Jonathan W. Friedberg, MD, MMSc
Edward A. Stadtmauer, MD
December 3, 2012

Slide 1: Title Slide

Operator
Good afternoon and welcome to Update on Autologous Stem Cell Transplantation for Lymphoma and Myeloma, a free telephone web education program. It is my pleasure to introduce your moderator, Mabel Maia.

Ms. Mabel Maia
Hello everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you and a special thanks to Dr. Friedberg and Dr. Stadtmauer for sharing their time and expertise with us today.

We have over 1,300 individuals participating today from across the United States and many international participants. We welcome all of you.

We would also like to acknowledge and thank Sanofi-Aventis for their support of today's program.

You should have received or downloaded materials for today's program. Dr. Friedberg and Dr. Stadtmauer have also provided slides, and they will explain the information on the slides during their presentation. If you have not already accessed the slides, you can view or print them now from the LLS website at lls.org/programs.

We are audiotaping and transcribing this program for future posting on the LLS website at lls.org/pastprograms. This provides an opportunity for you to read or listen again to today's program.

On your confirmation letter for today's program, there is a link to an online evaluation form. Nurses and social workers, you'll get a code for the CE evaluation later in the program. We encourage you to complete it online at lls.org/teleconeval. And we really appreciate your feedback.

Following the presenters' presentations, we will take questions from the telephone and web audience.

Slide 2: Faculty Information

I am now pleased to introduce Dr. Friedberg and also Dr. Stadtmauer. Dr. Friedberg is the Chief of Hematology, Oncology Division, at the James P. Wilmot Cancer Center, and Professor of Medicine at the University of Rochester in Rochester, New York.

Jonathan W. Friedberg, MD, MMSc
Edward A. Stadtmauer, MD
December 3, 2012

Ms. Mabel Maia
Dr. Stadtmauer is Professor of Medicine and Leader of the Hematologic Malignancies Research Program at Abramson Cancer Center at the University of Pennsylvania in Philadelphia.

You can read a complete biography of the presenters in your enclosed materials.
Dr. Friedberg and Dr. Stadtmauer, we are so privileged to have you both with us today. And I now turn the program over to Dr. Friedberg.

Slide 3: Dr. Friedberg Introduction

Dr. Jonathan Friedberg
Thank you so much, Mabel, for the kind introduction. And I would echo the welcome to everybody. It's really a privilege to be able to give this brief session on a very exciting therapeutic modality, autologous stem cell transplant.

Slide 4: LLS

And before we start, I also want to personally thank The Leukemia & Lymphoma Society for programs like this, as well as generous research support that they have provided me and my institution over the past several years.

Slide 5: The Autologous Transplant Process

I think, to begin, it's important to emphasize that autologous stem cell transplant is a fairly complicated procedure. And it's very important, too, for everybody to understand exactly what that procedure is.

The first thing I'd like to do is to take the word "transplant" essentially out of the terminology. This isn't really a transplant.

The concept here is a way of rescuing a patient from the effects of high dose chemotherapy, and you're using the patient's own cells. So, it's not a transplant. It's simply a way to use the patient's own cells to rescue that patient from the effects of high dose chemotherapy, or high dose chemotherapy and radiation.

And before we start to describe the procedure, the question is “why would we want to do this?” And the reason, quite simply, is that higher doses of chemotherapy might be able to overcome resistance that cancer cells have to standard doses of chemotherapy. I think most people are familiar with the fact that if you take more medication, sometimes it works better for certain types of problems. That's the same in cancer, but the problem with many of our chemotherapy treatments is that if you take more

Jonathan W. Friedberg, MD, MMSc
Edward A. Stadtmauer, MD
December 3, 2012

Dr. Jonathan Friedberg
chemotherapy, it not only affects the cancer cells, it affects the normal cells. And what autologous transplant is, it's a way of getting around that.

So, as shown on this picture, the first thing that's done, step one is collection. And what we do is we take some of the patient's grandfather or grandmother cells out of the body and freeze them. These are what are called stem cells, and these cells have the ability to make all types of blood cells.

There are multiple ways of these collections. Historically, they were usually done in the operating room with a procedure called a bone marrow harvest, and that's still occasionally done. But, for the vast, vast majority of patients now, these cells are relatively easily collected from the blood after some medication is given.

The next step is for these cells to be processed. And frequently, these cells then get frozen away for use at a later date.

Now, many patients ask “how do we make sure that tumor cells aren't contaminating this stem cell collection?” And although some studies have looked at various means of actually treating the collected material with either drugs or antibody type treatments, in most cases the collected material is actually not treated.

And that's because it is uncommon for many of these tumor cells to actually be in the circulation and because some of our new drugs, for example in lymphoma, like rituximab, do a reasonably good job at clearing the blood circulation so that the contamination is not a problem.

Then these cells are frozen away and the patients go on and get high doses of chemotherapy with or without radiation treatment. In some centers, this is done as an outpatient, and in other centers it's done as an inpatient.

And the regimen of chemotherapy depends critically on the disease being treated. For example, Dr. Stadtmauer is going to talk about myeloma. That's frequently a single dose of chemotherapy, whereas in lymphoma we often give chemotherapy for five or six days in a row.

Then the chemotherapy gets washed out of the patient's system and, usually about 24 hours later, these stored frozen cells are infused into the patient. And it takes between 10 days to two weeks for those cells to kick in and start to grow. And during that period of time, the patient often requires blood transfusions and careful monitoring for infections.

Jonathan W. Friedberg, MD, MMSc
Edward A. Stadtmauer, MD
December 3, 2012

Dr. Jonathan Friedberg
Therefore, the entire process is a multistep process. The stem cell collection phase often takes a couple of weeks. And then, the actual chemotherapy may take up to one week and the recovery after reinfusion may be approximately two weeks.

The risks of this procedure include short and long term risks, and I'm going to get into that in a minute.

Slide 6: NHL Subtypes

In lymphoma, which is going to be my section of the talk, it's important to recognize that there are numerous types of lymphoma, all of which are very different diseases. Shown on this slide are some of the common types of lymphoma. Diffuse large B-cell lymphoma and follicular lymphoma combined are only about half of the lymphoma in the United States. And all of these different types of lymphomas may use autologous transplant to a varying degree.

Slide 7: Issues with ASCT in lymphoma

So, therefore, some of the key issues with autologous stem cell transplant is the type of lymphoma that you're trying to treat. And I've listed on this slide really the top lymphomas where autologous transplant has a key indication, although there are certainly others, as well as what the goal of the transplantation procedure might be.
In some cases, the goal is curing the patient of the lymphoma and in others it's to prolong disease control. And then finally, another issue that comes up is, what is the time of doing this procedure? Do we do it as what's called remission consolidation, or we do it in the setting of relapsed disease?

So, very briefly I'm going to go through each of these diseases and just give you some broad strokes as to how this procedure might be used. In diffuse large B-cell lymphoma, autologous stem cell transplant has become the standard if the disease is not cured the first time around.

So, usually patients are treated with a chemotherapy regimen like R-CHOP. The majority of patients may be cured with that treatment. If the disease comes back and the patient is a reasonable candidate, autologous stem cell transplant may be considered with curative intent.

Mantle cell lymphoma is different. That's a disease that's much more difficult to cure, and the goal of autologous transplant here is to prolong disease control. And that's often done immediately after initial therapy in younger patients.

Jonathan W. Friedberg, MD, MMSc
Edward A. Stadtmauer, MD
December 3, 2012

Dr. Jonathan Friedberg
For follicular and other indolent lymphomas, autologous transplant may be used in second or even third recurrence of the disease or in high risk situations in younger patients.

Although uncommon, transformed lymphoma has historically been a key role for autologous transplant where the goal would be to cure the patient of the aggressive component of the lymphoma, but the indolent lymphoma may recur at a much later date.

And finally, Hodgkin lymphoma, although that is highly curable with standard initial therapy, up to 15 percent of patients may recur. And if that happens, autologous transplant is often the tool used to try to cure the patient.

Slide 8: ASCT in lymphoma: Challenges

There are a number of challenges that exist using this modality. First of all, the age of patients and comorbid medical problems limit eligibility for this procedure. Although there is now literature suggesting that this procedure might be reasonably well tolerated in patients up to about the age of 70, or in some cases even a bit older, the fact that many lymphomas have a median age of presentation around 60 to 70 years suggests that up to half of patients may never be eligible for autologous transplant.

In addition, because of the other effects of high doses of chemotherapy, if the patient has comorbid medical problems such as heart damage, lung damage, kidney, or liver damage, those patients may not be good candidates for transplant.
An even bigger problem in lymphoma is that many patients are not able to achieve adequate disease control prior to transplant. And this is an important point. Even though this is aggressive chemotherapy, transplants work the best if the disease is under optimal control.

So, usually standard chemotherapy is used prior to a transplant. And the goal is to get the patient to a minimal disease state, ideally with no evidence of disease even on a PET scan. Many patients are not able to achieve this state because of intrinsic resistance of the disease, and therefore autologous transplant may not work.

I mentioned the concern about contamination of stem cell products with lymphoma. Again, this has been more of a historical issue than a present issue. However, with certain diseases, certainly if you have lymphoma in the blood that would be a major concern.

Jonathan W. Friedberg, MD, MMSc
Edward A. Stadtmauer, MD
December 3, 2012

Dr. Jonathan Friedberg
And then finally, this procedure does have a lot of side effects. Early toxicity I divide into both what I call annoying side effects, as well as more serious side effects. The annoying side effects include standard chemotherapy types of side effects like hair loss, nausea, diarrhea, mouth sores, sometimes fevers, rashes, and reactions to the medication.

A subset of patients develop more serious side effects, including life threatening infection and organ damage. And in large studies, the mortality or the death rate of the procedure itself is approximately 2 percent.

Now, that's safer than many other standard medical procedures like heart surgery. But, it's still an issue for any individual patient, and that's why it's important that this procedure only be done in experienced centers.

What's evolved, because this procedure has worked so well, is an appreciation of late toxicity and, in particular, patients who have exposure to high doses of chemotherapy with radiation. They may be at risk for second cancers including leukemias, and this risk may be as high as 5 or 10 percent.

Now, it's still the case that the vast majority of patients who undergo this procedure do not develop second cancers. But, it is an issue and it's a reason why physicians often are very careful about choosing appropriate candidates.

In addition, sometimes there can be longstanding heart and lung toxicity that can occur as a consequence of the aggressive chemotherapy.

Slide 9: Improvements in ASCT for lymphoma

There are a number of things that are going on to try to improve the outcome for patients with autologous stem cell transplant. And the first is what I'm calling conditioning approaches.

And this is what is given to the patient prior to the infusion of the stem cells, in other words, the high doses of chemotherapy. So, people are looking at different chemotherapy drugs as well as whether or not radiation is required. And historically, when I trained, almost every patient got radiation as part of conditioning. Now very few patients do, and that has decreased the risk of second cancers after autologous transplant.

Jonathan W. Friedberg, MD, MMSc
Edward A. Stadtmauer, MD
December 3, 2012

Dr. Jonathan Friedberg
For lymphoma, it is very clear that incorporating rituximab, the antibody that's used for standard treatment of lymphoma, into the transplant paradigm has had an improvement on outcome. And that's done now routinely in many institutions.

In addition, using growth factors or ways to stimulate the body to recover from the high-dose chemotherapy quicker has been a major advance in transplantation. And that's allowed many centers to do components of this or even, in some cases, the entire procedure for patients as outpatient.

I think what's coming down the pike are the incorporation of some of the new, exciting novel targeted therapies into this modality. And studies are going on where, both before the transplant, as well as after transplant, people are looking at some of these new targeted therapies. Often these are pills that are extremely well tolerated and are ways to prevent the lymphoma from coming back after the procedure.

And many studies are looking at the so-called maintenance approach. Dr. Stadtmauer may speak later about maintenance approaches in myeloma, and that type of treatment is now being extended to lymphoma as well.

And finally, I think we're better at recognizing side effects in patients. And particularly at experienced centers, that has allowed us to minimize the patients who have permanent damage from these transplants as well as patients who die from the transplants. I should mention that these transplants also are a burden on families, because patients are often not able to work for a few months during and after the procedure, and that emotional support for both the patient and the family members is a key way that we've improved on the outcome.

Slide 10: Outcome of relapsed DLBCL and ASCT in the rituximab era

I do want to emphasize how this transplant might work in large cell lymphoma. And just to show you some of the limitations and where improvement in the field is going, if you start with 300 patients with large cell lymphoma, approximately 200 of them may be cured with upfront therapy.

That would leave a hundred patients who have relapsed disease or whose disease doesn't respond initially to treatment, half of which may never be eligible for autologous transplant because of age or other medical problems. That's the red line.

So, if you follow the green line that means only about 50 of these patients may be eligible for transplant. And of that group, only approximately half or somewhat less than

Dr. Jonathan Friedberg
half may actually proceed to transplant, because the disease needs to get back under control. And of that group, only a proportion of about 40 percent are ultimately cured.

Slide 11: To impact relapsed DLBCL

So, this demonstrates that, yes, transplant is an important curative modality. But, the ultimate benefit is only for a relatively few number of patients. And what that means is that what we need to do is improve these red lines, in other words, try to either make transplant more broadly applicable to older patients, or, more likely, use novel agents instead of transplant in that patient population.

And in addition, we need to improve the outcome once patients relapse from what we call salvage therapy, in other words, try to increase the percentage of patients who ultimately can go on and get the autologous transplant. And that's where most of the research is going on in relapsed and refractory large cell lymphoma.

You could draw a diagram like this for other histologies as well. And I think that's why there has been so much enthusiasm for these novel therapies.

Slide 12: Conclusions

So, I'm going to conclude by saying that autologous stem cell transplant remains an important modality in the treatment of lymphomas. It can cure diffuse large B-cell lymphoma and Hodgkin lymphoma. It can prolong remission in follicular lymphoma, mantle cell lymphoma, and T-cell lymphoma.

And novel targeted treatments represent an important opportunity to improve the outcomes of autologous transplant or perhaps to avoid autologous transplant entirely, which I believe is the ultimate goal. If we can avoid using high doses of chemotherapy and the side effects that go along with that, that's really the best for patients. And I think some of the new treatment modalities that are out there are curing more people so that patients don't have to go through this aggressive procedure.

Slide 13: LLS

I'll again thank The Leukemia & Lymphoma Society. And I'll turn over to my partner, Dr. Stadtmauer.

Slide 14: Dr. Stadtmauer Introduction

Jonathan W. Friedberg, MD, MMSc
Edward A. Stadtmauer, MD
December 3, 2012

Dr. Edward Stadtmauer
Hi, everybody. And I want to also welcome you to this wonderful program, and to once again show my appreciation for The Leukemia & Lymphoma Society, which really helps so many of our patients and fosters research.

I'm going to talk to you now about the role of autologous transplant for myeloma. Just to remind everyone, myeloma is a disease of the plasma cell. And I always feel that it really rationalizes me, having an internal medicine background, talking about multiple myeloma, because it can have manifestations in so many ways on the body, from these painful lytic bone lesions, with hypercalcemia and confusion. It can have fatigue and anemia because of the bone marrow filling up with these abnormal plasma cells.

Even though there is a large amount of a useless antibody that's produced by these plasma cells, generally there are low levels of normal antibodies, increasing patients' susceptibility to infection. And then, as the abnormal protein, the antibody that's produced by these cells, floats through the system, it frequently comes out in the urine and can gum up the kidneys or gum up the nerves and give neurologic and kidney dysfunction.

Slide 15: Hallmarks of MM

So, it's a very serious disease with serious complications. It is a disease that affects all adults at all ages, though its average age is around age 70. My youngest patient was about 16 and my oldest patient currently is 96 years old.

And this is important for the consideration of stem cell transplant because, though we try not to consider age as the primary decision making about whether a person is a candidate for stem cell transplant, certainly the majority of the patients are under the age of 70 who are treated.

Slide 16: Incidence Rates

Multiple myeloma comes in a number of different flavors. And many of the patients just have a monoclonal protein in their blood or have a smoldering phase of the disease, which the primary management is simply to do active observation.

So, these patients are certainly not yet candidates for a stem cell transplant or a bone marrow transplant. The primary patients who require therapy are the patients who have active disease, when one of those manifestations, bone lesions, kidney dysfunction, low blood counts occurs.

Dr. Edward Stadtmauer
And really, one of the major miracles of the last decade or so has been that, where maybe a decade ago I was happy if half of the patients responded to initial therapy, we now expect over 90 percent of the patients to respond wonderfully to therapy and to go into a remission.

The problem with myeloma, however, remains fixing it forever and ever. The vast majority of these patients will ultimately have their disease progress. And as time goes on, the chance of getting further responses becomes less and less, and the duration of the responses become shorter and shorter. So, most of our work is how do we prolong that duration of remission.

Slide 17: Challenges of Treating Multiple Myeloma

We now have sort of a strategy for long term remissions, and potentially even for cure. That includes a line of therapy, usually initial therapy to get a patient into remission and have all those active aspects of the disease go away. Once a patient's in remission, if they meet the eligibility criteria for going on to a stem cell transplant, we then, just like Dr. Friedberg suggested, we give high-dose chemotherapy.

The chemotherapy that we're giving is melphalan. And it's that chemotherapy that's overcoming whatever resistance biologically that the myeloma cells still have who have received this initial therapy. And the few that are left must have some sort of resistance to the initial therapy, and the hope is that the high-dose melphalan will overcome that and pound the disease into an even deeper remission.

Most recently we have been using techniques to now chip away, once a patient has a transplant, at the minimal residual disease that might be still there by using various techniques of vaccines, consolidation therapy, and then long term low doses of maintenance therapy.

Slide 18: Multiple Myeloma: Strategy for Cure?

You hear a lot about the biological aspects of multiple myeloma, particularly chromosomal abnormalities. Now, remember every time we talk about chromosomal abnormalities in a cancer, we're not talking about the genetic make up that you pass down to children or inherit.

What we're talking about is the cancer--the cells themselves; the myeloma cells themselves are sick and have broken chromosomes that have been translocated and twisted around. If you do sensitive enough testing, virtually in every patient with

Jonathan W. Friedberg, MD, MMSc
Edward A. Stadtmauer, MD
December 3, 2012

Dr. Edward Stadtmauer
myeloma you'll be able to detect some translocated or broken chromosome by the test we call FISH analysis, or the fluorescence in situ hybridization.

And there are certain chromosomal abnormalities that predict a more resistant or a harder time to get patients into remission or to keep them in remission, and others that predict that it will be a little bit easier. I think this is very interesting and important information for us moving forward with our new therapies.

But, as of this minute, I think it's very important to know that it remains too early to really utilize this information for direct decisions about treatment. I have patients who have purportedly really difficult chromosomal abnormalities, high risk chromosomal abnormalities, who do beautifully, and I have patients who have very good chromosomal abnormalities who have a lot of difficulty. So, as of this moment, we're still gathering information and don't necessarily make decisions based on it.

Slide 19: Genetic Abnormalities in Multiple Myeloma Affects Prognosis

Myeloma is the number one reason that we do stem cell transplant in North America and I think even in the world, followed by non-Hodgkin's lymphoma, ergo, the reason why these are the two primary diseases that we talk about when we talk about stem cell transplantation.

Slide 20: Indications for Hematopoietic Patients Requiring Disease-Specific Therapy

Again, in many ways, it is sort of easier to figure out who is not a stem cell transplant than who is a stem cell transplant, in that, we are able to do stem cell transplants—high-dose chemotherapy and stem cell transplants with the supportive care that we have and with making intelligent dose modifications to the medications for patients with various different aspects of the disease.

But, certainly patients who are frail, patients with severe organ dysfunction, patients who are really not responding to anything and are very sick with the disease, and of course if we're unable to collect stem cells, then those patients are not candidates for transplant. And again, the data that we have shows the strongest benefit in patients who are 70 years or younger, though age is not an absolute reason to not do a transplant.

Slide 21: Initial Approach for Myeloma Patients Requiring Disease-Specific Therapy

Jonathan W. Friedberg, MD, MMSc
Edward A. Stadtmauer, MD
December 3, 2012

Dr. Edward Stadtmauer
We've talked primarily about autologous stem cell transplant where the stem cells are harvested from you, and that is the current standard of care in multiple myeloma. There have been studies using donor transplants. And in some ways, using donor transplants makes even more sense than using your own bone marrow.

As we've discussed earlier, there's always the potential of contamination of myeloma cells within the cells that you take out when you harvest cells and then you give the patients high-dose therapy. No matter how much high-dose therapy you give, if you infuse cells that are full of the myeloma, then why would it work?

The reality is that, despite that logical conclusion, the high-dose melphalan in the stem cell transplant does seem to be beneficial. And it does not seem, as Dr. Friedberg said, that the infusion of a small number of these tumor cells really are responsible for the reason why people might progress after a stem cell transplant.

Nevertheless, donor transplants make sense. The problem has been that every time you put someone else's cells into you, those cells can see you are foreign and attack you. And we call that graft-versus-host disease, and that's definitely age related.

And as we've spoken, in myeloma, the average age is an older patient population, and so the toxicities of donor transplants have outweighed the benefits. And that's the primary reason why we do not do it as frequently.

Slide 22: Types of Stem Cell Transplant

So, to summarize, it's important that patients with myeloma have a nice response and generally have adequate organ function. And then, if you consider with each individual the risks and benefits, then there are many patients where it is a very reasonable choice for them.

Slide 23: Autologous Stem Cell Transplant

Once again, the harvesting of the stem cells are from their own body, and it's usually from the blood. It is very rare in myeloma that we're using bone marrow. The cells are frozen away. And the patients just receive a one-hour drip of high-dose melphalan, that's the name of the chemotherapy, and then the infusion of the stem cells.

Then comes a period of two to three weeks where the blood counts first go down and then come back up. And it's during that period of time where the side effects of a transplant occur. And you've heard about most of them: infection, low blood counts--the need for transfusions, and the potential for organ dysfunction.

Jonathan W. Friedberg, MD, MMSc
Edward A. Stadtmauer, MD
December 3, 2012

Dr. Edward Stadtmauer
And once again, even in myeloma, over 95 percent of the patients do recover and tolerate the procedure very well. And again, a 1 to 2 percent mortality rate, which of course is a tragedy every time it occurs. But, fortunately, it is an uncommon event.

Slide 24: Autologous Stem Cell Transplantation

So, a number of studies now show survival benefit when autologous transplant is added to a line of therapy that includes standard-dose chemotherapy over standard-dose chemotherapy alone. There are even a number of studies that show a benefit for two auto transplants compared to a single one.

And the way to really think about that is, just like in the initial phase of the treatment of myeloma, we give cycles of chemotherapy every month, getting a cycle of either bortezomib and lenalidomide or Cytoxan. Similarly, one cycle of high-dose melphalan may be benefitted by giving a second cycle of high-dose melphalan if patients tolerate the first one well.

Slide 25: High-dose Melphalan and Autologous Stem Cell Transplant

And then, there is a lot of recent evidence to suggest that the addition, after the transplant, of what we call continuous or maintenance therapy, in this case primarily using the drug lenalidomide, is very helpful at prolonging the duration of remission, and even there's evidence of overall survival advantage.

And in fact, there was a big national trial that was done here. There was also another trial in France where they randomly assigned patients lenalidomide maintenance therapy pills versus placebo after a stem cell transplant. And the patients who received the pills had, on average, two years longer duration of remission than the patients who didn't.

As you heard in the lymphoma talk, there is this increased risk of second cancers. And in fact, the patients who received lenalidomide on these trials did have a small percentage of an increased risk of second cancers relative to those who did not receive lenalidomide. Nevertheless, when you factor in the improvement in both the duration of remission as well as the length of survival overall, there was still a benefit to taking pills of lenalidomide over placebo.

Slide 26: Ongoing study of Lenalidomide As Maintenance Therapy Following Autologous PBSCT for MM

Jonathan W. Friedberg, MD, MMSc
Edward A. Stadtmauer, MD
December 3, 2012

Dr. Edward Stadtmauer
There's currently a big national trial that's actually comparing one transplant followed by lenalidomide to two transplants followed by lenalidomide to one transplant followed by some extra bortezomib and lenalidomide and then lenalidomide maintenance. So, perhaps in a year or so we'll have the optimal approach to treatment.

Slide 27: BMT CTN 0702: SCHEMA

I talked a little bit about this donor bone marrow transplant. We have been trying to make this a kinder and gentler treatment. But, in a big national trial, there was no clear benefit to doing the donor transplant over the autologous transplant. And currently, it is primarily conducted only in young patients with very high risk disease and usually in the context of a clinical trial.

Slide 28: Allogeneic Bone Marrow Transplantation

Speaking about clinical trials, I did want to end with some of that, just to give you a little science fiction in addition to all that we're talking about. We've talked about how autologous transplant appears to improve survival, but still, despite that therapy, the majority of patients ultimately will progress in their disease. We've talked about how donor transplants can lead to some patients who are long term doing well, but, because of the graft-versus-host disease or the immunologic effect of donor cells upon the recipients, that it can cause a lot of side effects.

Slide 29: BMT CTN #0102

One area of active investigation is to actually take a person's own immune cells and try to activate them and engineer them to have anti-myeloma properties. But, because they're your own cells, the likelihood that they will cause a graph-versus-host disease, or an attack on the body, is low.

Slide 30: Ex Vivo Activated T-cell Production

And there are a number of studies that have now been conducted that suggest that people who get these engineered cells may have improved immune responses. In this one slide I'm showing you, they have less pneumococcal pneumonia or, more importantly, they have more anti-pneumococcus antibodies.

Slide 31: Restoration of Immunity in lymphopenic individuals

And there are studies going on that are looking specifically about infusing these cells directly engineered against myeloma and, in fact, lymphoma also.

Jonathan W. Friedberg, MD, MMSc
Edward A. Stadtmauer, MD
December 3, 2012

Dr. Edward Stadtmauer

Slide 32: Engineering Tumor Antigen Specificity to Patient Cells

So, it's a very exciting area for the future.

Slide 33: Rationale for Therapy with Natural and Genetically Retargeted T-cells

So, to conclude, I think survival in myeloma has improved substantially over the last decade, particularly in patients under the age of 70. And it's due at least in part to the use of high-dose melphalan and autologous stem cell transplant. I think there is the potential for even longer survival and even for cure when we combine high-dose melphalan and stem cell transplant with the newer agents, lenalidomide and bortezomib.

And you all know that there is the next generation of each of these agents, pomalidomide and carfilzomib, for instance. There is still a lot of work being done utilizing the immune cells and cellular therapy to induce a graft-versus-myeloma effect. And hopefully, when we engineer your own cells, there'll be less of a graph-versus-host disease and the side effects. Though there are real side effects, as we've heard, the potential for GI upset, kidney upset, fatigue and low blood counts, these tend to be manageable in the vast majority of patients, and we continue to find new ways of improving them.

So, I think with that I'll conclude the myeloma session. And then, I think we'll be happy to answer questions on both topics.

Slide 34: Conclusions

Ms. Mabel Maia
Thank you so much, Dr. Stadtmauer, and also thank you to Dr. Friedberg for your clear and informative presentations.

Slide 35: Question and Answer Session

We're going to take our first question from the web audience. This question can actually be addressed by both of you. How do you find an experienced autologous stem cell transplant center?

Jonathan W. Friedberg, MD, MMSc
Edward A. Stadtmauer, MD
December 3, 2012

Dr. Jonathan Friedberg
I'll start and say that, in many cities, there are a limited number of centers that do autologous stem cell transplantation, and they are often affiliated with universities or large medical centers.

I think that this is clearly a procedure that you want to make sure that the team who's taking care of you has a reasonable amount of experience doing these types of procedures. And there are many centers in the country that do more than 20 to 50 of these procedures every year.

Dr. Edward Stadtmauer
I agree. I think that we're very fortunate that virtually every area in the country has one or two centers that are really expert in this procedure. And so, it's uncommon that someone really has to go very far from their home to get expert care.

Ms. Mabel Maia
Great. Thank you. Operator, we'll take a question from the telephone audience, please.

Operator
Thank you. Our next question comes from Barb calling from Wisconsin. Please state your question.

Barb
Hi. I have non-Hodgkin's lymphoma and I had CHOP without Rituxan in January of 2000. It recurred in September of 2006. And so, I was prepared for auto transplant, which I had in February of '07.

The scans showed following that there was success, but then in December of that same year it was back throughout my body. So, my question is, is it because I had not made it a year from the transplant, would you say that the transplant was successful or not, or that maybe there is perhaps contamination, like you said?

And then, also I do get pneumonias easily and often now after I've had a donor transplant. What can I ask my doctor about activating my stem cells? Can you speak to that again?

Dr. Jonathan Friedberg
Sure. I guess this brought up two issues. One is definition of success of a transplant like this. And as I tried to say, that the definition of success of a transplant might differ from patient to patient.

Jonathan W. Friedberg, MD, MMSc
Edward A. Stadtmauer, MD
December 3, 2012

Dr. Jonathan Friedberg
It was a little bit unclear as to exactly what type of lymphoma that this patient had. But, it sounds like it may have been one of the indolent lymphomas where the goal of treatment was simply to prolong a remission. I would say that, in aggressive treatment like this, you would like to see a longer remission than just several months.

Unfortunately, these procedures are only effective in a subset of the patients. And one of the other ongoing studies is to try to better figure out who is eligible from the standpoint of who is going to benefit from this procedure the most.

Dr. Jonathan Friedberg
I'll just briefly comment that the recurrent infections that this patient described are another type of side effect that some patients get after these procedures. In this particular patient's case, the fact that it sounds like she had a subsequent allogeneic transplant would really color the interpretation of what could be causing her pneumonias.

But, I'll say globally that longstanding immune defects do occur in subsets of patients who get autologous transplant. And there are mechanisms that people can look at to try to improve that, including sometimes requiring regular infusions of gamma globulin, which is an immune boosting protein.

Dr. Edward Stadtmauer
I agree with everything that Jonathan said.

Ms. Mabel Maia
Great. Thank you, Barb, for calling in. Our next question comes from the web. If you are a myeloma patient with renal failure and the autologous stem cell transplant is not effective, what are your options?

Dr. Edward Stadtmauer
I'm sorry, this was for myeloma?

Ms. Mabel Maia
Yes.

Dr. Edward Stadtmauer
So, what I primarily was presenting was sort of a first line of therapy for a patient with new myeloma: initial therapy, high-dose melphalan, and autologous stem cell transplant, and then maintenance therapy.

Dr. Edward Stadtmauer
There are many patients, though, for various reasons, who do not get their stem cell transplant in their first line of therapy, and then the disease--when the disease progresses, go back into another remission. And there is some very good data to show that patients who get high-dose melphalan and a stem cell transplant in a second line of therapy can do very well also.

Currently, the practice is, if the patient is younger and healthier, etc., to utilize it primarily in the first line of therapy. But, there is a national or an international trial actually going on right now where half the patients are going to transplant in their first line, half are going to transplant in their second line, and will once and for all determine whether one approach is definitely better than the other.

When a patient starts off with renal insufficiency, it will certainly complicate the side effects and the potential outcome of a stem cell transplant. We actually can routinely do high-dose chemotherapy and stem cell transplant in a patient even if they're on dialysis, but the procedure requires extra monitoring, adjustment of doses, etc.

And in general, that is enough for me to say it is not something that I tend to do in the first line of someone's treatment for myeloma since patients can stay in remission and do very well for a long period of time even without the stem cell transplant. If a patient progresses, however, if this is a patient with kidney dysfunction and dialysis, I tend to do more in a second line of therapy, some high-dose therapy and a stem cell transplant.

Ms. Mabel Maia
Great. Thank you. Operator, please, we'll take our next one from the telephone.

Operator
Our next question comes from Patricia calling from New York. Please go ahead.

Patricia
Hello. Thank you. I had a successful stem cell in 2009. Cytoxan was used initially with lots of very bad side effects. I was then put on Revlimid maintenance for one year, five milligrams, but was taken off because of severe anemia.

My platelets are now up to 120,000. Can I use any kind of maintenance at this time to help prolong the remission?

Dr. Edward Stadtmauer
Oh, that's a very good question. So, we now know that if you take patients who have an autologous stem cell transplant and if you utilize Revlimid maintenance therapy, then

Dr. Edward Stadtmauer
that group of patients seem to stay in remission longer and have improved survival over those who don't take it.

But, that doesn't mean that there aren't many patients who have never taken maintenance therapy. In fact, my longest patient doing well is 17 years now from her stem cell transplant, never had maintenance therapy at all. So, biologically there are still many people who do just fine without maintenance therapy.

And in fact, you've had maintenance therapy. It's just that you needed to stop it because of side effects. And in fact, that's the general indication to stop maintenance therapy, if you either have side effects or if the disease starts progressing.

Dr. Edward Stadtmauer
And so, it's unclear to me that adding more therapy at this point is better than just beginning a period of active observation. And then, should the disease start progressing, then there are many other alternatives for therapy.

That being said, there is one major other agent that has been used a lot as a maintenance therapy, and it's that bortezomib medicine. And so, occasionally that is also used as a maintenance therapy either instead of lenalidomide or in the circumstance when lenalidomide is no longer well tolerated.

Ms. Mabel Maia
Thank you, Patricia, for calling in. Our next question comes from the web. Do patients receive any drugs prior to stem cell collection that help with collection of stem cells from the blood?

Dr. Jonathan Friedberg
I'll start and say, in lymphoma, this has been one of the biggest advances. Historically, the way that stem cells were collected, were usually after standard chemotherapy was given. Sometimes the drug cyclophosphamide, sometimes combinations of chemotherapy growth factors such as Neupogen, G-CSF, or other growth factors would be given, and that allows the stem cells to go into the blood and be collected.

A couple of years ago a new drug called plerixafor was approved. And this agent has really been quite effective in helping the stem cells go into the blood, and frequently allowing us to eliminate chemotherapy from the collection part of the program.

Dr. Edward Stadtmauer
Yes, I agree. Basically all patients do require some form of medication, either chemotherapy, the Neupogen or G-CSF, and/or plerixafor. But, it's been a major

Dr. Edward Stadtmauer
advance to have another agent other than chemotherapy that stimulates the collection of the cells.

Ms. Mabel Maia
Great. Thank you for your responses. Operator, we'll take our next question from the telephone audience, please.

Operator
Our next question comes from Nora who's calling from Florida. Please go ahead and state your question.

Nora
Hi. I had my stem cells collected back in 1999. And I wanted to know, because I only had one transplant, how long would those cells survive? Would they still be good? Could I ever use them if I need them? And what is the shelf life?

Dr. Edward Stadtmauer
That's an interesting question. They have done studies looking back up to 30 years from the collection of stem cells, and stem cells are still alive. But, as time goes on, there is some loss. Some of the cells lose their viability or die, number one.

But, I think even more importantly, the longer we go, harvesting stem cells, storage of stem cells--it's a human endeavor. And, you know, it's in a freezer that's being monitored very closely, but still the longer you go, the more likelihood that there will be some glitch or something that happens.

And so, there is evidence that the longer the cells have been stored, the higher the chance, when the cells are used, that there might be a prolonged period of recovery or that they may not function as well as when they're newly used.

The longest that our institution has stored and then used cells successfully has been a decade, 10 years. But, you know, in fact, we're looking right now at someone who had cells that were stored 15 years ago. But, you know, it's a risk-benefit analysis whether you should harvest more cells or whether you should use the ones that were stored away at the time that you need a transplant.

Ms. Mabel Maia
Great. Thank you, Nora, for calling in. Our next question comes from the web. If someone has been treated with the drug Zevalin, are they able to have stem cell treatment?

Jonathan W. Friedberg, MD, MMSc
Edward A. Stadtmauer, MD
December 3, 2012

Dr. Jonathan Friedberg
I'll address that, and I'll first say globally in lymphoma, one of the issues that often comes up is that certain types of chemotherapy and antibody treatment can damage stem cells and limit our ability to collect sufficient numbers of stem cells in order to proceed with a transplant.

I can say that the plerixafor medication that we mentioned just a few minutes ago is certainly one way to overcome some of this. But, there has been a lot of concern that the drug Zevalin, which is radioimmunotherapy and involves a low dose of radiation that includes some bone marrow exposure, ultimately limits the ability to collect sufficient stem cells.

Dr. Jonathan Friedberg
There have been some patients reported who have had drugs like Zevalin and then gone on and gotten transplant. But, I think that one of the more general conclusions is that people have to be very careful in choosing appropriate agents if transplant may ultimately be something that the physician and the patient want to proceed with.

That's not in any way to say that it was a mistake to get Zevalin. In fact, it's one of the most active drugs for certain types of lymphoma. But, I'm saying generally there are different agents that can make transplant more difficult.

Ms. Mabel Maia
Great. Thank you for that question. Operator, we'll take our next one from the telephone audience, please.

Operator
Our next question comes from Andrea who's calling from New York. Please state your question.

Andrea
Yes. Hello. Thank you. I have multiple myeloma. I was diagnosed three years ago. I was on Revlimid on and off. Then I heard a conference. I decided to go for harvesting. The doctor said it was a very successful harvesting. He got harvesting for two transplants.

My question is, when I went back to the stem cell specialist, he said to me, "Do it now." When I went to my general oncologist, he said to me, "You know, you're in a good maintenance place. You take five grams of Revlimid one day and 10 the next day, and then you're off for a week."

Andrea
So, he said, you know, what would be--you know, if your doctor--what would be the long--the duration if you go for harvesting versus if, since you're in stage one, to just stay on the Revlimid? It's been about three years now.

Dr. Edward Stadtmauer
That's a very good question and a very common question. And it sort of illustrates what I was saying earlier, that the goal of stem cell transplant in myeloma is to prolong remission.

But, as of this moment, especially with the tremendous advances in the agents that we're using for myeloma, the non-transplant agents, the pomalidomides, carfilzomib, and the X new agents that are coming up, more and more the question is being asked,

Dr. Edward Stadtmauer
if patients are in a beautiful remission, how much incrementally does the high-dose chemotherapy and autologous transplant add to outcome?

And the answer is we're still trying to figure that out. There have been studies using lenalidomide from Italy that have recently been reported that show that, even in the era of the newer agents, a high dose of melphalan and a stem cell transplant in a first line of therapy appears to be helpful. But, as I said earlier, utilizing it in the second line of therapy may be similarly good. We don't know for certain.

So, it is an area where there is debate. And you have a perfect example of how very good physicians are thinking one way or the other. So, the ultimate decision is a negotiation with your physicians and also your philosophy, and then speaking to centers that specialize in the stem cell transplant.

Ms. Mabel Maia
Great. Thank you, Andrea, for calling in. Our next question comes from the web. It's a general question. Are there any clinical trials that are following stem cell transplant patients to assess side effects and treatments for them?

Dr. Jonathan Friedberg
I'll say in lymphoma there are a number of clinical trials that have been very important in improving stem cell transplantation, and then new studies that are going on. I think, for example, the role of rituximab in various stem cell transplants has been studied.

For example, a recent randomized study from Europe was published that demonstrated that giving rituximab maintenance after autologous transplant for follicular lymphoma, as well as during the collection phase in follicular lymphoma, had a significant impact on

Dr. Jonathan Friedberg
outcome. I think current studies are looking at different agents for maintenance and, in particular, some of the new targeted agents, following a similar paradigm to what was discussed in multiple myeloma.

And I think, whenever possible, people should seek out these types of studies, because it's only through these studies that we will get better at doing these procedures. And often, this allows patients to have access to some of the newest therapies before they're generally available.

Dr. Edward Stadtmauer
And I agree. I think it's an excellent question. And, you know, given that there are thousands of people in the United States now who have had a stem cell transplant and are long term doing well, the issue of what are the late effects is even a more important question.

Dr. Edward Stadtmauer
And there are retrospective analyses that are going on automatically on patients who have transplant. Most transplant centers in the United States and, in fact, the world register all patients that they see on the International Bone Marrow Transplant Registry, where there's a constant updating and analysis for what are the late side effects, what are the true outcomes going forward. And so, there is a constant surveillance of this question.

Ms. Mabel Maia
Great. Thank you.

Slide 36: Co-pay Assistance and more information

And actually, thank you all for your questions. Our program has come to a close. Please help me thank Dr. Friedberg and Dr. Stadtmauer. We're so grateful to them that they have donated their time with us today.

We hope many of your questions were answered and that the information provided will assist you and your family in your next steps. If we were not able to get to your questions, please call an LLS information specialist toll free at 1-800-955-4572, or you can also reach us by e-mail at Infocenter@lls.org.

Our specialists can provide you with information about lymphoma and myeloma research and clinical trials, health insurance coverage, and other financial assistance for treatment, and other questions you may have.

Jonathan W. Friedberg, MD, MMSc
Edward A. Stadtmauer, MD
December 3, 2012

Ms. Mabel Maia
On behalf of The Leukemia & Lymphoma Society, Dr. Friedberg, Dr. Stadtmauer and I, we'd like to thank you for sharing this time with us today. Good-bye and we wish you well.