some common side effects that we see as inpatient providers through our patient's transplant course.

These complications can occur pre-engraftment and early post-engraftment. So, aligning these complications with where the patient is during their transplant timeline is imperative to establishing a differential diagnosis. Again, this is where a strong foundation in medicine comes in handy as transplant affects all organ systems and may affect coexisting comorbidities.

We see pancytopenia in every single transplant patient, which is typically directly related to the conditioning chemotherapy they've received prior to transplant. The degree and length of cytopenias can vary by many factors, such as bone marrow reserves, preparative regimens, and type of stem cell source used. In addition, pancytopenia can also be caused by infections, graft-versus-host disease, and medications.

Cytopenias can also lead to bleeding, so we closely monitor for any signs or symptoms of bleeding and routinely give all of our patient blood products in the form of either packed red blood cells or platelets. Those patients usually require transfusions up until the transplanted marrow cells and graft.
Conditioning chemotherapy can also affect mucosal layers, so we typically see dry eyes, various grades of mucositis, mouth sores, ulcerations, thrush, painful swallowing, and difficulty swallowing.

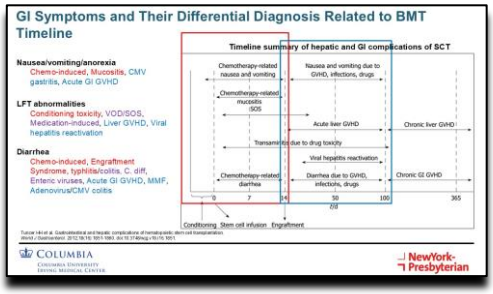
Neutropenic fever is one of the most common and serious complications of stem cell transplants, and we will discuss this further in the presentation. We also see various viremias and even PCP in these patients. We rarely ever see cardiac abnormalities such as hyper- and hypotension, arrhythmias, and heart failure exacerbations. We also see respiratory complications such as dyspnea, which could be attributed to volume overload

or pleural effusions, infections like pneumonia, pulmonary edema, or engraftment syndrome.

We see a lot of acute kidney injury during transplant with many possible causes: calcineurin inhibitor toxicity, acute tubular necrosis, dehydration secondary to poor oral intake, or large volume diarrhea or vomiting.

Given poor oral intake or GI losses, we often see electrolyte abnormalities as well. Hemorrhagic cystitis is also a common side effect of post-transplant Cytoxan® (cyclophosphamide) which we have been utilizing more frequently for graft-versus-host disease prophylaxis. In addition, hemorrhagic cystitis could be due to UTIs and virurias. During a patient's transplant course, we also see neurological or psychological complications such as altered mental status. Altered mental status is a complication that has many broad etiologies but during transplant could be due to infections, hospital delirium, elevated tacrolimus (Prograf®) levels or PRES, which is posterior reversible encephalopathy syndrome, which is a serious post-transplant complication that must be on everyone's differential diagnosis in the setting of altered mental status, headaches, and visual changes in a patient who is also on immunosuppression such as a calcineurin inhibitor.

We also routinely see skin changes during transplant such as rashes and petechiae, which could be related to chemotherapy, antibiotics, or other medications; but it could also be due to engraftment or even skin graft-versus-host disease.



Slide 91: GI Symptoms and Their Differential Diagnosis Related to BMT Timeline

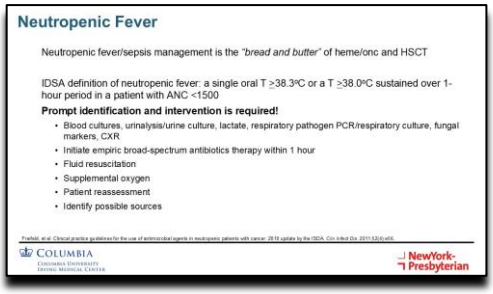
Recognizing these symptoms and aligning with the current timeline of the patient during their transplant helped guide the differential diagnosis. In red, we have symptoms that are typically seen pre-engraftment. In blue are symptoms that we see after engraftment. And in purple are symptoms that we see both before and after engraftment.

For example, developing nausea and vomiting, either prior to the stem cell infusion or in the days shortly after the stem cell infusion, is more likely to be related to the chemo conditioning that you received prior to transplant. However, nausea and vomiting, starting around the time of engraftment, may reflect acute upper GI graft-versus-host disease.

Another example is weight gain, right upper quadrant pain, jaundice, and liver function test abnormalities within one to two weeks of conditioning could be a side effect of the conditioning regimen or other drug-induced liver injury, perhaps from an antifungal agent that the patient is currently receiving as infection prophylaxis.

However, these same symptoms, one to three weeks after conditioning, could be indicative of VOD, which is veno-occlusive disease, or otherwise known as SOS, sinusoidal obstruction syndrome, a rare, but serious, potential fatal complication of transplant. After engraftment, any liver function test abnormality would be suspicious for liver graft-versus-host disease or a viral hepatitis reactivation.

Diarrhea pre-engraftment could also be due to the conditioning regimen, engraftment syndrome, or infection such as typhlitis or colitis. However, surrounding engraftment time frame, diarrhea could be due to infections such as bacterial or viral infections, colitis, acute graft-versus-host disease of the GI tract, or CellCept toxicity.



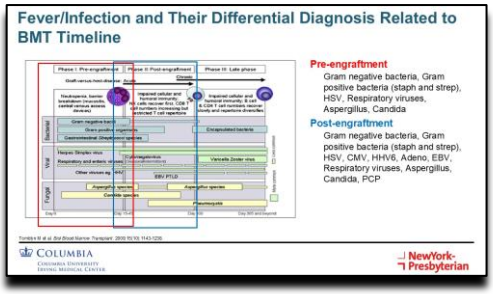
Slide 92: Neutropenic Fever

Neutropenic fever or infection is one of the most common complications seen in the first 100 days after transplant, and it is something we are very familiar and comfortable with managing as we see it quite often.

The Infectious Disease Society of America defines neutropenic fever as a single temperature greater than or equal to 38.3˚C or a temperature greater than or equal to 38˚C sustained over one hour with a neutrophil count of less than 1,500. Neutropenic fever requires prompt identification and intervention to decrease the incidence of mortality. Initial management of neutropenic fever includes blood cultures from central lines and peripherally, urinalysis and urine culture, lactate, respiratory pathogen PCR, or a respiratory culture if possible, fungal markers, a chest x-ray, and a rapid initiation of broad spectrum antibiotics within 60 minutes. Most of the neutrophil patients are already on prophylactic antibiotics prior to developing neutropenic fever, so sometimes our infectious workup will remain negative. However, we still escalate to broad-spectrum antibiotics in these patients given the new onset of fever.

If sepsis is suspected, we also initiate IV fluid resuscitation and supplemental oxygen when indicated. It is in these cases that knowing your patients well and how they routinely look and behave comes in handy as even the slightest bit of lethargy or changing altered mental status or alertness may tip us off that there is an infection brewing before there are any concrete signs.

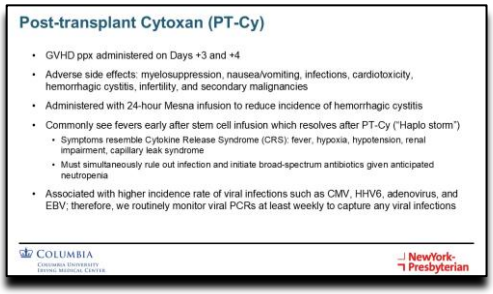
This allows us to act faster in obtaining cultures, imaging studies, and initiating antibiotics. Infection is always at the top of our differential for managing stem cell transplant patients as it is something we do not want to miss.



Slide 93: Fever/Infection and Their Differential Diagnosis Related to BMT Timeline

This picture highlights the different types of infections in relation to the day of transplant. Pre-engraftment infections, circled in red, are typically due to the mucosal damage and destruction of the mucosal barrier which allows translocation of bacteria. So, we see a lot of gram-negative and gram-positive bacteria, HSV, respiratory viruses, *Aspergillus*, and *Candida*.

Post-engraftment infections, seen circled in blue, also include both gram-negative and positive bacteria, HSV, *Aspergillus*, and *Candida*, but we also see more bioactivation such as CMV, HHV6, adenovirus, EBV, respiratory viruses and PCP.



Slide 94: Post-transplant Cytoxan, or PT-Cy

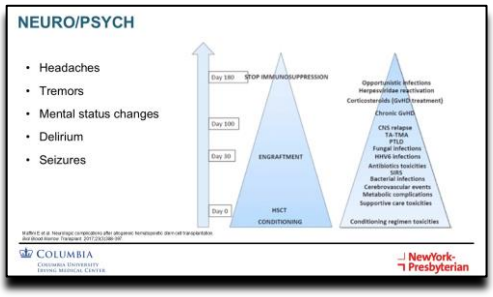
Post-transplant Cytoxan®, or PT-Cy for short, is used for graft-versus-host disease prophylaxis. It is originally used early in haplo-identical allogeneic stem cell transplants. However, research has shown that PT-Cy lowers the incidence of both acute and chronic graft-versus-host disease in allogeneic stem cell participants. At our institution, we've been using PT-Cy now not only for graft-versus-host disease prophylaxis amongst other allogeneic stem cell transplant patients in addition to those receiving a haplo-identical transplant.

PT-Cy is given in Days +3 and +4 after the graft was administered to remove the allo-reactive T-cells and stimulate regulatory T-cell recovery. Adverse events of PT-Cy include myelosuppression, nausea and vomiting, infections, hemorrhagic cystitis, infertility, secondary malignancies, as well as cardiotoxicity such as myocarditis, arrhythmias, and congestive heart failure.

At our institution, we administer PT-Cy alongside a continuous infusion of Mesna to reduce the risk of developing hemorrhagic cystitis. As we mentioned earlier, hemorrhagic cystitis could also be a sign of bio infections in the urine, such as adenovirus, BK virus, or JC virus. Thus, we must also rule out infection in the presence of hemorrhagic cystitis. We commonly see fevers shortly after patients receive their stem cell infusions due to the alloreactive T-cells after the infusion. This is called haplo storm which can mimic the symptoms of cytokine release syndrome or CRS. Patients may develop high fevers, hypoxia, hypotension, renal impairment, and capillary leak syndrome. These symptoms usually resolve shortly after receiving PT-Cy on Days +3 and +4, although given that these

patients' neutropenia and immunosuppression of them, we also simultaneously send an infectious workup to rule out infection and empirically treat with broad-spectrum antibiotics.

Although PT-Cy does decrease the incidence of acute and chronic graft-versus-host disease, an unfortunate sequalae of PT-Cy has been an increased incidence of viral infections and reactivations, including CMV, HHV6, EBV, and adenovirus. We routinely monitor these viral PCRs at least once a week to closely track any viral infection.

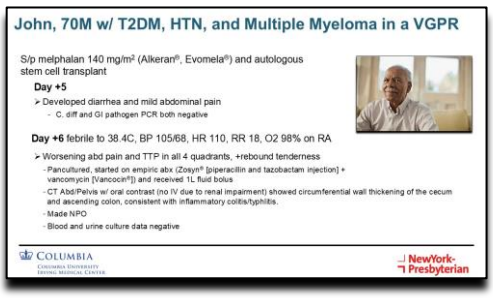


Slide 95: NEURO/PSYCH

This graph highlights some neurological side effects we can see in the transplant setting, alongside a graft of the timeline of transplant and their associated possible causes. Neurologic complications after stem cell transplant can be very threatening and where clinical management can be very challenging.

There is a wide spectrum of causative factors, including drug-related toxicities; infections that can be either bacterial, viral, or fungal; metabolic encephalopathy; cerebrovascular disorders; intermediary disorders; and disease recurrence. During transplant, we can see neuro side effects such as headaches, tremors, mental status changes, delirium, and even seizures. Now, looking at the graph, early in the transplant around Day zero, these side effects would likely be due to the conditioning regimen toxicity. During the period between transplant and engraftment when the patients are pancytopenic, we can see more infectious etiologies of these neuro symptoms to just fungal, bio, and bacterial infection, SIRS, as well as metabolic complications or cerebrovascular events.

Headaches, for example, are often a frequent side effect experienced by our patients. However, we must look at the entire clinical picture to differentiate of a regular headache from something more serious such as a cerebrovascular event or even PRES, which I mentioned earlier is a complication thought to be due to the damage to the vascular endothelium from calcineurin inhibitors.



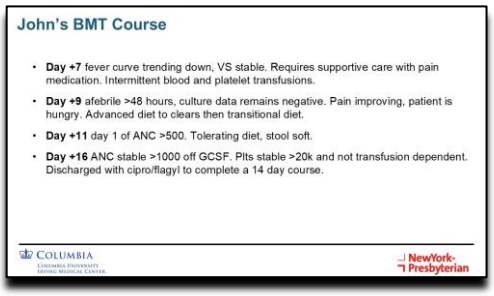
Slide 96: John, 70M w/ T2DM, HTN, and Multiple Myeloma in a VGPR

Now we are going to review some cases. John is our 70-year-old male with CKD and myeloma in a very good partial remission after several rounds of chemo. He was admitted for mel 140 conditioning, a reduced dose based on his age and kidney function, as well as an autologous stem cell transplant.

On Day +5, John started having diarrhea and mild abdominal pain. Stool studies were sent and were negative for infection. On Day +6, he developed a fever of 38.4˚C, as well as some lower than baseline blood pressures and tachycardia to the 110s. He was not tachypneic, and he was stating well on room air.

Cultures were obtained, and he was started on empiric Zosyn® (piperacillin/tazobactam), which has broad spectrum coverage. He also received additional fluids for blood pressure support and hydration. Later that day, the abdominal pain worsened. A CT abdomen and pelvis was obtained which showed evidence of inflammatory colitis consistent with neutropenic colitis which is also called typhlitis, which is a complication resulting from a breakdown of gut mucosa from chemotherapy.

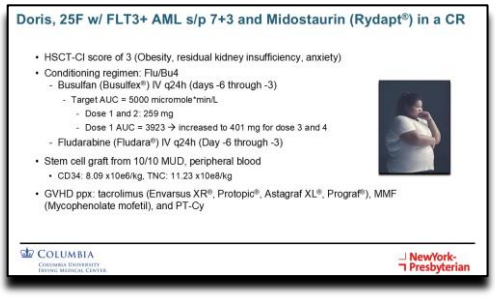
Given these findings on CT scan, he was made NPO or nothing by mouth. His additional infectious workup remained negative.



Slide 97: John's BMT Course

The next day, on Day +7, John's fever curve began to improve; and his current antibiotic regimen was continued. His vitals were stable, his pain was well-controlled with pain medication, and he required blood and fluid transfusions.

On Day +9, his fever had completely resolved, his culture data continued to remain negative, he continued on Zosyn, and his abdominal pain improved, thus his diet was advanced as tolerated. On Day +11, he engrafted his counts, and he was tolerating a diet. On Day +16, his counts were stable without any need for transfusions, so he was discharged home to complete a 14-day course of antibiotics for his colitis.

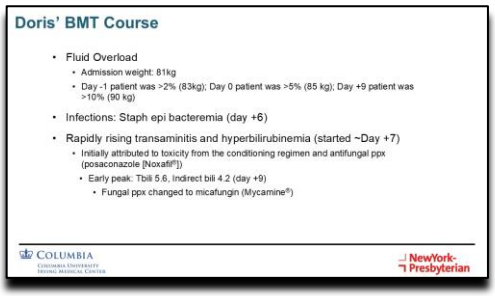


Slide 98: Doris, 25F w/ FLT3+ AML s/p 7+3 and midostaurin (Rydapt®) in a CR

Now let's talk about Doris, a 25-year-old with FLT3-positive AML, status post 7+3 and midostaurin (Rydapt®) induction chemotherapy who was now in a complete remission. Of note, Doris has a comorbidity index of 3, receiving points for obesity, residual kidney insufficiency, and anxiety.

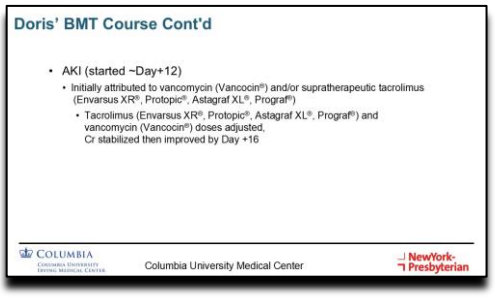
Doris is admitted for fludarabine (Fludara®) and busulfan (Myleran®) conditioning over four days. Pharmacokinetic drug levels were checked for Doses 1 of busulfan (Myleran®) and was also received in time to modify Doses 3 and 4 in order to achieve the desired therapeutic level. She received a peripheral blood stem cell transplant from a 10 out of 10 matched unrelated donor with a CD34 count of around 8 million cells per kilogram. She

received GVHD prophylaxis with tacrolimus (Prograf®), MMF or CellCept, and post-transplant Cytoxan®.



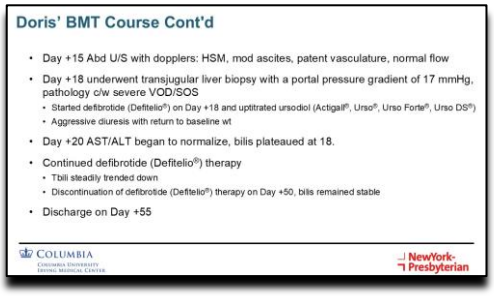
Slide 99: Doris' BMT Course

Her course was quite complicated. She developed progressive volume overload over the course of ten days, gaining over 10% of her baseline weight. She was febrile and found to have a staph epi bacteremia and was thus started on vancomycin (Vancocin®) and cefepime (Maxipime®) for broad coverage. On Day +7, she began having a notable rise in her transaminases and bilirubin. Initially, it was thought to be attributed to her conditioning regimen with busulfan and the azole that she was receiving as prophylaxis. Eventually, her fungal prophylaxis was changed to micafungin (Mycamine®).



Slide 100: Doris' BMT Course Cont'd

On Day +12, Doris developed acute kidney injury, therefore, her vanc and tacrolimus (Prograf®) doses were adjusted.



Slide 101: Doris' BMT Course Cont'd

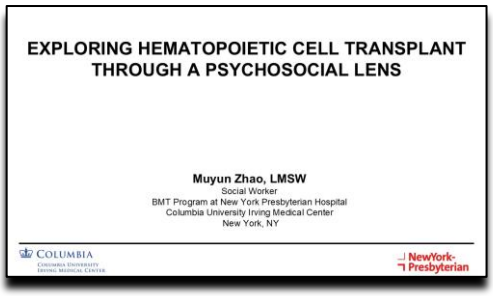
On Day +15, abdominal imaging was obtained which showed an enlarged spleen and liver, moderate ascites, patent vasculature, and a normal flow in the liver.

On Day +18, a transjugular liver biopsy was obtained and showed an elevated portal pressure gradient and pathology consistent with sinusoidal obstruction syndrome. She was started on defibrotide (Defitelio®), and her ursodiol (URSO Forte®) dose was increased. She was aggressively diuresed with a goal to return to her baseline weight.

On Day +20, her transaminases began to normalize and her bilirubins plateaued. Over the course of the next few weeks, she continued on defibrotide (Defitelio®) therapy. Her bilirubins began to steadily trend down, and by Day +50, the defibrotide (Defitelio®) was discontinued, and her bilirubin remained stable. She was discharged home on Day +55. I hope the information I presented on these slides give you a better understanding of the vital roles the nurses and the physician assistants play in the management of stem cell

transplant patients. And furthermore, how important the team-based approach is for the optimal management of these complex patients.

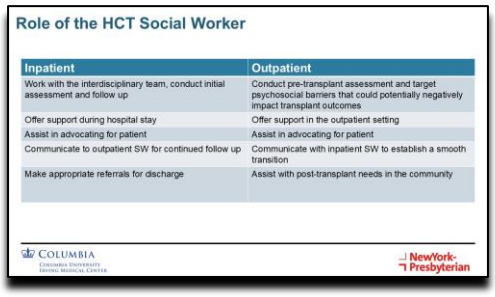
Thank you.



Slide 102: Exploring Hematopoietic Cell Transplant Through a Psychosocial Lens

Muyun Zhao, LMSW: Thank you for having me. I'm grateful for this opportunity to present with this excellent team. I'm going to be sharing some of the psychosocial aspects of transplant and discussing how social workers take part in planning and implementing psychosocial interventions.

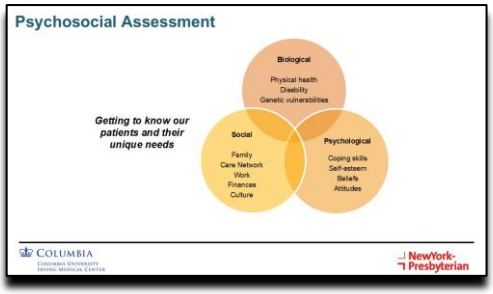
We will touch upon some unique needs of the transplant patient and ways that social workers can support patients throughout their journey.



Slide 103: Role of the HCT Social Worker

We'll start off with what does a social worker do? Social workers consistently strive to meet the patient where they're at, and our role is very much defined by what patients need in that very moment. We help to implement community outreach, provide case management, offer psychosocial support, make referrals, and the list goes on. Although every day is different, there are some constants that we do, both in the inpatient and the outpatient setting.

We're constantly collaborating with the interdisciplinary team to identify psychosocial challenges that have the potential to complicate treatment. In the outpatient setting, we conduct a pretransplant assessment and then the assessment continues inpatient. Once we've identified barriers, we implement social work interventions that target them. We also offer support in all settings, and we assist in advocating for the patients as needed. We coordinate with our team members to make sure the plan is understood, and we make referrals and connect patients to resources to ensure a smooth transition.



Slide 104: Psychosocial Assessment

So how do we start identifying these needs? This is where the psychosocial assessment comes in. This is one of the most crucial steps in getting curious about a patient and their network.

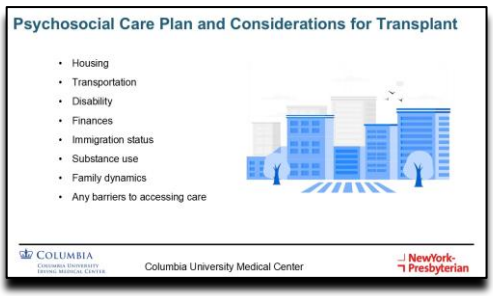
The assessment is broken into three categories: biological, psychological, and social. Under the biological, we have factors such as how have you been tolerating treatment physically? We assess for symptoms like fatigue, pain, problems with appetite, also functional status. Are patients doing activities of daily living independently, or will they need medical equipment or homecare to assist? Do they live in a walk-up, for example? Can they navigate stairs?

Under psychological, we have things such as how are you coping emotionally? What steps are you taking to build self-care into your day? And how are you managing your anxiety or adopting to loss?

Many aspects fall under the social category that we as social workers are especially interested in. These are things such as educational background, family network. We explore their care partners, their work history, finances, cultural and spiritual needs just to name a few. Once we have an idea of what makes up these categories for our patient, we can start developing a plan.

Unique to the transplant social worker, we want to identify anything that might become a barrier to transplant admission or to an overall positive outcome. Identifying these factors is crucial in helping a transplant team and the patient weigh risks versus benefits of such a complex medical procedure.

Once the patient is admitted, the inpatient social worker will then reassess patients shortly after admission, check in throughout, and assess their needs at discharge. Discharge needs can include factors such as home IV antibiotics, visiting nurse, home health aide, medication management, and if they are deconditioned enough, even things like subacute rehab or acute rehab.



Slide 105: Psychosocial Care Plan and Considerations for Transplant

This brings us to the care plan. These are some, but not all, of the important topics to cover the transplant patients. I'll go into detail on some of these.

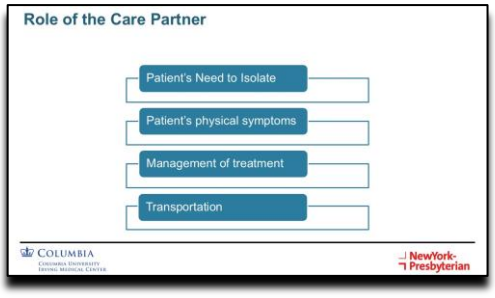
Housing is often a big topic that comes up. Following discharge, there will be many follow-up

appointments, likely two to three times a week. Sometimes more. Complications can also arise requiring immediate medical intervention. Because of that, we want to ensure that the patient resides within a manageable distance from the clinic. This varies from program to program, but usually patients should remain within one hour from the transplant center where the social worker can stop in as to help with applying for programs such as Hope Lodge which is a hotel run by the American Cancer Society where patients can stay for free as they are recovering. This can also look like helping them and identifying people who they can stay with or with grants that can assist in covering some parts of their lodging.

After transplant, patients should avoid public transportation as they are immunocompromised and can be deconditioned. As social workers, we can look into assisting patients with applying to their local paratransit program or Medicaid taxi if they have Medicaid. As patients won't be able to work for a time after transplant, sometimes even a year or more helping patients navigate the disability field, figuring out where they can go to apply is very important. Along with not being able to work, their financial situation may take a hit. Disability may help with a portion of this. However, there are other public benefit programs that social workers can explore with patients.

Immigration status impacting such as insurance and how long they are able to stay. Is a patient here on a visit or visa? How long is the visa good for? And how long they can extend it. Do they need the help of a lawyer? These are important things to know as it can impact their recovery process and plan of care. For transplants, patients should not be smoking or taking illicit substance as this will impact their recovery. Social workers can connect them to smoking cessation programs and substance use resources .Family dynamic is a big one as that will impact who will be the patient's care partner after transplant. We will go more into that in the next slide.

Our role ultimately is not to directly fix anything with these interventions but rather to help engage patients, their care partners, and their families in exploring and processing all the available options. Our interventions are actually the tools that we both use and share with our transplant patients.



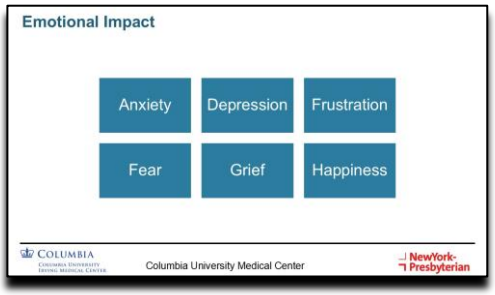
Slide 106: Role of the Care Partner

We often hear the word caregiver" being used. It is what we're accustomed to hearing. However, I like to think of the patient's identified support person or persons after transplant as their care partner. This is because a giver can sound like a solo responsibility when really it is the idea of working together to find the best path to recovery.

Instead of simply doing things for them, their partner do things with them. All patients respond to treatment differently, but at the time of discharge, they may be fatigued, deconditioned, or remain susceptible to infection. They leave the isolation of the hospital room, and continue to recover at home also in a state of isolation. This is where the care partner or care partners can step in and work together with the patient. This role varies, but I can include things such as providing transportation, accompaniment to the outpatient clinic, assistance with medications, home tasks, and daily chores. An extra year can also help submit the necessary medical information, and they can assist in providing reminders to the patient of medications and future appointments.

They also help the clinical team by monitoring for adverse side effects and reporting observed changes together with the patient. It's for this reason that the care partner should ideally be a family member or close friend, somebody who knows the patient well enough to sense when something is off. Social workers can be instrumental in this process, having family meetings, and helping care partners figure out a complete plan such as who's rotating, how to figure out time off, and managing expectations between family members.

As transplant can be taxing to both parties, it is important to provide support, not just to the patient, but also to the care partner. The Leukemia & Lymphoma Society has many resources for the care partner that they can access, and I welcome you to take a look.



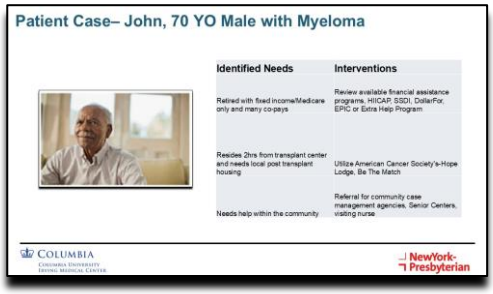
Slide 107: Emotional Impact

Transplant is a huge process, and it naturally comes with different emotions. Just to name a few, this can look like anxiety, depression, frustration from stressors, a lack of control, fear, not knowing what's to come, anticipatory grief, and upcoming loss, even happiness. And it's often a mixture of many of these things. Getting a cancer diagnosis and also going through transplant flips your life around. It is a process that naturally comes with loss. When we think of loss, we often think of it in terms of losing a loved one. However, loss can come in many forms. There's loss of independence and autonomy, a loss of safety, loss of control, loss of previous lifestyles and hobbies, and much more. And these things can come out as patients go through a transplant.

Additionally, patients may feel a sense of relief and hope after transplant; and then those feelings can become mixed at the reality they face. It's not the perfect road to recovery that they were expecting. For example, they face a setback such as a rehospitalization or developing GVHD. Chronic GVHD symptoms may last years, even a lifetime. We want to help patients figure out ways of managing the emotional aspects of it and maybe even adapting to their new normal.

In the pretransplant phase, we can provide more educational resources. We can assist them with figuring out questions to ask, provide support, and connect them to peer-to-peer programs or support groups. Peer-to-peer programs are very helpful because it connects them to somebody who's gone through similar experiences.

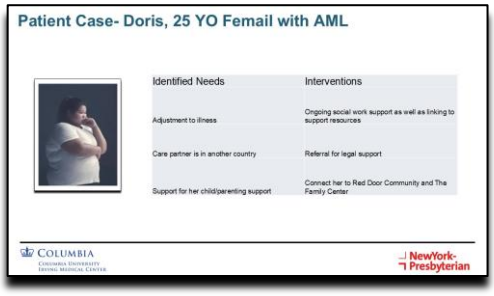
Throughout the entire transplant process, we can help patients in identifying which coping strategies work best for them. Not everyone responds to strategies the same. For one patient, the strategy may be meditation, guided breathing, or journaling. But another patient may need something more physical – going on walks. Do patients have any hobbies, and how can that be incorporated into their coping strategy?
We also help them in identifying what is within their control and what isn't, focusing on things they can do to help build power back into their life.



Slide 108: Patient Case- John, 70 YO Male with Myeloma

We'll now move into some patient examples to really tie it together. This is John, a 70-year-old male with myeloma. He is retired with a fixed income. He has Medicare only and many copays. For John, we can review different financial assistance programs, both with independent organizations and with the hospital. In different states, there are different types of programs that you can look into that are government funded. We can also help this patient look into disability and to Dollar For, which is a national program that helps people in applying for charity care within the hospitals.

John resides two hours from the transplant center and needs post-transplant housing. In this instance, we can look into American Cancer Society's Hope Lodge and programs such as Be the Match for grant support. After transplant, John needs help within the community. Social workers can help by making referrals for community case management agencies, senior centers, and putting in referrals for programs such as visiting nurse.



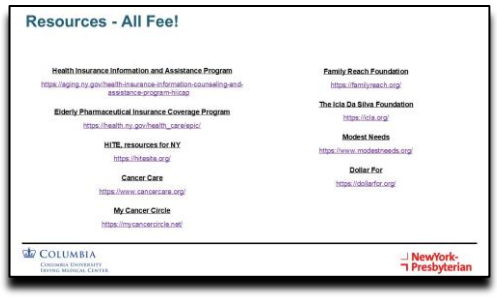
Slide 109: Patient Case- Doris, 25 YO Female with AML

Doris is a 25-year-old female with AML. She is having a lot of troubles adjusting to her illness. In this instance, social workers can assist with ongoing psychosocial support, talking to the patient, as well as linking her to support resources such as mentioned before, the peer-to-peer program or group support programs.

Doris's care partner is in another country, and on this instance, she doesn't have any other identified care partners in this country that can support her. In this instance, we can refer her for legal support to really figure out what her options are and how to best get her care partner into the country. She needs support for her child, and she needs parenting support. There's organizations such as the Red Door Community and The Family Center and many others out there that can support specifically children who have parents who have been diagnosed with cancer. These are all amazing resources that you can look into, and I've attached more resources in the following slides.

Slide 110: Resources- All Free!

Here I've attached a lot of new sources. A lot of these I use a lot and I love. Some of these resources are New York-specific, but there are lots of resources out there for different states. So definitely take a look.

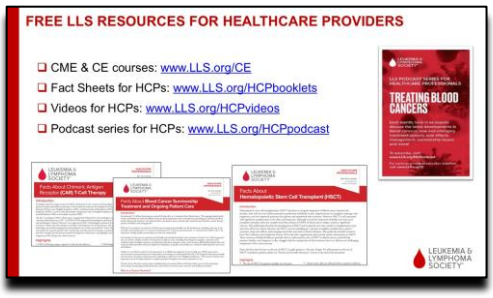


Slide 111: Resources- All Free!

Social workers are instrumental in helping patients in navigating these resources and figuring out where to go. It is a lot for patients to think about, and they don't necessarily know all the things that are out there. This is where social workers can really step in and help relieve some burden for the transplant patient.

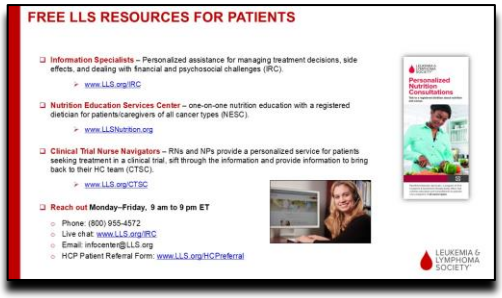
Thank you so much for having me today, and thank you for, The Leukemia & Lymphoma Society for giving me the opportunity to talk on this platform**.**

Lauren Berger: Thank you, PA Skvarce and Social Worker Zhao.



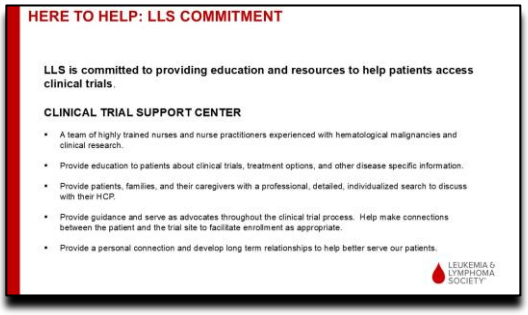
Slide 112: Free LLS Resources for Healthcare Providers

I am now pleased to share free resources for you and your patients. The Leukemia & Lymphoma Society offers free CE and CME online webinars such as this one, in-person regional programs, and a podcast channel for Healthcare Professionals, where you can listen to discussions on treatment, side-effect management and more. New and interesting topics are added every few weeks. Access these, as well as Videos as well as Fact Sheets for HCPs, including a Fact Sheet on Transplantation@www.LLS.org/CE.



Slide 113: Free LLS Resources for Patients

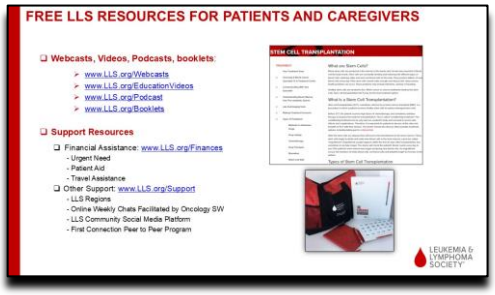
LLS Information Specialists are highly trained Oncology Social Workers and Nurses who provide accurate, up-to-date disease, treatment and support information, including financial. Patients can contact them directly, or you can complete a Referral form. Information Specialists can also help you order free copies of booklets to give to your patients. LLS offers free nutrition consultation to patients and caregivers with any type of cancer diagnosis in a 30-minute phone call with one of our registered dietitians. Contact them using the link or phone number listed here to refer a patient. Our Clinical Trial Support Center Nurse Navigators are RNs & NPs with expertise in blood cancers. CTSC Nurse Navigators work one on one with patients, via telephone, to provide user friendly information, help find appropriate clinical trials, personally assist them through the clinical trial process and provide info for the patient to bring back to their healthcare professional. They also work with Healthcare Professionals, and this is unique service from The Leukemia & Lymphoma Society. I hope you will consider all of these specialists as an extension of your team.



Slide 114: Here to Help: LLS Commitment

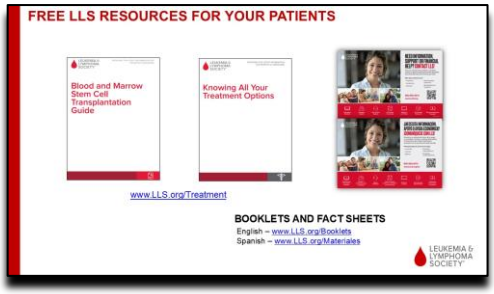
Here is a brief overview of the Clinical Trial Support Center process for Supporting Patients.

The goal is not to enroll every patient into a trial, rather to increase opportunities for participation by facilitating informed decision making and minimizing logistical barriers for the patient. They work in collaboration w/the patient's healthcare team to decide if a clinical trial is right for them. Ultimately, they educate, support, and empower patients to be active participants in and have control over their treatment decisions.



Slide 115: Free LLS Resources for Patients and Caregivers

LLS offers blood cancer disease specific information and support resources for patients and caregivers, including telephone and web education programs, videos, podcasts and booklets. I encourage you and your colleagues to stay up to date on the availability of LLS' Financial Assistance programs, and other resources, using links on these slides.



Slide 116: Free LLS Resources for Patients

Through targeted and culturally appropriate programs and services, we are committed to addressing needs of minoritized communities impacted by a blood cancer and those facing barriers to optimal care. Our materials are available in English and Spanish, and our Information Specialists and other specialists, consult with patients in additional languages. If you would like more information for yourself or support for your patients, please contact an Information Specialist at LLS at 800.955.4572 www.LLS.org/support.

Slide 117: American Society for Transplantation and Cellular Therapy

I am pleased to share a link to resources from the American Society for Transplantation & Cellular Therapy. They offer opportunities to connect with colleagues and to participate in continuing medical education.

Slide 118: Thank You

Thank you to our presenters and thank you to everyone listening. I hope this information will be helpful as you care for your patients. For additional information and resources, please contact an Information Specialist.