WELCOME AND INTRODUCTION

Operator Introduction

Greetings, and welcome to the Autologous Stem Cell Transplantation: Current Perspectives in Myeloma and Lymphoma telephone and web education program.

It is now my pleasure to introduce your moderator Lizette Figueroa-Rivera. Thank you. You may begin.

Lizette Figueroa-Rivera, MA

Thank you and hello everyone. On behalf of The Leukemia & Lymphoma Society (LLS), a warm welcome to all of you. Special thanks to Drs. Joseph Alvarnas and Ivan Borrello for sharing their time and expertise with us today. We have over 850 people participating in today's program from across the United States and several countries around the world, including Afghanistan, Canada, India, Israel, and the Philippines.

Before we begin, I'd like to introduce The Leukemia & Lymphoma Society's Executive Research Director, Yixian Zhang, who will share a few words. Yixian, please go ahead.

Yixian Zhang, PhD

Yes, thank you, Lizette. I would like to add my welcome to the patients, caregivers, and healthcare professionals attending the program today. The Leukemia & Lymphoma Society exists to find cures and ensure access to treatments of blood cancer patients. Our vision is a world without blood cancer. For more than 60 years, LLS has helped to pioneer innovation such as targeted therapy and immunotherapy that have improved survival rates and quality of life for many blood cancer patients.

To date, we have invested over $1 billion in research to advance therapies and save lives. Until there's a cure, LLS will continue to fund promising research from bench to bedside. Additionally, as this program demonstrates, we're the leading source of free blood cancer information, education, and support; and we touch patients in their communities through our 56 chapters across the US. The Leukemia & Lymphoma Society also acts as a voice for all blood cancer patients. We advocate for patients, survivors, and their families, helping them navigate their cancer treatment and ensuring that they have access to quality, affordable, and coordinated care.

We're very fortunate to have as our presenters today Dr. Ivan Borrello and Dr. Joseph Alvarnas, two of the nation's leading experts in myeloma and lymphoma. We appreciate their dedication to supporting our mission and their commitment to caring for patients living with blood cancers. On behalf of LLS and all those we serve, I would like to thank them for providing us today with important information on transplantation as a treatment option for myeloma and lymphoma patients.

And now I will turn the program back to Lizette.
Thank you, Yixian. We would like to acknowledge and thank Takeda Oncology for their support of this program.

PRESENTATION

Lizette Figueroa-Rivera, MA

[Slide 3 – Ivan M. Borrello, MD]

I am now pleased to introduce Dr. Ivan Borrello, Associate Professor of Oncology, Cellular and Molecular Medicine, Director of the Cellular Therapeutics Center, at Johns Hopkins School of Medicine in Baltimore, Maryland.

On behalf of the Leukemia & Lymphoma Society, thank you for volunteering your time and expertise. Dr. Borrello, I am now privileged to turn the program over to you.

Ivan M. Borrello, MD

Thank you, Lizette, and thank you everybody who is online and on the phone for this program. My topic today is discussing the role of autologous transplantation in myeloma.

[Slide 4 – Disclosures]

These are my disclosures, and I would like to start by talking a little bit about the disease.

[Slide 5 – Incidence of Myeloma by Age]

As you can see, this is primarily a disease of the elderly. The median age at diagnosis is around 65 years old, and it continues to go up after that. Unfortunately, what you can also see is that this disease is not unheard of, although somewhat rare, in patients that can be as young as in their early 20s and I've even had cases referred to me of children that were 10 years old. But for the most part, it's a disease of the elderly.

[Slide 6 – Myeloma Symptoms: CRAB]

And I think in contrast to pretty much any other type of cancer where the diagnosis of the disease is pretty much based on the fact that there are malignant cells that can be seen on the biopsy, diseases such as multiple myeloma actually fall into a broader category of diseases known as plasma cell disorders. With the plasma cell being the malignant cell that’s associated with multiple myeloma. Its normal function is to make antibodies; and, obviously, as with any other malignancy, an increase in plasma cells is accompanied with the diagnosis.

However, active myeloma, which is what we will be talking about, is illustrated here. The criteria include at least 30% plasma cells in the bone marrow, and just to know that less than 5% is considered the normal. And there is also a range between 5% and 30%, which are a variety of diseases, including a premalignant condition known as MGUS or monoclonal gammopathy of undetermined significance. Normally these are patients that have up to 10% plasma cells, and the
likelihood of actively developing myeloma is roughly 1 to 2% per year. And so, the vast majority of patients with MGUS never actually go on to develop myeloma. Then there's a disease called smoldering myeloma, which, for the most part, is associated with between 10 and 30% plasma cells and the absence of these CRAB (calcium, renal insufficiency, anemia, and bone disease), which I'll get to in a second. Those patients have, as I mentioned, smoldering or otherwise known as Stage I myeloma; and they have, on average, about a 10 to 20% per year likelihood of conversion to active myeloma. So those patients, unfortunately, at some point will go on to develop multiple myeloma or active myeloma but do not need treatment for the most part in the smoldering stage. And then, there are the patients that have active myeloma, which, as I mentioned, are those that we'll be talking about today.

So, the definition of active myeloma is defined as greater than 30% plasma cells and the presence of these CRAB symptoms and it's an easy acronym to remember. The C stands for a high calcium level, the R stands for renal failure or kidney failure, the A stands for anemia or low red cell counts, and the B stands for bone disease. And you only have to have one of these to be considered symptomatic and to, thus, fall into the category of active myeloma. And you can actually also have less than 30% plasma cells and have one of these symptoms and still be considered active myeloma requiring treatment.

[Slide 7 – Trends in Overall Survival of MM]
This slide shows where we have come, stopping at 2006. And the interesting thing is if you look at the overall survival data, for the most part, until we got to the turn of the century, the curves are practically superimposable, going back as early as 1971.

Now, the interesting thing is that autologous stem cell transplant actually came into effect for myeloma sometime in the mid ’80s; and despite that, it didn't really shift the curves all that much. But we only started beginning to see an improvement in overall survival at the turn of the century; and that has, for the most part, been attributable to the introduction of what we are still calling the new drugs. With the first new drug being thalidomide, then followed by Velcade® (bortezomib), and more recently Revlimid® (lenalidomide), carfilzomib or Kyprolis®, and pomalidomide (Pomalyst®). And, if one were to look at the curves from 2006 on, you would see that they are continuing to improve. And I think this is the one area in which there is much reason for optimism because we are making significant headway pretty much since the turn of the century, due to a variety of aspects, but the major one being the introduction of many of these new drugs.

[Slide 8 – Meta-Analysis of Autologous Transplant vs Conventional Chemotherapy – Overall Survival]
So, the topic of today is to talk about autologous transplant or stem cell transplant. And what this graph shows is what we call a meta-analysis. What that means is that statisticians examine a whole bunch of different studies that reported outcomes comparing transplant versus no transplant and ultimately took all the data from these different trials and tried to come up with a conclusion as to whether there was a specific benefit or not from transplant.

And so, the way to interpret this data is that the line that runs down the middle is the line showing that there is no difference. And on the left, it says "Favors HDT," which stands for high-dose therapy, and on the right it says, "Favors SDT," which stands for standard dose therapy. So, HDT is transplant,
and you can see in the black boxes that most of the black boxes fall to the left, so they're in favor of high-dose therapy or a stem cell transplant; but there have been some trials that actually showed that there was a, that stem cell transplant actually had a negative effect. And, in fact, the patients that didn't get transplanted had a better outcome.

However, when you look pretty much at the last open diamond at the bottom, you can see that that diamond is to the left of the curve; and it really does not overextend past the midline. So, that would, for the most part, the interpretation of that would be that when you take all of these data together, looking at some trials that showed a benefit and other trials that didn't show a benefit of transplant, that in the wash there appears to be evidence of a benefit to transplant.

[Slide 9 – Improving Response Rates with Combination Therapies]
But as I mentioned to you earlier, one of the biggest impacts that we've seen, and since the turn of the century, has really been the introduction of novel therapies. And what we're showing here are a variety of combinations, and I'll highlight a few of them in a second, and what the response is. So, the blue bar is ORR; it stands for overall response rate, which basically means how many patients that received the therapy achieved at least a 50% reduction in their disease burden. So, if their M spike (monoclonal) was two to start with, that means that their M spike got to one or less. And then the bar in the green shows the patients that achieved a complete response, which means that their M spike ultimately became undetectable.

So, going through this a little bit, you can see on the left the first combination is VAD. This was a chemotherapy regimen that was developed in the 1980s. It stands for vincristine-Adriamycin® (doxorubicin)-dexamethasone. This was chemotherapy that was given by IV, and because of the A, the Adriamycin, we could only give between four and six cycles because of the significant heart toxicity. It would cause heart failure. And with that, only about 50% of patients had a response, and the complete response rate, as you can see in the green, was in the single digits.

The first novel drug to come out was thalidomide (Thalomid®), and so the next column of bars is TD, which stands for thalidomide and dexamethasone. And already what you see now is that we went from chemotherapy that required IV infusion over four days and caused people's hair to fall out and caused significant heart problems to two pills that patients would take with the major toxicity being significant neuropathy. But, importantly, both the overall response rate, the blue bar, as well as the green bar, the complete response rate, started to increase.

And so, that was really the introduction of this whole new era. Now skipping ahead, you can see that there is RVD, which stands for Revlimid-Velcade-dexamethasone. Now we are achieving response rates that are over 80%, with complete response rates that are over 20%. And more recently, there has been data, which is the last column, of CarRDex, which is carfilzomib or Kyprolis-Revlimid-dexamethasone, where virtually 100% of the patients are achieving a response. So, again, 100% of the patients are having at least a 50% reduction in their disease burden, with a complete response rate that is over 60%. This alone, chemotherapy alone has really shown the in-ways that we've made; and the take-home message of this chart is that the novel agents have made a difference. But the second important point is that for the most part, and there are a few exceptions, but for the most part combination chemotherapy with three drugs is really what has provided most of this clinical benefit.
[Slide 10 – Is There a Role of Transplant in the Era of Novel Drugs?]
So, because of these incredible response rates that we've seen, and specifically with RVD that I just mentioned that showed roughly a 25% complete remission rate with an overall response rate well over 80%, there was a very important trial that was reported this year at ASH. ASH is our American Society of Hematology meeting that is held in December, and this is data that was reported from a large randomized French trial. And I wanted to walk you through this because this gives some insight as to, whether transplant, is still playing a role in myeloma.

So, these were patients that were newly diagnosed. All patients received three cycles of RVD chemotherapy, so that's Revlimid-Velcade-dexamethasone; and then their stem cells were collected. At that point, the patients were randomized either to go on to get a transplant or to continue with chemotherapy. As you can see, another five cycles of RVD followed by Revlimid maintenance therapy, so just Revlimid alone. And those patients would then get transplanted at relapse.

Now patients that got transplanted received an additional two cycles of RVD chemotherapy after the transplant and then went on to Revlimid maintenance.

[Slide 11 – Transplant Delays Disease Recurrence]
And what you see on this slide is very interesting. That's the three-year PFS, stands for progression-free survival. So, in other words, the patients that were still free of disease at three years were 61% in the patients that got transplanted. ASCT stands for autologous stem cell transplant and versus 48% for the patients that did not get a transplant.

Interestingly, if you look at the complete remission rate, the CR percent, it's significantly higher in the transplant arm compared to the non-transplant arm. So this is interesting and this is significant because we are now dealing with a chemotherapy that is highly effective and overall giving significant response rates; and this really was a question that was out there in the community is with these significantly better drugs, do we even need to do transplants? And I think the answer from this trial is yes, we still do need to do transplants because those patients are doing better.

[Slide 12 – Depth of Response Correlates with Improved Outcomes]
And this really relates to this whole concept of what the depth of response is or what the overall goal of therapy should be. So what this trial, what this data shows is data that was put together by the Spanish Group, that shows that if you look at patients, both in terms of how long it takes for the disease to come back, the PFS, or the overall survival, the OS, you can see that patients with the blue line, those are patients that achieved a complete remission, overall did significantly better than patients that had a partial remission or a VGPR (very good partial response) which means a 90% or a 50% reduction in their disease, which is the red line, which, obviously, did better than patients that had stable disease, which is the light brown line.

So, the conclusions from this data is that the overall goal of therapy should be to try to drive the disease burden down as low as somebody can because the deeper the response, the better their overall outcomes.

And how do we drive that disease burden down? Well I think one way, as I just showed you, was from the transplant itself. But the other way is this concept of maintenance therapy. So, we have known for
many, many years, pretty much since the 1980s when transplant came out, that transplant was capable of reducing or delaying the time to relapse. But unfortunately, in myeloma, it did not appear to be curative.

[Slide 13 – Role of Revlimid Maintenance Following Transplant]

And because we didn't have any drugs that had a relatively low toxicity profile, we were really not capable of giving long-term therapy to patients following transplant. But then these new drugs came out, and that completely changed the scenario. So, this whole concept of giving therapy, even after the transplant, really began to be tested in full starting with the turn of the century, first with thalidomide but more recently with Revlimid.

And what you see, if you look at the graph on the top, is these were patients that were transplanted and either given placebo or given Revlimid as maintenance therapy afterwards, starting roughly somewhere between three and five months after transplant.

And if you look at the upper graph, you can see the blue line are the patients that did not get maintenance therapy, and the red line are the patients that did get maintenance therapy. And there was roughly doubling of the progression-free survival. So, for the patients that were on maintenance, the average time for the disease to come back was around 24 months. And for the patients that got Revlimid as maintenance therapy, the average time for the disease to come back was 48 months. Now when this trial was published in 2012, there did not appear to be any difference in terms of overall survival, but further follow-up data has really shown that even those curves are beginning to separate out.

So, sort of summarizing the salient points that I've discussed so far, the first thing is, is that for the most part, and there are exceptions, patients that are newly diagnosed should be on a three-drug regimen. And the second point is that patients, if they don't achieve a complete remission, should probably consider going on to transplant if they are transplant eligible. And I guess the third point is that maintenance therapy should for the most part, be part of people's treatment regimen. And the reason for that is, again, to drive the disease burden down.

[Slide 14 – The Role of Minimal Residual Disease on Myeloma Outcomes]

One thing that is slowly finding its way into the treatment paradigm of myeloma is this idea of trying to measure the disease burden, even at a molecular level. And so, what we call this is minimal residual disease testing or MRD testing. Now historically the definition of a complete remission is basically an M spike that's undetectable and potentially another test, which is slightly more sensitive, called an IFE or immunofixation electrophoresis, of that also being undetectable. But we now have DNA (deoxyribonucleic acid) tests that can be used to measure the amount of DNA that is still present in the patients at defined times. That's called MRD testing.

And what this data shows, if you look at the graph in the upper left, is you can see that there's a black line on the top and then there's a red line and a green line. What this is looking at is patients that were going to transplant. They looked at how many tumor cells were still present in the graph, in the collected bag of stem cells that were there. And what they showed is that if there were no cells present, which is the black line, their likelihood of progression, of having a relapse, was basically zero going out to seven years.
And in contrast, if you look at the green line, if they had, or even the blue line, if they had a higher amount of tumor present in the bag, then those patients had a very high likelihood of progressing. That pretty much went out to only about a year to a year and a half.

Now this is telling us that getting rid of disease, as to a molecular level, is translating into improvements in long-term outcomes. Well, if you're not able to get to that point with the chemotherapy that you're getting prior to transplant, is there any way that you can alter that?

I just showed you in the previous slide that the use of Revlimid as maintenance therapy translated into improvement in outcomes in patients. And what these graphs on the bottom now are showing is pretty much the same thing. So, if you look at the graph letter D, which is the lower left, what you can see are a red line and a black line. Red line are the patients that had a transplant and then went on to receive maintenance treatment. And you can see that those patients had a significant increase in progression-free survival compared to the patients that were not treated and that basically a lot of this was ultimately a result of converting these patients from detectable minimal residual disease to undetectable minimal residual disease. So, basically the idea is again, that the deeper you go with the overall response, the better your overall outcomes will be.

[Slide 15 – Maintenance Revlimid Improves Minimal Residual Disease]
And that's also shown again here, that patients that underwent transplant, that were MRD-negative, so there was no evidence of disease in these patients, after the transplant and before they started the maintenance therapy did better than the patients that still had some residual disease there. But again, even these patients that were positive, the addition of maintenance therapy could still improve their overall outcomes. So, as a result of that, we have begun to incorporate this MRD testing into, one, a determination of whether patients should go to transplant and, two, how to monitor them afterwards.

[Slide 16 – The Autologous Transplant Process]
Now I recognize that there are probably some people on the line that are relatively new to the whole field and may just have been newly diagnosed, so I thought I would take time to talk a little bit about what transplant actually is, or certainly autologous transplant.

So, really, what autologous transplant is, is a way of delivering high doses of chemotherapy. It's a way of delivering a dose of chemotherapy that basically kills the bone marrow, and so the only way for the patients to survive this high dose of chemotherapy is to then give the bone marrow back.

And so depicted in this cartoon are sort of the steps that are involved in that. The first thing that needs to be done is that the stem cells need to be collected. And the way that's typically done; now historically we actually went into the bone marrow of patients. We took patients to the operating room and took their bone marrow out.

The way it's done nowadays is what's called a peripheral stem cell mobilization. So, this is done with a combination of chemotherapy with some injections that help to detach the cells from the bone marrow or it can just be with these injections alone. And that process is called stem cell mobilization, and it normally takes anywhere from a few days to up to about seven to ten days. Where these cells are detected in circulation, and normally they're removed from a catheter that is present and placed under the patient's collarbone in a procedure that's called pheresis that resembles a lot like dialysis.
for patients that have kidney failure. Basically they have two lines coming out; one line sucks the blood out, collects the stem cells, and the other line sucks the blood in. Once that stem cell product is collected, we freeze it down, and we store it. And then what happens is that patients, when they're actually ready for the transplant, get the high-dose chemotherapy that can be delivered over one to two days. And normally the day after the chemotherapy is given, the stem cells are reinfused; and this is a very anticlimactic process. Basically, these cells are brought to the patient's bedside. They're thawed, hooked up to the IV that's sticking out from under the patient's collar bone, and they're reinfused into the patient. What happens after that is that the patient's blood counts fall, and they normally come up, and it takes about two weeks before their counts are up to a safe point.

[Slide 17 – Transplant Logistics]

The other point that I was asked to sort of highlight was sort of the logistics of this. And, in general, this is what's involved. So, once a patient decides to go to transplant, the first thing we need to do is make sure that their insurance will pay for it. And the second thing after that is to make sure that the patients are actually healthy enough to go to transplant, and so that generally involves several weeks of what we call a pre-transplant evaluation or pre-transplant workup. Which normally entails checking that their heart is okay and making sure that their lungs are okay, repeating a bone marrow biopsy, as well as doing a whole bunch of other tests to make sure that there aren't any viral infections or other issues that may cause problems.

That basically is a mechanism in place to assure the overall safety of the transplant, and I would like to say that although the word sounds bad, for the most part, these have become very safe procedures. And at least at our institution, our likelihood of dying, our transplant-related mortality for an autologous transplant for myeloma has been zero for the past 15 years. So, we have not lost anybody, and I think that's true of most major transplant centers.

So, once patients are given the green light to move forward, they go through what I just mentioned to you earlier, this process of stem cell mobilization, which takes about two weeks. And then once the stem cells are collected, there's a few days' break, and then they start the transplant process, which again, is two days of chemotherapy. Then the stem cells are put in and the day that the stem cells are put in is called Day Zero. And so, when we talk about how many months or weeks after that, it's always in relation to the day that the transplant actually occurs.

And from that Day Zero, it takes about two weeks for the counts to come up, and most patients generally stick around for about another week. And so, the active period of transplant, as outlined here, is about four to five weeks. In general, with the kind of transplant that patients get for myeloma, most patients are able and capable of going back to work by around two months after the transplant.

[Slide 18 – An Approach to High-Risk Disease Marrow Infiltrating Lymphocytes (MILs)]

So, I just want to finish a little bit with some of the work that we’re doing here. And one thing that we’re doing is we have developed this approach of using the patient's cells from the bone marrow called MILs, which stands for marrow infiltrating lymphocytes. We currently have a protocol here that is specifically targeted, patients with high-risk myeloma.
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And so, what we do is we have the patients undergo a bone marrow aspiration like they normally would, but in this case we take out a few more cells. And these cells are then grown up in the lab, and given back to the patient in the context of an autologous stem cell transplant.

[Slide 19 – MILs Logistics]
And so, this cartoon sort of shows that process. So, the patient’s MILs are harvested. This is the bedside procedure that takes about a half an hour. Then the cells are grown in this contraption, which is called a Wave, which basically rocks back and forth. It allows us to grow these cells up to large numbers. Patients then undergo a standard stem cell transplant, and that’s associated with the infusion of these MILs a few days after the transplant.

[Slide 20 – MILs Trial for High-Risk Myeloma J1343 (n=90)]
And out here is outlined the logistics of this, so everybody is getting their bone marrow harvested, and then the patients are randomized. For every two patients that get the MILs, one patient isn’t. And in the context of a transplant, another starting with Revlimid maintenance, roughly two months afterwards.

For the patients that are randomized to the non-MILs arm, they are actually eligible to get the MILs at the time of relapse. And so, what we’re ultimately hoping with this trial to achieve is demonstration that we can make a significant impact with the use of these cells, of these T-cells, in a subset of patients that have this high-risk myeloma, which represents approximately 20% of all newly diagnosed patients. And this is a subset of patients for whom a standard transplant has, for the most part, been a relatively suboptimal type of therapy.

So with that I have concluded. Thank you for your attention.

Lizette Figueroa-Rivera, MA

Thank you so much, Dr. Borrello for your very clear and informative presentation.

PRESENTATION

Lizette Figueroa-Rivera, MA

[Slide 21 – Joseph C. Alvarnas, MD]
It is now my pleasure to introduce Dr. Joseph Alvarnas, Director of Value-Based Analytics and Clinical Quality-Based Analytics, an Associate Professor, Department of Hematology and Hematopoietic Cell Transplantation at the City of Hope in Duarte, California.

Dr. Alvarnas, I am privileged to turn the program over to you.
Joseph C. Alvarnas, MD

Thank you very much for the opportunity to visit with you today. I very much appreciate the dedication of The Leukemia & Lymphoma Society helping to spur better understanding. As Dr. Borrello conveyed, I think, incredibly well, what is inspiring in this field is that the state of the art is changing at a pace that would have been unimaginable. As Dr. Borrello was reviewing transplant and indeed the current standards of care for multiple myeloma, I can go back in my head over the last 20 years to see how rapidly the state of the art has evolved and to the effect that it has really produced better and more meaningful outcomes for patients in ways that I think continue to inspire us.

So, as a patient or a family member or a health care professional, I think part of what's really difficult is not only navigating the complexities of understanding these sets of diseases, but also getting a sense of what are the trends in terms of new technologies, of new opportunities, and of new options for cure in the care of patients.

So, I think what I'd like to do over my discussion is take a broad thematic view of what I view as the start of the art, and also talk about real outcomes for patients produced by existing technologies.

[Slide 22 – Disclosures]
These are my disclosures. I'm consulting for Juno Therapeutics. I serve as a panel co-chair for the National Comprehensive Cancer Network. I’m the Editor-in-Chief of one of the American Journal of Managed Care journals, and I’m on the speaker’s bureau for the Ultimate Medical Learning Company.

[Slide 23 – A Rapidly Evolving Understanding of Lymphoma]
So, going back to the origins of this, I think it’s good to have a historical perspective. The idea of lymphoma, or of cancers that grew within the lymph nodes, were originally described by Thomas Hodgkin back in 1832. He actually described Hodgkin lymphoma. It wasn’t until 1956 that a classification for non-Hodgkin lymphoma was proposed, and over the early portion of my career, we went through four different classification systems. We’re now in the midst of a rapidly evolving other classification system in which nearly 80 different kinds of lymphoma are differentiated on some level, which as a physician is intimidating, as a patient or as someone whose family member may be facing a diagnosis of lymphoma, it makes it seem almost unnavigable.

So, part of the arc in this evolution isn’t that we didn’t suddenly have all these different diseases. It’s that conceptually we’ve moved from a mindset that takes us from looking at what cells look like to understanding them on a far more sophisticated level. That now includes genetic and molecular, and gene-based data or genomic data, protein-based data, proteomic data, and even viral information that may exist within these lymphoma cells to differentiate them in ways. Not to make them intellectual curiosities, but so to find more appropriate individualized medicines to treat them.

[Slide 24 – Incidence of Non-Hodgkin (NHL) and Hodgkin Lymphoma (HL)]
When we look broadly at the non-Hodgkin lymphoma and Hodgkin lymphoma, these are some of the more common blood-based cancers. For non-Hodgkin lymphoma that’s, in fact, the most common of the blood-based cancers. And in 2015 in the United States, 71,850 people were diagnosed with non-Hodgkin lymphoma. It’s about 4.3% of all new cancers. About 19,790 people died from non-Hodgkin lymphoma, but that includes people diagnosed well before 2015.
Over the course of my career, the percentage of patients surviving five years with non-Hodgkin lymphoma has risen from somewhere around 40% to now 70%, and that number continues to rise rapidly.

Hodgkin lymphoma is a, I would call it a subtype of lymphoma. It's a rare entity in that about 9,050 people were diagnosed in 2015. It's only 0.5% of all new cancers. And when you look at overall survival outcomes, nearly 86% of patients diagnosed with Hodgkin lymphoma survive five or more years.

[Slide 25 – Factors That Increase Risk of, or Contribute to Development of Lymphomas]

So, a fair question and, honestly, when I meet with patients and families for the first time, after the initial shock of discussing the diagnosis, the first question is, "Why did this happen?" And for most of the time, we can't say. There are relatively few patients for whom we can say that there was a single event or an exposure that accounted for the development of lymphoma, either non-Hodgkin lymphoma or Hodgkin lymphoma. But at the same time, while we're limited to say exactly why the lymphoma arose, for some patients we do have a sense of why lymphomas can arise.

For those who are progressively older, age is a risk factor. There are also inherited genetic disorders, typically those associated with immune or blood abnormalities. These include Wiskott-Aldrich syndrome, X-linked hypogammaglobulinemia, Chédiak-Higashi syndrome, and ataxia-telangiectasia syndrome.

Viral infections, actually, can play a very important role in the evolution of non-Hodgkin lymphoma and Hodgkin lymphoma. Epstein-Barr virus is associated with Hodgkin lymphoma and also particularly highly associated in patients with HIV-associated non-Hodgkin lymphoma. Cytomegalovirus, human herpesvirus 8, the human T-cell leukemia virus and hepatitis C viruses can all be associated with an increased risk of the development of non-Hodgkin lymphoma, and even bacterial infections.

The *Helicobacter pylori*, which is an organism associated with gastric ulcers, can also lead to the development of relatively unaggressive lymphomas of the stomach. These are sometimes called MALTomas. So, there's a variety of factors that can contribute to the evolution and development of lymphoma.

[Slide 26 – Hodgkin Lymphoma (Reed-Sternberg Cells)]

So, what I'd like to do is give you some pictures without belaboring this idea. When people talk about Hodgkin lymphoma, they talk about the Reed-Sternberg cell being the classic cell that defines the diagnosis. So, you can see the red arrow pointing at something that looks like a sideways set of owl eyes. That's a Reed-Sternberg cell, and on morphology, or what the slides look like, this is classically how the diagnosis of Hodgkin lymphoma is made.

[Slide 27 – Diffuse Large B-cell Lymphoma]

For the next slide, this is diffuse large B-cell lymphoma. Now typically a lymph node has a structure to it, almost like the plan of your house, rooms organized in various ways. In a diffuse lymphoma, the entire architecture of the lymph node is replaced by cells, often, which many of these cells look
exact like each other. And this is the most common form of non-Hodgkin lymphoma, diffuse large B-cell lymphoma, accounting for about 40% of all patients diagnosed with non-Hodgkin lymphomas.

[Slide 28 – Burkitt Lymphoma]
The next slide is one conveying a picture of Burkitt lymphoma. This is a more aggressive form of non-Hodgkin lymphoma. But, I have to say that the whole idea of how we diagnose lymphomas has changed in that we’ve now moved into using additional information.

So, taking that information of Burkitt lymphoma, we actually look at the genetic information.

[Slide 29 – Characteristic Genetic Changes Associated with Burkitt Lymphoma]
Burkitt lymphoma can be associated with a nonrandom chromosomal translocation between chromosome 8 and 14 that allows us to be more refined in the diagnosis of that lymphoma. And, as you’ve heard in the last two State of the Union Addresses, there’s been a push towards this idea of personalized medicine, in which we’re going to leverage genetic data and protein-based data to make even more specific diagnoses.

[Slide 30 – Characterizing Aggressive Non-Hodgkin Lymphoma on a Genomic Level]
And in this slide, you can look at what represents a gene set of tens of thousands of genes where you’re able to simultaneously look for either overactivity or underactivity of genes. And in doing so, you can see that you can take a lymphoma that for all purposes looks exactly the same on a slide and differentiate it into five different kinds of lymphomas. The ABC is activated B-cell lymphoma, the GCB is germ cell B-cell lymphoma, the PMBL is primary mediastinal B-cell lymphoma. So, based upon this appearance, we can actually move forward in terms of more specific therapies.

[Slide 31 – Immense Diversity of Lymphoma Subtypes]
So, again, there’s an immense diversity of lymphoma subtypes. So, I think part of what I’ve been trying to frame is this idea that as someone who may be diagnosed with lymphoma, as you speak with your physician, your lymphoma may be radically different than that, of someone else seeing the same doctor. And, again, there are nearly 80 subtypes of lymphoma. The prognosis and treatment may markedly differ broadly in terms of categories. More than 80% of lymphomas diagnosed in the United States are B-cell lymphomas. T-cell lymphomas are relatively rarer.

In general, when we describe lymphomas, one of the things that enters into that description is whether or not the lymphoma maintains an architecture that you might see in a normal lymph node. So follicular lymphomas, those that in general maintain that architecture, are likely to be less clinically aggressive; whereas those with a diffuse architecture are those that are going to likely be more clinically aggressive.

And one of the questions that this begs is often patients ask, "Do I really need to have a lymph node biopsy in order to make the diagnosis of lymphoma? Can’t I just have a fine needle aspirate?" And I think that one of the things that’s really important for our pathologists is having enough tissue to make a correct diagnosis. Because every other decision you’re going to make comes based upon having the diagnosis correct. So, in general, a biopsy is going to be superior to a fine needle aspirate, which is why the doctor may need to repeat a procedure for diagnosis. Or, alternatively, even if you have a
tentative diagnosis, a lymph node biopsy may still be necessary in order to give us the best and most relevant information to help make the best therapeutic decisions for the patients for whom we care. One of the things I was going to add is, and this is very important conceptually about lymphoma, is that unlike some solid tumors where once the disease has returned after initial therapy, it may be incurable. For diseases like lymphoma, both non-Hodgkin, some of the non-Hodgkin lymphomas and Hodgkin lymphoma, following a relapse or following a failure to achieve an initial remission, we still have potentially a second or even a third chance to cure that person.

And one of the ways that we can get toward that cure is through a use of an autologous blood stem cell transplant.

[Slide 32 – Autologous Blood Stem Cell Transplantation] Now I don't want to repeat a lot of what Dr. Borrello covered, but here's a graphic kind of talking conceptually about a transplant.

[Slide 33 – Cumulative Plot of Transplant Recipients in the US by Transplant Type] In the United States, you can see that the number of transplants performed annually has gone up quite dramatically with the blue line showing autologous transplants and the green line showing allogeneic transplants.

Now we haven't really differentiated what an allogeneic transplant is. An autologous transplant is a transplant where a patient serves as their own donor. And, as Dr. Borrello mentioned, what that transplant is achieving is that it's using far more intensive chemotherapy as a way of eradicating the lymphoma. But your body has a speed limit on how much chemotherapy you can get, and that speed limit or intensity limit, if you will, is one in which the bone marrow is most likely to be damaged before your heart, lungs, liver, kidneys, or bladder get damaged. Now normally when we're giving standard combinations of non-transplant chemotherapy, we're not able to exploit that difference because if we tried to give you more, we would risk wiping out the bone marrow.

So, what the bone marrow transplant does or blood stem cell transplant does it basically allow us to put someone's bone marrow or blood stem cells into witness protection while very strong chemotherapy is given; and then those cells can be returned to the patient. They're given intravenously. The transplant itself is a nonsurgical procedure, and it's extraordinarily well tolerated, as Dr. Borrello indicated.

[Slide 34 – Autologous Hematopoietic Cell Transplantation BMT CTN/AMC 0803/071] Here's kind of a graph showing how this works. So, people's blood stem cells are mobilized. So, one way to think about this, there's a lot of discussion about stem cells these days. But think of the stem cells as a cell that has two really important capacities. One is it can make everything within a tissue. And the other important capacity that it has is it can make itself and many copies of itself. So, within the bone marrow, about one cell in 10,000 is one of these mother cells or hematopoietic stem cell. And that cell can make everything within the bone marrow, all the cells that will go on to form every element of blood. It can also go on to form more stem cells. So, these cells get cryopreserved. They get collected. Usually people may get a combination of chemotherapy and a growth factor like filgrastim (Neupogen®). And then using a machine, which is the same machine they used to collect
platelets in the hospital, they can collect blood stem cells and, as Dr. Borrello indicated, freeze these cells.

And then we’re liberated to give either a combination of chemotherapy and radiation therapy or a combination of several chemotherapy drugs. In this instance in the slide, a regimen called BEAM (carmustine, etoposide, cytarabine and melphalan), and then it's followed by the stem cell transplant.

[Slide 35 – Collection of Autologous Blood Stem Cells]
This is actually the catheter that Dr. Borrello referred to. This is a Hickman catheter that's used to collect the stem cells.

[Slide 36 – Autologous Stem Cell Transplantation]
And that’s actually a bag of stem cells. So, the cells are given IV.

[Slide 37 – Reconstitution of Hematopoiesis After Transplantation]
They have a way of migrating back into the bone marrow where, over time, they can fully and totally reconstitute all of the elements of the blood for the life of the patient.

[Slide 38 – Criteria for Autologous Stem Cell Transplantation]
A good question is who should get a transplant? Well, for people with non-Hodgkin lymphoma, those who would benefit from a transplant are those with a chemotherapy-sensitive, relapsed, and persistent aggressive non-Hodgkin lymphoma. So, if someone has a non-Hodgkin lymphoma where there’s a question of whether or not they’ve achieved a remission or if they failed to achieve remission or if they were once in remission and it's come back, then that’s someone who can potentially benefit from a transplant.

Those patients who we do consider to be transplant candidates need to have adequate organ function. So, part of the pre-transplant process involves testing heart function, lung function, liver function, kidney function to ensure that the chemotherapy combination used prior to transplant will be tolerable. And then the ability to collect and mobilize adequate stem cells, like we talked about, would be necessary because we cannot do a transplant in any patient for whom we can't collect stem cells. That's a deal breaker. So, part of what patients will contend with over time is that as you're going through the collection process, your doctor will fill you in on how many stem cells you've collected.

[Slide 39 – Trends in Autologous Transplants by Recipient Age*]
So, a couple of trends that we've seen, these are national data from the Center for International Bone Marrow Transplant Research (CIBMTR); and these are transplants for people with leukemias and lymphomas, and they show three important trends.

The first is, is that the number of transplants that have gone on nationally remain at a very high number for this indication. Transplant constitutes a very important form of therapy for patients with these diseases. The second thing is that in the past, transplant was restricted to patients less than 50 years of age, when I started, then later people less than 60 years of age; and now we can transplant patients based upon their organ status, their performance status, and I've actually transplanted patients up to 80 years of age. So, this is a technology and a form of therapy that may be more broadly applicable than when we started.
[Slide 40 – Indications for Hematopoietic Stem Cell Transplants in the US, 2013]
In terms of who gets transplants, again, I just want to show you one of those middle columns that autologous transplant plays a very, very important role for patients with NHL, that's non-Hodgkin lymphoma, and HD, which is Hodgkin lymphoma. The majority of patients who get transplants for either Hodgkin lymphoma or non-Hodgkin lymphoma get autologous transplant. Some, however, may get a transplant from a brother, sister, unrelated donor, cord blood unit, half-matched donor. Those are called allogeneic transplants; and I'm not going to touch upon those today, but just to say that if someone's in a discussion with their physicians and an autologous transplant is not appropriate for some clinical reason, that it may be preferable to move on with an allogeneic transplant.

[Slide 41 – Survival After Autologous Transplants for Hodgkin Lymphoma, 2003-2013]
So, in terms of survival, I'd like to kind of reiterate the story that Dr. Borrello mentioned, which is transplant can be extraordinarily effective and helpful in helping patients survive either recurrent lymphomas or lymphomas that never went into remission. So, for patients with Hodgkin lymphoma who are sensitive to chemotherapy and undergo transplant, at six years post-transplant, more than 65% of patients are alive and doing well. Even those with Hodgkin lymphoma who have disease that's resistant to chemotherapy may benefit from an autologous transplant.

[Slide 42 – Survival After Autologous Transplants for Follicular Lymphoma, 2003-2013]
The next slide shows outcomes for patients undergoing transplant for follicular lymphomas. Follicular lymphomas are those that tend to be less aggressive. But patients can also potentially benefit from an autologous transplant for follicular lymphoma. Again, the outcomes are better for those with chemotherapy-sensitive disease versus those with a chemotherapy-resistant disease. And follicular lymphoma is one in which the patient and their physician may have a discussion as to whether or not an allogeneic transplant, that's the brother, sister, unrelated donor transplant, may be preferable to an autologous transplant.

[Slide 43 – Survival After Autologous Transplants for Diffuse Large B-cell Lymphoma (DLBCL), 2003-2013]
For diffuse large B-cell lymphoma, this is, again, the most common lymphoma diagnosed in the United States. And it was the first disease really for which to show that autologous transplant was the standard of care for the treatment of patients with relapsed and persistent lymphoma, and we continued to show the ability to cure about 60+% of patients who have relapsed or refractory lymphoma.

[Slide 44 – Survival After Transplants for Mantle Cell Lymphoma, 2003-2013]
In terms of mantle cell lymphoma, mantle cell lymphoma is a variant of non-Hodgkin lymphoma that's very aggressive and may often have a complete remission with standard chemotherapy that's very brief in nature. So, a number of institutions have looked at using either autologous or allogeneic transplant as a way of preventing the disease from coming back. And, again, by using these more aggressive augmented strategies that integrate transplant, we can potentially improve survival outcomes for patients affected with even very, very aggressive variants of non-Hodgkin lymphoma.
[Slide 45 – HIV Infected CD4+ T-cells]
I'm just going to take a minute here to talk about HIV-related lymphomas. I've chaired some national trials on HIV-related lymphoma. And this is actually, the little yellow particles, are HIV infecting a T-cell. There used to be an idea that for patients with HIV infection or those who were immunocompromised that transplant may not be appropriate or that standard therapies might not be appropriate.

[Slide 46 – Autologous HCT for ARL]
Since the availability of highly active antiretroviral therapy, what we've seen is that numerous groups, including groups at City of Hope, groups in Europe, groups in the United States based out of Johns Hopkins, have demonstrated that patients with AIDS-related non-Hodgkin and Hodgkin lymphoma can achieve survival outcomes equivalent to those of patients not infected with HIV.

[Slide 47 – Progression-Free Survival]
The next slide actually compares – this is a study that I helped co-chair, along with Dr. Richard Ambinder, from Johns Hopkins that looked at progression-free survival for patients with AIDS-related lymphoma, and that's indicated in the black line versus patients without HIV infection with the same lymphomas.

[Slide 48 – Overall Survival: HIV-Infected Patients vs. 151 CIBMTR non-HIV-Infected Patients]
And survival outcomes and progression-free survival outcomes are comparable between these groups.

[Slide 49 – CD4+ T-cell Reconstitution Post-AHCT]
So, when we talked about the issue of autologous transplant, the standards of care that apply to people not infected with HIV apply to those infected with HIV; and that includes using autologous transplant. After an autologous transplant, the T-cells recover very nicely in patients with HIV infection.

So, what's coming in the future? And I'm just going to take a few seconds here to think differently about this. So, if autologous transplant is one of the standards of care for managing persistent or relapsed non-Hodgkin lymphoma, we're still in an era where not everyone is cured at this moment. So, as we see these new molecules and Dr. Borrello talked about a host of new therapeutic molecules sort of being combined in creative ways, that's also being seen in non-Hodgkin lymphoma.

Transplant can provide a platform where we can adapt these immunological therapeutics or small molecules in the context of transplant in order to better improve patient outcomes.

[Slide 50 – Growing Armamentarium of Immunotherapeutic Agents for B-cell Malignancies]
Here's a list of some of the important immunotherapeutics that are available for patients with B-cell malignancies. They include monoclonal antibodies, monoclonal antibody and drug conjugates, bispecific antibodies, and then one of the, I would say, hot areas of new therapeutic growth is in the use of T-cell-based therapeutics.

So, I'm just going to take a moment here to talk about chimeric antigen receptor T-cells.
So, again, we talked about the issue of non-Hodgkin lymphoma and diffuse large B-cell lymphoma in particular that not everyone is cured. So, how can we potentially leverage the opportunities created by transplant to improve patient outcomes further?

Slide 52 – CAR T-cell Therapeutics

Well, one way is to adapt the power of the body's own immune system in order to target it against residual lymphoma cells post-transplant. So, T-cells, I characterize them as the traffic cops of the immune system. They restore order; they hunt down cells that don't belong, like cancer cells. And they can target tumors through a T-cell-specific tumor, killing a series of mechanisms.

So, the whole idea here was can we create T-cells that are specifically targeted at killing the diffuse large B-cell lymphoma or other B-cell malignancies.

Slide 53 – Adoptive T-cell Therapy for Cancer

So you can, in fact, take cells from a person, reengineer the T-cell receptors so it will recognize a molecule found on a tumor, like CD19, which is surface protein, expand those cells, and then give them to the patient.

And you might even use those cells after transplant where you maximally reduced the tumor burden in patients.

Slide 54 – Platform for manufacturing TCM Derived CD19CAR+ T-cells

So, we can take these cells again out of the body and through a series of steps reengineer them; and you actually see in that little flask on the right growing T-cells that can be reinfused back into the patient.

Slide 55 – Promise and Risks of CAR T-cell Therapeutics

So, right now, we have a number of therapeutic trials using CAR-engineered, that's chimeric antigen receptor T-cells, in patients who have undergone prior autologous transplant. Some of the potential risks of using these immune system-based therapies include cytokine release syndrome, where as these cells go about hunting down tumor cells, they can release an enormous number of immune-mediating hormones that can cause blood pressure changes, fever. You can also get tumor lysis syndrome, which can injure the kidneys as a result of breaking apart large amounts of B-cell tumors. Patients can get neurological toxicities, and even for some they can have persisting low normal B-cell counts after therapy.

Slide 56 – Summary of Future Directions

So, I think that while I haven't given you one specific treatment for one particular type of patient, what I hope to convey is that the treatment for patients with relapsed/refractory non-Hodgkin lymphoma and Hodgkin lymphoma is increasingly effective and that autologous transplant plays a very, very important role in the cure of patients with relapsed, persistent, non-Hodgkin lymphoma and Hodgkin lymphoma. Even patients with HIV infection can benefit from transplant with outcomes equivalent to those without HIV infection. And over time you may see transplant evolve to not only be a therapy in
and of itself, but also to provide a platform where we can better target the immune system to help improve cure rates and help bring meaningful therapy to patients in need.

[Slide 57 – Why This Work is Never Complete]
Ultimately, this work is never complete because we serve the patients who we have the fortune to meet, encounter, and speak with.

This is our picture from our recent bone marrow transplant reunion, and at the City of Hope, we’ve performed more than 13,000 transplants over the last 40 years. And, over the course of each year, we’ve seen not only the technologies evolve in ways to make this more meaningful for patients, but we’ve also seen that science and the continued innovations coming daily really make a profound difference in people’s lives.

I thank you very much for this opportunity to speak with you today; and, again, I thank the organizers of this talk and Dr. Borrello for my opportunity to participate here.

Lizette Figueroa-Rivera, MA

Thank you so much, Dr. Alvarnas, for your very extensive presentation.

QUESTION-AND-ANSWER SESSION

Lizette Figueroa-Rivera, MA

[Slide 58 Question & Answer Session]
It is now time for the question-and-answer portion of our program.

Lizette Figueroa-Rivera, MA
We’ll take the first question from our Web audience. Dr. Borrello, Ernestine asks, "I only have one kidney. I lost the other one to cancer, then diagnosed with myeloma. Could I be a candidate for autologous stem cell transplantation?"

Ivan M. Borrello, MD

The answer is assuming that the kidney function of the remaining kidney is intact, yes. We have a cutoff here at Hopkins of a creatinine of 2.0, so we do not take patients that have a creatinine that is greater than 2.0. But if it's less than that, it should be fine.

Lizette Figueroa-Rivera, MA

Thank you. And the next question, Dr. Alvarnas, Liz asks, "I had my stem cell transplant for non-Hodgkin lymphoma almost 14 years ago. I would like to know if there are any long-term effects that I should be concerned about or watching for. Thank you."
Joseph C. Alvarnas, MD

I think you've asked a great question. As we watch patients who survive transplants longer and longer, I think that part of what we realize is that transplant can have some long-term impacts. Depending upon the type of therapy that people receive, whether it was radiation containing or non-radiation containing and whether or not drugs like etoposide were used to help mobilize stem cells, there are some side effects.

So, one is that the chemotherapy and mobilization sometimes can cause damage to blood stem cells, resulting in the development of a malignancy or pre-malignancy like a myelodysplastic syndromes. Patients can also have long-term toxicities like neuropathies; and we know that certain forms of delivering high doses of radiation can cause scarring to the lungs or even to the heart.

So, I think part of what's really important for anyone who's undergone a prior transplant is that their primary care is fully informed of that transplant and can work closely with expert centers to ensure that screening is necessary or certain risk reduction strategies, as necessary, are implemented.

Lizette Figueroa-Rivera, MA

Thank you, doctor, and we'll take the next question from the telephone audience please.

Operator

Our next question comes from Elizabeth, calling from Massachusetts.

Elizabeth from Massachusetts

Hello, yes, thank you for taking my call. Please discuss the effectiveness of a second autologous stem cell transplant with original stem cells collected maybe eight to ten years prior to the patient's initial autologous stem cell transplant.

Ivan M. Borrello, MD

Is this for myeloma or for lymphoma?

Elizabeth from Massachusetts

Oh, for multiple myeloma, yes.

Ivan M. Borrello, MD

Oh, okay. So, the idea of a second- there are two types of second transplants that can be done. One is an approach called tandem transplant, where the second transplant is done somewhere between four to six months after the first, and then there's what you're referring to, a second transplant at the time of relapse.
In general, our approach has been, and this is different in the different institutions, but our approach has been that if patients—So the second transplant will give you roughly about half of the benefit that you got from the first transplant. So, if you relapse after a year from the first transplant, you'll probably only get six months with the second transplant.

And so, our approach has been that we generally consider a second transplant in patients that are at least five years out from the first one because then you're talking about a reasonable benefit. So, if you're eight years out, I mean I think that certainly would be something that would be very reasonable to do.

In terms of the source of stem cells. If your stem cells have been collected and they're frozen in a place in which you can be sort of assured of the overall quality, there's probably a better reason to use those cells than to undergo collection of a new product that may have been a little bit more beat up with more chemotherapy after the time of relapse.

**Lizette Figueroa-Rivera, MA**

Thank you, Elizabeth, for the question. And our next question comes from the Web audience. Dr. Alvarnas, Dawn asks, "Is it true that the best success rate for follicular transformed to diffuse large B-cell lymphoma is a stem cell transplant?"

**Joseph C. Alvarnas, MD**

You know, you've asked a very interesting question, and I like the caveat. So, I do believe that for patients with chemotherapy-sensitive transformed lymphoma, an autologous transplant would be the best approach.

For the general audience, one of the things that I did not mention in my talk is that the type of lymphoma that someone has can change over time. So with follicular lymphomas, somewhere around 1% of people per year have an evolution from that less aggressive follicular form to a more aggressive form of lymphoma, usually a diffuse large B-cell lymphoma or a Burkitt lymphoma because the lymphoma changes its biology and becomes much more aggressive. Than the standard approach, that we would recommend at my center would be treatment with a standard chemotherapy regimen, collection of blood stem cells, and then an autologous transplant for those patients.

**Lizette Figueroa-Rivera, MA**

Thank you, doctor. And Dr. Borrello, the next question is for you. Joel asks, "Is autologous stem cell transplant ever appropriate for Stage I smoldering multiple myeloma? If so, what are the criteria?"

**Ivan M. Borrello, MD**

That's a very interesting question. As I mentioned, when I was sort of going through the staging, right now the standard of care for smoldering myeloma is no therapy. Although, I will say that there has been some very interesting data with the use of Revlimid in combination with dex (dexamethasone)
that is showing a potential benefit and I think over the next five to ten years we'll start seeing subsets of smoldering myeloma treated.

Basically, what's happening in the smoldering category is that patients now are being divided into low, intermediate, and high risk, based on their likelihood of progressing to active myeloma. I would say the short answer would be I would only even contemplate something like that in the context of a clinical trial. I don't think it would be appropriate to undergo something as significant as an autologous stem cell transplant in a person who has overall a very long, natural progression of the disease if there wasn't a specific question that was being answered, as would be in a clinical trial.

*Lizette Figueroa-Rivera, MA*

Thank you, Dr. Borrello. We'll take the next question from the telephone audience please.

*Operator*

Our next question comes from Gerald, calling from Maryland. Please state your question.

*Gerald from Maryland*

Hello, I am a mantle cell lymphoma patient. I had high-dose Cytoxan® seven years ago. I'm still in remission. If my disease returns, my problem is that I have 2.8 cr-, I can't think of the word for it. My kidney function is 2.8. What would be the most likely course of treatment?

*Joseph C. Alvarnas, MD*

This is Joe Alvarnas. You know, I think that you've asked a great question, which is you've done very well with your form of mantle cell lymphoma, and I think your desire to know what to do next is important. I think that there are a number of medications available that can be used to treat mantle cell lymphoma. Drugs like Velcade® would not have been used 14 years ago. That's the drug bortezomib. It belongs to that class of proteasome inhibitors. There are also several medications on clinical study that might be able to play a role.

My hesitance at giving you a specific answer is that there are a number of new technologies in play that could potentially play a role, everything from the new therapeutics that are on clinical trials to CAR T-cells, to other medications. So, I think that when we think about the possibilities, there's such a rapid evolution in technology that I'm loathe to give you a global answer.

As Dr. Borrello indicated, kidney function can play a role in our decision-making, but for drugs like bortezomib, we can use them in people whose kidneys are impaired. So, I wish I could give you a precise answer, but the good news is that the state of the art is evolving at such a rapid pace that whatever answer I give you now might be superseded by something new that could come up quite quickly.
Lizette Figueroa-Rivera, MA

Thank you, doctor, and thank you, Gerald, for the question. The next question is from Nora. "What is the life expectancy of stem cells that are stored? Mine were stored in the fall of 1999. Should I need them now or in the future, would they still be useful or should a new collection be performed?"

Joseph C. Alvarnas, MD

This is Joe Alvarnas. I'm going to take that one because I ran a stem cell lab for many years. So, unlike most medicines that are on the shelf with an expiration date, blood stem cells don't have an expiration date. When they're well preserved, as Dr. Borrello indicated, in a very high quality, controlled laboratory setting, we don't know how long the cells can go.

I know of one example from MD Anderson Cancer Center where someone was transplanted successfully using cells that had been cryopreserved 17 years beforehand. So, ultimately we don't know the answer. Cells may be viable far, far longer than we anticipate. And I think if those cells were required, then the two questions that might arise are is your marrow healthy enough to be mobilized successfully again, and based upon studies that can be done with reference files, how does the quality of those preserved cells look? But, as of right now, we don't know what the expiration date is for these cells, as long as they're cared for well. And that would be the industry standard, honestly.

Lizette Figueroa-Rivera, MA

Thank you, doctor, and we'll take the next question from the telephone audience please.

Operator

Thank you. Our next question comes from Karen, calling from Michigan. Please state your question.

Karen from Michigan

Yes, I have a question with regards to something Dr. Borrello mentioned a little bit ago. If a person has had a stem cell transplant for multiple myeloma, were you saying that after a certain period of years of being in remission you could actually have more stem cells harvested?

Ivan M. Borrello, MD

No. What I was saying is that our general approach has been to only consider a second transplant if patients have been in remission for an extended period of time and we've arbitrarily set five years. I mean you can, however, and maybe this may be what you're asking. If you were to go seven, eight years with a first transplant, then relapse, and you did not have stem cells saved, you could have your stem cells recollected at that point, after you've gotten chemotherapy at the time of relapse. I would not necessarily recommend arbitrarily collecting stem cells when you're in remission because it's unclear what one would actually do with those cells at that point.
Thank you. Now we'll take the next question from the Web audience. Doctors, Kathy asks, "Is there a way to give chemotherapy to the cells when they are outside of your body?"

Joseph C. Alvarnas, MD

This is Joe Alvarnas. So, it's interesting you ask that because that takes me way back to my early transplant days. We used to do something called purging where we would collect, back then it was typically bone marrow, and we did this often for patients, at least back when I was at Stanford, for people with acute leukemia where we would take their bone marrow and then baste them with a version of the drug cyclophosphamide and then wash that out. And the idea was that you were purging the bone marrow of any bad residual leukemia cells there.

These days, the idea of purging marrow or blood stem cells is something that we have in general gotten away from, but I don't know of any center still using chemotherapy on blood stem cells ex vivo. It's something that I think historically we have done in the past. But as technology has advanced and as our information has advanced as well, we really don't do that anymore.

Ivan M. Borrello, MD

I would just like to add, for those of you interested in the myeloma side, that there was, in addition to the chemotherapy that Dr. Alvarnas mentioned, there was also a trial done for myeloma in the 1980s. Where stem cells were collected and then they did a process where they saved the actual stem cells, which are cells that are called CD34 cells. And so, they basically showed that they could get about a thousand-fold reduction in the amount of tumor contamination, so this is without chemotherapy.

And so, they had these two groups of patients, and the ones that had the stem cells that were clean versus the ones that had nothing done to them, and there were no differences in outcomes. And so, the conclusions of that study were that when patients relapsed with myeloma, it's not because of the contaminating tumor in the stem cell product; but it's because of the tumor in the body that has not been effectively killed by the chemotherapy that the patients receive. Which is why we've gotten away from this whole concept of cleaning up the bone marrow or the stem cell product.

Lizette Figueroa-Rivera, MA

Thank you, doctors. We'll take the next question from our phone audience please.

Operator

The next question comes from Richard, calling from New Jersey. Please state your question.

Richard from New Jersey

Hello, doctor, how are you?
Joseph C. Alvarnas, MD

Fine, thank you. How are you doing?

Ivan M. Borrello, MD

Good.

Richard from New Jersey

Good. Thank you for being advocates and actually crusaders for the fight against multiple myeloma. My question is in '09 I received a stem cell transplant, which only lasted two years. Then I had to wait 16 months after that to have at least 10% of the cancer back in my plasma. But the thing was I went on that clinical trial for ixazomib. Now it's called Ninlaro®. So, anyway, I had a choice three months ago because I relapsed of having Ninlaro.

I said to the doctor, "I would like to know if I was part of the 720 people who half got a placebo and half got the real medicine. I said my choice would be a lot easier if I knew if I got the placebo or not," and they won't tell me.

I wanted to know if I was on part of the trial with the placebo or the Ninlaro, and then my choice would be a lot easier versus the other three regimens that they recommended.

Ivan M. Borrello, MD

So, I mean, I can tell you that normally when I've been involved in placebo-controlled trial, when patients relapse, we're able to tell them what arm they're on. So, I would maybe go back to your doctor and ask them if there's any way that that can be found out.

Joseph C. Alvarnas, MD

This is Joe. I would agree. I think one of the key priorities in a trial is to ensure that the trial is conducted in a way that's beneficent for patients. And if you're having difficulty in getting those results, then I would very strongly encourage you to speak with the trial sponsor, and then escalate that conversation further if you're not getting the answers that you deserve. Because when we take patients into clinical trials, and I think at both of our centers that's a very important part of what we do, protecting the rights of research subjects is our highest priority, rather than protecting any other interest related to that. So, I think it's well within your rights to ask to have your concerns escalated and get the answers that you deserve.

Lizette Figueroa-Rivera, MA

Thank you, doctors. And the next question comes from Karen. "Do you feel a person should be considered transplant ineligible based on age alone?"
So, I can tell you that here at Hopkins we have gotten away from that. What we do is we look at a biological age. So, I think we all know of 50-year-olds that look like they’re 80 and of 80-year-olds that look like they’re 50. So, our general cutoff for myeloma stem cell transplant has been 70, but we’ve certainly transplanted people up to 75, and we’ve also excluded people in their 50s because of significant complications.

Joseph C. Alvarnas, MD

I agree 100% with that, and even on our clinical trials, we’ve now really embedded a functional approach, rather than a particular fixed age limit.

Lizette Figueroa-Rivera, MA

Thank you, doctors. And the next question comes from the Web, from Alexis. "Is it common to continue to experience chronic pain and fatigue, even after achieving remission?"

Joseph C. Alvarnas, MD

This is Joe. I can tell you from the lymphoma perspective for patients who’ve undergone intensive therapy; it can take a long time to feel yourself. For patients with autologous transplants, even though many of them can return to work relatively quickly, patients may report fatigue, the need for naps, not feeling their usual level of energy for a year or more after an autologous transplant and far longer after transplant from brother, sister, unrelated donor. So, fatigue and this issue that we call asthenia, just not feeling right, can be a significant complication of cancer care.

Lizette Figueroa-Rivera, MA

Thank you, doctor. And the next question comes from the Web. Grace Ann asks, "Are there any current treatments, drugs that will or would interfere with patients' ability to medically qualify for transplant?"

Ivan M. Borrello, MD

You know, in myeloma for a standard transplant, I can't think of anything. Now there are drugs that may make collecting stem cells a little bit more difficult. So, for example, Revlimid can interfere with our ability to collect stem cells; but I can tell you that, and this is what we've started doing, stopping the drug about three weeks prior to beginning the stem cell mobilization process has basically guaranteed close to 100% success rate in terms of collecting the stem cells.

And in the era of chemotherapy, multiple cycles of melphalan (Alkeran®), true chemotherapy would basically burn out the bone marrow. And so, we had to limit that patients couldn't have more than ten cycles of melphalan. But in the United States, we really don't use a lot of oral melphalan for patients. The plan is to ultimately get them to transplant so that's really no longer an issue.
Joseph C. Alvarnas, MD

I'm going to agree with everything said.

Lizette Figueroa-Rivera, MA

Thank you doctors. And the next question, from the telephone audience please.

Operator

Our next question comes from Millicent, calling from Maryland. Please state your question.

Millicent from Maryland

Yes, yes, thank you. I wanted to know whether my multiple myeloma, is it hereditary like diabetes? Right now my cancer doctor is testing me for, I guess, the gene or whatever or, yes, yes, something like that.

Ivan M. Borrello, MD

Yeah, so in general, the answer is no. I mean I can tell you that I have sisters that have myeloma. I have currently a patient whose father died of myeloma, but the short answer is that it's not. I think what you're referring to in terms of what your doctor is testing isn't so much the genes to determine whether you can pass that on to your children, but it's more the genes to determine what kind of myeloma you actually have. And because there are some gene markers that would put you into a slightly more favorable or less favorable category, based on what those genes actually are.

Lizette Figueroa-Rivera, MA

Thank you, doctor, and we'll take the next question from the Web audience. Participant asks, "Hello. I have read that there is a concern that Revlimid can cause secondary cancers. What is considered long term when being on Revlimid?"

Ivan M. Borrello, MD

Yeah, so this is a very good and relevant question. There is a risk of secondary malignancies with Revlimid that is estimated to be somewhere between 2 and 4%. In general, this risk is associated with high-dose chemotherapy. So, for example, patients that get a transplant and then go on Revlimid several months later. I have certainly seen, I mean this is a real problem. I've seen patients get it as soon as two to three years out, but I've had patients that have been on it for eight years and are doing completely fine. What the other causes that are contributing to the secondary malignancies are, are currently unclear. And Celgene has actually done a very good job in terms of understanding or trying to understand what the causes of this are. And I think overall in the field the conclusion has been that when one weighs the risks and the benefits, the overall benefit that Revlimid imparts is so much greater than the potential risk that I think it's incumbent upon us as physicians to advise the patients
of this risk. But for the most part, we are still actively using that drug, just because it’s such a good drug in terms of treating myeloma.

_Lizette Figueroa-Rivera, MA_

Thank you and we’ll take the next question from the telephone audience please.

_Operator_

Our next question comes from Sean, calling from Kentucky. Please state your question.

_Sean from Kentucky_

Hi, my question is for Dr. Alvarnas. At 42, I was diagnosed with non-Hodgkin lymphoma. It's follicular, and I'm in complete remission after six rounds of bendamustine (Treanda®) and Rituxan and about to undergo Rituxan maintenance therapy and was advised by my team to do a collect and store for an auto transplant and travel to a major transplant center to get a second opinion on the collect and store. Where I was told that it might be best to not do a collect and store but to consider an allotransplant. You had mentioned in your talk that with follicular, sometimes allo is preferable. Can you expand on that a little bit?

_Joseph C. Alvarnas, MD_

Sure. I think you've encapsulated all the issues that we as transplanters wrestle with as well. So, for follicular lymphomas, we can do autologous transplants for follicular lymphoma, but it's not clear that we cure patients with any consistency using an autologous transplant for follicular lymphoma. There's a very broad literature for that. So, in general, I have not favored collecting and storing stem cells in people with follicular lymphomas.

The reason that allo transplant may, in fact, cure people with follicular lymphoma or selected people with follicular lymphoma is that an allo transplant has one additional quality beyond an autologous transplant, which is the capacity of the donor immune cells to recognize the tumor cells as being immunologically distinct and attack and kill them. And in a lot of ways, that encompasses the same sort of mechanisms that you would get from CAR T-cells.

So, you know, given the rapid evolution of not only new drugs for follicular lymphomas but also these new immunological therapeutics, I can't whole-heartedly endorse for myself collecting autologous stem cells at this juncture. And I think that watching and waiting not only, hopefully, enjoying your time with your disease in remission but also watching technology evolve at this really breakneck pace may give you a full breadth of understanding of what your real options are.

_Lizette Figueroa-Rivera, MA_

Thank you, doctor. And our last question today comes from Robert. He asks, "If chemo is working and keeping my disease in check, is it necessary to have a stem cell transplant? As time goes on, treatment drugs keep improving."
Ivan M. Borrello, MD

What's the disease?

Lizette Figueroa-Rivera, MA

It is myeloma.

Joseph C. Alvarnas, MD

Okay.

Ivan M. Borrello, MD

Okay. Right, because it's very different if it's myeloma or lymphoma.

Joseph C. Alvarnas, MD

Yeah.

Ivan M. Borrello, MD

So, that's a very important question, and what we know is that even though I showed you one of the earlier slides, and we're up to about 100% response rate with very high complete remission rates, we're not curing anybody. Where I think we've come with a lot of this, and I tried to emphasize this in the presentation, is that we've started measuring this minimal residual disease based on this gene testing because that really gives the answer. I mean if patients do not show any evidence of residual myeloma, and that they can get there without chemotherapy, I'm not sure that a transplant is going to necessarily add anything.

In contrast, if patients, despite being in a complete remission, still have evidence of minimal residual disease, then we know also from the data that I showed you, that transplant will hopefully deepen that response and, therefore, increase the likelihood of even a longer disease-free remission. So, that's the approach that we've been taking. And short of that approach, I think all of the data has really shown that in contrast to lymphoma, the paradigm that has now become instituted in myeloma is that the longer you treat, the better you do. And unless there's a reason to stop, most people should continue treatment sort of forever, as if they had high blood pressure, diabetes, or high cholesterol.

CLOSING REMARKS

Lizette Figueroa-Rivera, MA

Thank you so much. Thank you all for your questions. Thank you so much, Dr. Alvarnas and Dr. Borrello for your continued dedication to patients. You and your colleagues’ research successes have
really made a positive impact on people's lives, and we are so encouraged by the success that autologous transplants have had in your treatment centers.

[Slide 59 – Autologous Stem Cell Transplantation: Current Perspectives in Myeloma and Lymphoma]
The Leukemia & Lymphoma Society offers online chats for non-Hodgkin lymphoma and myeloma patients, as well as young adults and caregivers. The chats provide forums for patients and caregivers to share experiences and support one another. For information on how to participate, please review the flyer in your packet or go to www.LLS.org/chat.

If we were not able to get to your question today, please call a Leukemia & Lymphoma Society Information Specialist at 1-800-955-4572. Information specialists are available to speak with you from 9 AM to 9 PM Eastern Time or you can reach us by email at infocenter@LLS.org. We can provide information about treatment, including clinical trials, or answer other questions that you may have about support, including questions about financial assistance for treatment.

Again, thank you so much, Dr. Alvarnas and Dr. Borrello, for sharing your knowledge with us today. To all the patients, caregivers, and professionals participating in today's program, on behalf of The Leukemia & Lymphoma Society, thank you for sharing your time with us. Goodbye and we wish you well.