

Adult Acute Lymphoblastic Leukemia (ALL): Update on Diagnosis and Treatment

February 17, 2015

Speaker: Mark R. Litzow, MD



Slide 1. Welcome & Introductions

OPERATOR:

Greetings and welcome to *Adult Acute Lymphoblastic Leukemia: Update on Diagnosis and Treatment* telephone and web education program.

It is now my pleasure to introduce your moderator, Lizette Figueroa Rivera.

LIZETTE FIGUEROA RIVERA:

On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you.

Special thanks to Dr. Mark R. Litzow for sharing his time and expertise with us today.

Before we begin, I'd like to introduce The Leukemia & Lymphoma Society's Senior Vice President of Research, Dr. Rick Winneker, who will share a few words. Rick, please go ahead.

DR. RICK WINNEKER:

Thank you, Lizette. I'd 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 treatment for blood cancer patients. Our vision is a world without blood cancer.

For more than 60 years LLS has helped pioneer innovation such as targeted therapies and immunotherapies that have improved survival rates and quality of life for many blood cancer patients, and you'll be hearing about some of those new therapies today.

To date we have invested over \$1 billion in research to advance therapies and save lives. Until there is a cure, LLS will continue to fund promising research from bench to bedside.

In addition, as this program demonstrates, we are the leading source of free blood cancer information, education and support, and we touch patients and their communities through our 58 chapters across the U.S. and Canada.

LLS also acts as the voice for all blood cancer patients. We advocate for patients and survivors and their families, helping them navigate their cancer treatments, and ensuring that they have access to quality, affordable and coordinated care.

So we are very fortunate to have as our presenter today Dr. Mark Litzow, one of the nation's leading experts in acute leukemia. We appreciate his dedication to supporting our mission and his commitment to caring for patients living with blood cancers. I'd like to thank him for providing us today with important information on acute lymphoblastic leukemia.

Thank you all and now I'll turn the program back to Lizette.

LIZETTE FIGUEROA RIVERA:

Thank you, Rick.

And we would like to acknowledge and thank Onyx Pharmaceuticals, an Amgen subsidiary, for support of this program.

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Slide 2. Title Slide

LIZETTE FIGUEROA RIVERA:

I am now pleased to introduce Dr. Mark R. Litzow, Professor of Medicine and Director of the Myeloid Disease Oriented Group in the Division of Hematology at the Mayo Clinic in Rochester, Minnesota.

I am now privileged to turn the program over to you, Dr. Litzow.

DR. MARK LITZOW:

Thank you very much. It's a great honor and privilege for me to be here today and to give this presentation to you. I would like to update you on the diagnosis and treatment of adult acute lymphoblastic leukemia, which I will refer to as ALL through this presentation.

Slide 3. Disclosure

I have done some consulting for Amgen and also Sigma-Tau Pharmaceuticals.

Slide 4. Presentation Objectives

So my objectives today are outlined on the slide you're seeing here. I'll talk briefly about how ALL is diagnosed. I will talk about the role that cytogenetics play in treatment planning. Will talk briefly about treatment options for newly diagnosed patients and for patients where the leukemia has recurred or not responded to initial therapy. These are relapsed/refractory patients. I will discuss the role of clinical trials and the advancement of ALL treatment. I will discuss some of the side effects that can complicate the treatment and how we manage those. And then I want to make a few comments about the importance of open communication with your healthcare team.

Slide 5. Hematopoiesis

So on this slide, it's titled Hematopoiesis, and that's blood cell production, is what that word means. If you look at the very top of the slide you see a cell that's described as the stem cell. And I sometimes refer to this as the mother cell of a bone marrow. And if you look across the bottom of the slide, you see the blood cells that circulate in our blood including the red blood cells, the platelets, and then some of the different white blood cells including the neutrophils, the eosinophil, the macrophage there, the basophil. And over on the right in the red box are the lymphocytes. So these develop from the stem cell and there's two broad categories of lymphocytes. We call some B lymphocytes and that stands for actually an organ in chickens called the bursa of Fabricius, which is why we use that term B lymphocyte. And then T lymphocytes are cells that arise from the thymus gland in the middle of our chest. Most patients that develop ALL have the B lineage type or the B lymphocyte type, but about 20% have the T lymphocyte or T cell ALL. So we refer to these as B-ALL or T-ALL.

Slide 6. Bone Marrow & Blood Cells

On the next slide I just show this again, that these cells arise from the bone marrow and these are the normal cells that are produced – the red blood cells that carry oxygen, the various types of white blood cells, and then the platelets that help our blood to clot.

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Slide 7. Bone Marrow Biopsy

DR. MARK LITZOW:

So we diagnose ALL typically when people present to us not feeling well, either fatigued or they may have developed an infection that's not responding to treatment, and we notice that their blood counts are abnormal and most frequently we need to do a bone marrow biopsy, where we actually sample their bone marrow, and you can see how that's done here in the pelvic bone, either on the right or the left side, and we go into what's called the marrow cavity and collect cells from there that we can analyze under the microscope.

Slide 8. [Figure]

And what we see under the microscope are these kind of cells that you see in front of you. We refer to these as blast cells, B-L-A-S-T. And oftentimes they are the dominant cell in the bone marrow. They crowd out the normal cells and replace those cells, which is why people's blood counts become abnormal.

Slide 9. [Figure]

And I just have several examples on these couple of slides here, just showing different variations on what ALL blast cells look like under the microscope.

Slide 10. Chest Mass in a Patient with ALL

Now I mentioned this gland in the middle of our chest called the thymus gland, where the T cells can develop. And so it's common, particularly with the T cell ALL, that the thymus will enlarge and get filled with blast cells. And I've tried to show this, we call a mass in the middle of the chest, which is outlined by the arrow, the red arrows, which is sometimes another manifestation that we can see as the leukemia develops.

Slide 11. Acute Lymphoblastic Leukemia-Epidemiology

So in terms of the epidemiology or the population demographics of ALL, there's only about 6,000 cases of ALL diagnosed per year, so it's relatively rare, compared to some of the other common cancers. Many of you may know that this is a more common malignancy in children and it's a dominant malignancy, 75% of cases in children, whereas in adults it's the minority of patients that have acute leukemia. Its counterpart, acute myeloid leukemia, is more common. When this develops in children the peak age is around age 4, but it can occur at any age. And it can occur in any aged adult, whether young adult, middle-aged, but it is somewhat more common as people get older as well.

Slide 12. World Health Organization Classification of Lymphoid Neoplasms

So we categorize leukemias and other malignancies using a worldwide classification system that's been developed by the World Health Organization or the WHO. And so you can see in red here, that these are the varieties of B lymphoblastic leukemia. That basically means B-ALL. And if you look down these listings here, these are the different cytogenetic abnormalities that we can see. So when we sample the bone marrow, we take some of the cells, some of the blast cells, and we send them to a lab where they

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can look at the chromosomes inside the cells and see if there's any abnormalities in those cells. And these are some of the varieties that we see. And I'll talk about this a little bit more. We're not going to go into great detail on this, but this is important information that we use to help us with treatment.

Slide 13. Philadelphia Chromosome

And one of the most common chromosome abnormalities, particularly in adults, is what we call the Philadelphia chromosome. And this is – on the slide here you see a set of chromosomes that any one of us has in most of our cells. There are 22 what we call somatic chromosomes and we have one from our mother and one from our father. And then we all have two sex chromosomes. Either two Xs in women or an X and a Y in men. And you can see with this Philadelphia chromosome, for reasons that we don't fully understand yet, one of the chromosome number 9 and one of the chromosome number 2 swapped material. And you can see that small number 22 down at the bottom, shown by the arrow, and that was actually the chromosome abnormality that was seen by some doctors in Philadelphia in 1961, when this was first identified, and they called it the Philadelphia chromosome. And we didn't realize until years later there was actually a swap of material. So this is just one example, one of the more common examples that we see in ALL. Not all patients with ALL have a Philadelphia chromosome, but a number do.

Slide 14. WHO Classification of Lymphoid Neoplasms

And then I mentioned the T-ALL, the T lymphoblastic leukemia. And some patients there's a more lymphomatous form and when I say that that means that there's more lymph node involvement. So some patients present also in that way. And there are chromosome abnormalities that we see with the T-ALL also, but I don't describe those here. I show just some of the different subcategories of the T lymphoblastic leukemia or T-ALL.

There's also another ALL that's less common. It's named after Dr. Burkitt. That's called Burkitt cell leukemia. And I won't spend a lot of time on that today, but it is another variant of ALL.

Slide 15. [Figure]

So this slide I'm not going to go into in detail, but it's a pie chart that shows the distribution of these different chromosome abnormalities that I was just talking about a couple of slides ago, particularly with the B cell or B-ALL. And what I tried to highlight here is you can see where I wrote Philadelphia chromosome on the left and I pointed the arrow – in the top pie chart is the frequency of chromosome abnormalities in children. And you can see that the BCR-ABL or this Philadelphia chromosome is fairly rare in children, but you can see that in adults it makes up almost a quarter of the abnormalities. So you can see how these can vary from children to adults. And ALL in children does not necessarily behave in the same way that it does in adults.

You can also see in the purple, where there are some of the chromosome abnormalities that we can see in T-ALL. So as I mentioned, we also see those there.

This is a very complex subject and I don't have time to get into that, but I wanted to give you a flavor for the spectrum of chromosome abnormalities that we can see and some of the more common ones.

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Slide 16. Adverse Prognostic Factors for Adult ALL

DR. MARK LITZOW:

So when we have a patient who comes in with ALL, we look at what we call prognostic factors that help us predict a bit how things are going to go with treatment. These are not precise, but they're information that help us in determining sometimes how we approach treatment. And unfortunately as I'm getting older, I'm recognizing that I don't tolerate things as well as I used to and, unfortunately, as people get older with ALL, that does impact how they're going to do.

If they have a very high white count, and it depends on the subtype, but that can suggest to us that it may be a somewhat more stubborn leukemia. These cytogenetics or chromosome abnormalities that we've been talking about, there are certain ones of those that predict that it may be a more stubborn leukemia.

The next bullet says time to CR. That's time to complete remission. And if it takes longer for a person to respond to chemotherapy, that concerns us somewhat, that they may also have more resistant disease.

And then there's this concept that we use called minimal residual disease. So as our treatments and our testing has improved, we've been able to detect lower levels of leukemia than we used to. So a person can have a normal looking bone marrow, they can have good looking blood counts, but we can still find small amounts of the leukemia in their bone marrow. And we call this minimal residual disease. And I throw some numbers out there. They're not so important, but they're something that is actually emerging as one of the strongest predictors of how someone might do after they start treatment. So they're into treatment, it looks like they're responding, they're getting better, but we can still find small levels of disease and that sometimes influences how we approach their treatment.

Slide 17. Chemotherapy of Childhood ALL: Historical Perspective

So how do we treat patients with ALL? Well, I wanted to give some historical perspective because the history of treatment of cancer in general is relatively short and only goes back about 50 to 60 years. And you can see that just using these single drugs, that many patients can get a CR or a complete remission. But we've learned over the years that it won't last unless we combine these drugs and continue treatment. But it just shows you that even with relatively simple treatment, we can get improvement in how patients will respond, but the key, once we get a response, is also keeping a person there and not letting the leukemia grow again.

Slide 18. Chemotherapy of Childhood ALL: Historical Perspective

And so some of the principles of how we treat ALL was actually developed by Dr. Pinkel, who published an article in the Journal of the American Medical Association, that's JAMA, back in 1971.

So back at that time we didn't have as many of the medications that we have now. But even then these principles were developed and they apply to today.

So our first goal is to try to get a person into complete remission and at that time, using prednisone and a chemotherapy drug called vincristine or VCR, could do that. Then there were another set of drugs, methotrexate is an example, or 6-mercaptopurine. These are called anti-metabolites. And giving high doses, particularly of methotrexate for a week, was helpful. Back then we used more radiation than we do now. But we know that ALL can be sensitive to radiation treatment and so we would radiate the brain

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and the spinal cord. And then we've learned that giving low doses often of oral medications for a longer period of time, over two to three years, what we call maintenance therapy, we're trying to maintain the remission we've achieved, can help keep people from the leukemia coming back.

Slide 19. Improvements in Outcome of Pediatric ALL in 2255 Pts. At St. Jude's 1962-2005

So in children, you may know that we've made remarkable advances in the treatment of ALL. And these are what we call, in these graphs, survival curves. So they show in a population or a group of patients how long they can live with ALL. And you can see on that yellow curve, back in the 1960s, that unfortunately not many children survived their ALL. But you can see now in the last ten years, the cure rates for children are up over 90%. And this has really been quite remarkable and is one of the great success stories of cancer treatment.

Slide 20. Survival of 18,772 Patients with ALL Treated on Sequential CCG Clinical Trials over Three Decades

And another interesting phenomenon is that a lot of this improvement came not because we had great new treatments necessarily, but many of the drugs that we had available were combined in different ways, used in different schedules, in different doses. And this is just showing where you see at the top there, where it says no new drugs and that arrow, that we were able to make these improvements just by learning how to sequence these drugs in different ways. And this also points out the very great importance of clinical trials in helping us to develop these new treatments and new sequences and combinations, to move the treatments and our success rates forward.

Slide 21. Therapy of Adult ALL

So the pediatricians, the kids' doctors who treat ALL, have led the way in helping us as adult doctors treat ALL, and so we've built on their experience, the pediatric experience. We followed the outline of the four phases of the total therapy that I showed you in the last slides. We incorporated new drugs as they became available and some of these drugs that we're using still now are quite old, from the 60s and 70s. And then we intensified the treatment as we could. And we use this term non-cross-resistant drugs. So we try to use drugs that have different mechanisms of action. So if a leukemia cell becomes resistant to one drug, we can use a drug that has a different way of working to try to attack it and hope the leukemia cell will still be sensitive to be killed by that drug. So these are some of the principles that we use in the treatment.

Slide 22. Contemporary Adult ALL Treatment Regimens

And our contemporary regimens now give one to two months of what we call induction chemotherapy. We're trying to induce a remission. And these are the drugs that we use – daunorubicin, prednisone, vincristine, asparaginase, cyclophosphamide, cytarabine, methotrexate. We'll either treat the brain and the spinal cord because we know that leukemia cells can hide in the spinal fluid and not be as sensitive to the chemotherapy drugs that we give intravenously, so we use methotrexate into the spinal canal. We'll inject it. And sometimes we use radiation. We'll then take some of these same drugs and we'll intensify the treatment and then we'll consolidate the remission we've achieved, again with many of

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these same drugs, and then eventually go to prolonged maintenance with a drug called 6-mercaptopurine. And again you see methotrexate, vincristine and prednisone. So that's kind of the overall approach that we use in treating patients when we first see them.

Now one thing I didn't mention in the previous slide is there's also new drugs that we use, particularly for the Philadelphia chromosome type that I talked about earlier. There are some newer drugs that are very active in that setting. One is imatinib or Gleevec®. Another is dasatinib. It's also called Sprycel®. As two examples.

Slide 23. USA CCG-CALGB Comparison

The point I want to make with this slide that I'm showing now is we realized about ten years ago, and Dr. Wendy Stock at the University of Chicago made one of the initial observations, that when young adults between the ages of 16 and 20, when they went and saw a pediatrician and got treated for their ALL, that they did better, and that's the yellow curve, and CCG is the Children's Cancer Group, than if these adolescents went to an adult doctor and were treated by adult leukemia doctors. And that's the CALGB, that's the Cancer and Leukemia Group B. It's just the name of a group that treated these patients. So this was quite a startling observation, that the same aged patients would do better with pediatric treatments than with adult treatments. And this got a lot of attention from all of us.

Slide 24. Specified Cumulative Postremission Doses

And some of the reason for this is shown in the next slide and it's because the pediatricians, the kids' doctors, the CCG group, they used higher doses of drugs like vincristine – I've outlined these in orange on this slide – DXM is dexamethasone, that's a form of cortisone, and then this other drug called asparaginase, ASP. They used much higher doses of those drugs. And we think that this may be an important reason why these young adults did better when they were treated by the pediatricians. And we adult doctors were a little bit scared to use such high doses of these drugs because adults don't tend to tolerate these treatments as well as children. So we didn't want to make people too sick or even cause them to get a bad infection and pass away from our treatments. So that led to some of our reluctance.

Slide 25. Pediatric Approach to Adult ALL

But when we saw this information, a number of groups, and this is results from France, from the GRAALL Group, and this showed – if you look especially at the lower graph, the yellow curves are where they said, well, we're going to take a pediatric- intensive regimen, we're going to do what the pediatricians did, and we're going to treat young and middle-aged adults and we're going to see how they do and see how they do compared to one of our old adult regimens. And you can see that those yellow curves are higher than the blue curves and that means that they got better results using the more pediatric, I'll say, intensive treatment program.

Slide 26. Favorable Outcomes for Older Adolescents and Young Adults (AYA) with Acute Lymphoblastic Leukemia

And here in the United States, Dr. Stock and her group, along with my colleagues in a group that we participate in, we did what we call an intergroup trial, where all the different cancer treatment groups in

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the United States got together, and we said we're going to use a pediatric-intensive regimen in our younger adults, and this was up to the age of 40, and see what kind of results we get.

Slide 27. US Intergroup study for AYAs 16- 39 years old: C-10403

And this just shows the different phases of the chemo they went through. I is induction, C is consolidation, IM is interim maintenance, DI is delayed intensification, and M is maintenance in those boxes. And then you can see all the different chemotherapy drugs that we talked about, that were used in this program.

Slide 28. Overall Survival

And we found that we got similar results to the French and that the survival rate was much better using this more pediatric-intensive regimen. And it seemed to be as good whether someone was aged 18 or whether they were in their 30s. So we were quite encouraged by these results. And Dr. Stock had just presented these results in December at our national hematology meeting.

Slide 29. Abstract #319 Superiority of Pediatric Chemotherapy (Chemo) over Allogeneic Hematopoietic Cell Transplantation (HCT) for Philadelphia Negative Adult ALL in First Complete Remission

So it's also raised the question about if we're using these intensive regimens and getting better results, do we need to do bone marrow transplants or hematopoietic cell transplantation – that's listed here, that's the same as a bone marrow transplant – for adults, if we're getting such good results with chemotherapy. And Dr. Seftel and colleagues, from one of our bone marrow registries, compared results of chemotherapy to patients who had gotten a transplant. And these were people that were treated in the past.

Slide 30. [Figure]

And I won't go through all of this, but if you look in the upper left curve you can see that the patients who got chemotherapy actually did better than the patients who had a transplant. And so we now think in most younger adults – and you have to individualize things, we can't generalize too much – but we think that in many younger adults, we may not need to give them a transplant. And in the past we thought that most adults should be considered for a bone marrow transplant as part of the treatment of their leukemia.

So these studies have helped evolve our thinking about how we approach these situations.

Slide 31. Treatment of Relapsed or Refractory ALL

So let me turn now and talk about what do we do if a patient gets treated for their ALL and unfortunately the leukemia starts growing again after they've gotten into remission, or we get into a situation where this chemotherapy that we give at the beginning is not working, and they have what we call refractory ALL.

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So our options there are to use some different chemotherapy drugs that we have available and different schedules. We think about a bone marrow transplant or I also call it a blood or marrow transplant. Then there's also some new treatments that are based on what we call monoclonal antibodies. And so these are proteins that our body makes that help us fight infection, but scientists have been able to make these antibodies bind to cancer cells and harness the immune system to help get rid of them.

Slide 32. Mechanisms of Action of Monoclonal Antibody Conjugates

And this slide is complicated, but if you look on the upper left you can see some examples of antibodies that we have – and we call them naked antibodies because they're just the antibody itself – that we've used in the treatment of leukemia and other cancers. And then there's a lot of different variations on these. We can link things to these antibodies. You can link toxins to them, you can link drugs to them. You can actually insert them in other cells. And this is this CAR T-cell therapy that I'm going to talk a little bit more about.

And then I want to mention this one in the upper right, blinatumomab, combines two antibodies, one directed against the leukemia cell and one that takes an immune cell, called a T-cell, this is a normal T-cell, not a leukemia T-cell, and brings it close to the leukemia cell to get rid of it.

Slide 33. Breakthrough Therapy Designation for Blinatumomab

And blinatumomab, this new combination of antibodies, has shown some exciting results. It's been mostly tested in relapsed and refractory patients. But the FDA approved it in December for treatment of ALL. And this was a news release and they say a rare form. This is for the B-cell type. It's not all that rare, but less common. They said that the company still has to do further studies to confirm that it's of benefit. And this medicine has to be given, it's injected in an IV, and is given round the clock for a whole month. It can be done as an outpatient. But it's expensive, as you can see here. So that's just something that I wanted people to be aware of as we deal with these expensive – some of these expensive treatments that are being developed, but look very promising.

Slide 34. E1910: Randomized Ph III Adult Frontline ALL

So in the cancer group that I work with, called the Eastern Cooperative Oncology Group, we are doing a trial in newly diagnosed patients, to see how well blinatumomab works. And I don't want to go through all the details of this, but basically patients are getting all the chemotherapy that I talked about earlier, and then half the patients are going to be randomized to receive or not receive blinatumomab on top of their other treatment, to see if we can improve their outcomes. And you can see in green on the left where they're going to get the blinatumomab in the course of their treatment. So this is a clinical trial that's being done across the country now, at multiple centers, to see again if we can improve the treatment and if adding blinatumomab to our chemotherapy can make outcomes better. And there possibly may be some of you that are even participating in this trial.

Slide 35. Inotuzumab ozogamicin

Now another exciting drug I just want to mention that's still in development is another monoclonal antibody-based treatment and it's called – this is the generic name and it's a mouthful – inotuzumab

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ozogamicin. You can see on the left in the picture, the green and yellow, that's an antibody and you can see that it's linked to this chemotherapy drug that's got a complicated structure, that's called calicheamicin. And that's the arrow that you see there. And so basically what we're trying to do here is have this antibody attach the leukemia cell and then the chemotherapy drug goes into the cell and kills it. And we think this approach is attractive because we're not attacking all the cells in the body like chemotherapy can, but trying to focus primarily on the leukemia cells. It hits some of the normal cells, but mostly we're attacking the leukemia. And this has shown interesting and encouraging results. And it's in further development and may get FDA approved itself, even within the next year or two.

Slide 36. Chimeric Antigen Receptor-Modified T Cells

Now I want to talk toward the end here about these cells that have gotten a lot of publicity, a lot of interest, called chimeric antigen receptor modified T-cells. So CAR is CAR, so we call these CAR T-cells. And basically they're taking one of these antibodies and they're putting it inside a T-cell or in the membrane or the lining of a T-cell, so that it actually sticks out. And T-cells are one of our important immune cells that are important in infections, particularly viral infections, but we also know can kill cancer cells. And so this is trying to bring a cancer cell, in our case a leukemia cell, right next to this T-cell, so that it will kill it. So it's kind of like the blinatumomab that I talked about, but it's using a different approach.

Slide 37. Chimeric Antigen Receptor-Modified T Cells

And these CAR T-cells are collected from the patient and you can see that, you see the little person there, you see the arrow coming out of their head, it says isolation of T-cells. So we get T-cells from their blood. We then mix it with this virus that inserts the antibody into the cell and then we expand those T-cells, it's called T-cell expansion, and then we can give those back to the patient and hopefully they'll work and attack the leukemia.

Slide 38. Summary of Clinical Outcomes

And this approach has shown high rates of success. This is a study from the Memorial Sloan-Kettering Cancer Center in New York. And these were patients who had had relapsed or refractory disease. And you can see that in these 27 patients, 24 had a complete remission, so 89%. And most of them this Minimal Residual Disease test, or MRD test, was negative. It allowed many of these patients to go on and have a transplant. Unfortunately, this treatment is not perfect, though, and so the leukemia did come back in some patients afterwards. But it looks encouraging and is in further development. And we know that some of these cells can hang around for quite a while after they're infused and hopefully keep fighting the leukemia.

Slide 39. Side Effects Management

So I want to touch on side effects a little bit. Obviously going through treatment like this is not easy. We have much better anti-nausea drugs or antiemetics now than we had in the past and so nausea and vomiting, while still can be a significant problem, is honestly not as bad as it used to be. Going through these treatments, and as many of you likely know, having leukemia is fatiguing. We know that regular

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exercise can counteract some of the effects of that. The chemotherapy we give causes the blood counts to go low, so people become anemic. And we need to give red blood cell transfusions. Their platelets can get low and they can be at more risk for bleeding because platelets help prevent bleeding, so they need platelet transfusions. We have to worry about infections. And often antibiotics are added. Some of the chemotherapy drugs can damage the nerves in our hands and feet and then we can get numbness and even pain. We call that neuropathy. And so there's actually medicines that were originally developed to treat seizures, or anti-seizure medicines, that we use. They actually have a pain effect and they can help with the pain of the neuropathy. And pain medication obviously can be important there.

And certainly we want to be open and consider complementary and alternative approaches to treating some of these symptoms. Sometimes acupuncture can be helpful. Massage. Meditation. Mindfulness approaches. Can just help with a person coping with obviously the tremendous challenge of dealing with ALL.

Slide 40. Early Survivorship Issues

And we are also becoming more and more cognizant of – we use this term being cancer-free – it does not mean being free of cancer. So one can get through their treatment beyond maintenance or beyond that and be done, but they can have lingering side effects. And we as doctors need to and want to be aware of these and help people deal with these. I've listed some of the ones – these are some of the ones from the previous page, the previous slide – neuropathy, fatigue, there's chemo-brain, this is cognitive dysfunction that people can develop. Sometimes with steroids that we use, prednisone, dexamethasone, it can damage the joints. Sometimes people can have a type of swelling called lymphedema. We know that these treatments can affect sexual function and so we want to be aware of that as well and help people deal with that.

Slide 41. Long-Term Medical Issues

Some of the other long-term issues. Unfortunately, there is a risk of other cancers developing and so regular preventive maintenance is important. Cardiac issues, cardiovascular disease should not be neglected. The treatments can affect the endocrine system, that people can get low thyroid. Children can have growth issues. We talked about cognitive dysfunction. The fatigue, lymphedema. Some of the treatments that we do in, particularly transplant, can affect male or a woman's fertility, and that's also something that we want to be cognizant of and aware of as we take patients through these treatments.

Slide 42. Open Communication with your Healthcare Team

So I want to conclude by just reminding you that it's important that you be open in your communication with your healthcare team and we really try to think about the care of patients with ALL as a team approach. And we need people from multiple disciplines, chaplains, social workers, nurses, physician assistants, nurse practitioners, pharmacists helping us. And patients and their caregivers are an important part of that team.

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Slide 43. Open Communication with your Healthcare Team

DR. MARK LITZOW:

So these are just things to think about. Sometimes when you're in the spur of the moment in an appointment, it's hard to remember your questions. So never hesitate to make a list prior to your appointment. Never hesitate to ask questions. You know, if your doctor or healthcare provider doesn't want to answer your questions, maybe they're not the right healthcare provider for you. It's good to take notes. It's good to have a second or third set of ears at those appointments. And we also want you to be honest about your symptoms, so that we can make sure that we're not missing anything. I've sometimes had patients tell me when they're talking about their other doctor, they say, oh, I didn't want to bother him with my symptoms, my pain or this or that. But it's important to let us know, so we can make sure that we address those and make sure that we take them into account as we develop your treatment plan. So don't hesitate to ask your doctor to write down things for you. There's a lot of printed resources available. The Leukemia & Lymphoma Society has just wonderful education material that can help you understand what you're dealing with. And again, the other members of the healthcare team can be important sources of information. So don't hesitate to talk to them and ask them questions as well.

Slide 44. Question and Answer Session

So that concludes my presentation and I'm happy to answer questions.

LIZETTE FIGUEROA RIVERA:

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

We'll take the first question from our web audience, Dr. Litzow. Sarah states that she is in remission, but on maintenance pill as she has PH-positive ALL. And she's inquiring if she'll always need to take this drug or if this drug can be discontinued after a short time.

DR. MARK LITZOW:

That's a good question. It's a question that we don't actually know the precise answer to, as to how long – and I assume you're on a tyrosine kinase inhibitor, probably imatinib or dasatinib. Those are the two most common ones, Gleevec or Sprycel, the other names. We think that probably at least a year of treatment is warranted. There was actually just a clinical trial that completed here in the United States and that's requesting that patients take that medicine for up to five years after they complete their treatment, whether they've had a transplant or not. So I think it's something worth discussing with your doctor and getting their opinion, but I have to be honest with you and say it's not something that we've worked out in detail to know exactly what the best time frame is.

LIZETTE FIGUEROA RIVERA:

Thank you, Sarah, for the question. And Dr. Litzow, the next question is also from the web audience. Michael states that he's 23 and worried about fertility issues. He stated that he did not have time to bank sperm before he required treatment and wanted to know the probability of him becoming sterile since his treatment.

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DR. MARK LITZOW:

I would need to know more detail to answer that more precisely. I assume probably transplant's not been done. And if that's the case, in particular, I think there's still a fairly good chance that you will remain fertile. It would again be important to discuss this with your doctor. The test we do to assess fertility is a semen analysis. Be worth discussing the timing of that. There is, with the advances in fertility, there's a lot more that can be done with a smaller number of sperm cells. So one shouldn't be too discouraged about that. But again, the hope would be that fertility could be preserved.

LIZETTE FIGUEROA RIVERA:

Thank you, Michael, for your question. We'll take the next question from the telephone audience, please.

OPERATOR:

The first question comes from Alice in Illinois. Alice, please state your question.

ALICE:

Yes, hi. I'm asking whether the T-cell inhibitor therapies are also being looked at for children with ALL, who've refractory or relapsed at this point.

DR. MARK LITZOW:

If you're referring to the CAR T-cell therapy, as I think you are, actually they are being looked at in children and actually children were some of the first patients that got these treatments. And actually we're moving more now to treating more adults. So definitely they have been utilized in children and shown success.

LIZETTE FIGUEROA RIVERA:

Thank you for the question. And we'll take the next question from the web audience. Laura asks what are some of the frequently found comorbid conditions found in adults with ALL?

DR. MARK LITZOW:

Comorbid conditions in ALL? Well, ALL can present – leukemia can present outside the bone marrow, so it can involve virtually any organ in the body. As I mentioned, the spinal fluid can be one of the more common areas and that's why we have to give treatment into the spinal cord, even if we don't find any leukemia there, because we know it can develop. So that can cause nerve damage. So that's one of the more prominent ones. The lymph nodes can be involved and enlarged and affect people. But almost any organ in the body can be affected by leukemia. And then our treatments can also sometimes cause comorbid conditions to develop. People on steroids can become diabetic. Chemotherapy sometimes can damage the heart. So we monitor for that and have to be aware of that.

LIZETTE FIGUEROA RIVERA:

Thank you. And we'll take the next question from the telephone audience.

OPERATOR:

The next phone question comes from Susan in New York. Susan, please state your question.

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SUSAN:

Doctor, I'm just curious. I've been under chemo for three years at the hospital. Just finished that. My doctor put me on Gleevec now. I'm on that every other day. But the reason for the call is that this weakness and tiredness, when does it go away?

DR. MARK LITZOW:

That can take time. It can take months and sometimes longer. I can tell you that exercise and fitness can counteract some of that and accelerate your recovery. So I would encourage you to get into an exercise program and start where you are and build up gradually. Perhaps work with a trainer. There's programs that LLS could help you with, I think identify – I know at our local YM-YWCA, there's programs for patients that are in recovery, to help them with their fitness. So good nutrition and exercise can help counteract some of that fatigue. But it does take longer than one thinks it might to come back from that.

LIZETTE FIGUEROA RIVERA:

Thank you. And the next question is from the web audience. Justin asks if it's true that men's treatment protocols are longer than females' treatment protocols?

DR. MARK LITZOW:

Yes, the pediatricians noted this, and it's not totally understood why that is, but the maintenance treatment tends to go – many programs, it's a year longer for men than – for male children than females. In adults we haven't tended to see the need for that as much, but in pediatrics they often treat the boys longer than the girls.

LIZETTE FIGUEROA RIVERA:

Thank you. And we'll take the next question from the phone audience, please.

OPERATOR:

The next phone question comes from Martha in South Carolina. Martha, please state your question.

MARTHA:

Yes, I was wondering other than nausea and vomiting, what other side effects is there to be looking for in adult population in relation to the drug treatment plan? And fatigue.

DR. MARK LITZOW:

Well, fatigue is a prominent one. The nausea, vomiting. Sometimes people can get reflux symptoms related to the steroids that are used. You know, acid reflux. You know, the low blood counts can contribute to fatigue. Sometimes there can be easy bruising, bleeding that can occur. Those are the main, what we call the acute effects, or things that will happen earlier on. Some of my slides I showed some of the last effects, you know, the nerve damage that can take more time to come on. The thyroid issues. Things like that. The steroids can thin the bones some, people can be more prone to osteoporosis. Again that's a longer term effect. And there can be quite a list. It depends on the person. It doesn't mean one person is going to get all of them and oftentimes people don't get any of them or they're minimized. So again it's not something that one can easily generalize it, but those are some of the things that we think about.

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LIZETTE FIGUEROA RIVERA:

Thank you for your question. We'll take the next question from the web. Rachel asks will immunotherapies in the future replace traditional chemotherapy for ALL?

DR. MARK LITZOW:

At this point I will say that they will likely play a more and more prominent role. I mentioned the blinatumomab. This interesting antibody construct. There's a clinical trial that my colleagues in the Southwest Oncology Group have developed, where they're giving blinatumomab to patients over the age of 70 with ALL, combined with vincristine and prednisone, so fairly small amounts of chemotherapy or steroids and trying to rely more on the blinatumomab. So I think immunotherapy will play an increasingly prominent role and maybe even some day will replace chemotherapy entirely. I think it's too early to tell that with certainty, but I think it's going to play a more and more prominent role.

LIZETTE FIGUEROA RIVERA:

Thank you for that question. And the next question does come from the web. Mark asks, since my immune system is compromised, should my family take additional precautions around me like receive certain vaccinations or not visit me if they're sick?

DR. MARK LITZOW:

Well, it's correct that they should not visit you if they're sick. That's very important. In general, they should have their immunizations up to date. Certainly every Fall we encourage caregivers and family members to get flu shots to help protect themselves, so they can be good caregivers, but also help protect their loved one from getting influenza from them. So having immunizations up to date in general is a good idea and being cautious with people that have infections is important.

LIZETTE FIGUEROA RIVERA:

Sure, of course. And the next question comes from the telephone audience, please.

OPERATOR:

The next phone question comes from Linda in Arizona. Linda, please state your question.

LINDA:

Yes. In 2007 I was diagnosed with ALL and I had a bone marrow transplant and they gave me, you know, two years to live. But anyway, it's been this long and I've been on Gleevec. And my numbers, I've never been in remission, but I've been stagnant the whole time. And last three months – or three months ago my doctor put me on Sprycel. I had a reaction, was intubated, almost lost my life, and have now survived that, and now he wants to put me on – it's B-O-S-U-L-I-F. And I'm wondering if I'm going to have the same side effect and if it's a wise thing for me to do or just stay back on the Gleevec.

DR. MARK LITZOW:

Well, it's hard for me to answer that without knowing the details of your situation. I can say Bosulif® is – its generic name is bosutinib – it's not been utilized very much in ALL. I assume you have Ph-positive or Philadelphia chromosome positive ALL. So I wouldn't say it would be wrong to do the bosutinib. It would be unlikely that you'd have the same reaction that you had with Sprycel. I mean one thing with thes

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DR. MARK LITZOW:

medicines is if one of them has a certain side effect, it doesn't necessarily mean that its counterpart or that its neighbor is going to have the same side effect. So I think the Bosulif is not unreasonable, but there isn't as much experience with it. Going back on Gleevec would also not be unreasonable. But I can't really be more specific and shouldn't be, without knowing more details.

LIZETTE FIGUEROA RIVERA:

Thank you for the question. And the next question comes from the web audience. Margaret asks, how prevalent is avascular necrosis as a side effect of treatment and if there is anything in the area of prevention that's being done at this time.

DR. MARK LITZOW:

Well, fortunately it's fairly rare. And obviously there's varying degrees of severity of avascular necrosis. But it's probably not much more on the range of 10% or so. I apologize, I don't have precise number on the tip of my tongue. But it's not much more in that range. And I'm not aware of any preventive measures that can be taken to prevent it. I could be wrong about that. But there's not anything certainly that's become widespread that we're using as a routine in practice. There are some new approaches when it develops. Actually been some studies actually injecting bone marrow into the bone where it's developing, to try to prevent it from progressing. So that's preventing it from getting worse. So that looks of some encouragement in trying to deal with it before the joint can collapse and then a person needs to have a joint replacement. So fortunately it's not real frequent, but it's still a challenging – can be a challenging problem to deal with.

LIZETTE FIGUEROA RIVERA:

Sure. Thank you for that question. And the next question comes from the web audience. And it's from Suzette. Suzette asks about the incidence of relapse after five years off therapy and choice of treatment for relapse.

DR. MARK LITZOW:

Well, fortunately that's rare. Unfortunately, those still can occur. I have to tell my patients I can never say never. But it's infrequent that that would happen. Treatment in that situation again would have to be somewhat individualized. In general, I would say, though, that if someone is out that far and the leukemia comes back, we often think about going back to their original treatment that they got at the beginning and using that again, with our logic being that it worked well and held things for that long period of time, let's go back and try that again. And again these are some of the most effective drugs that we have. So in general that is often our approach. We do, in that situation, give consideration to a transplant if someone hasn't already had one. So that would need to be carefully thought about. But it is, fortunately, a rare occurrence. And so there's not one right answer to how that's best treated.

LIZETTE FIGUEROA RIVERA:

Thank you for your question. And thank you all for your questions. We hope this information will assist you and your family in your next steps.

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Slide 45. LLS Resources

LIZETTE FIGUEROA RIVERA:

If we weren't able to get to your question today, please call The Leukemia & Lymphoma Society's Information Specialists at 1-800-955-4572 from 9 AM to 9 PM Eastern Time, or reach us by email at infocenter@LLS.org. Information Specialists are available to answer your questions about treatment, including clinical trials, or answer other questions you may have about support, including financial assistance for treatment.

The Leukemia & Lymphoma Society offers online chats for patients and caregivers to share experiences and support each other. The chats are moderated by oncology social workers and the Adults with Acute Leukemia Chat is held on Thursday evenings. For information or to register to participate, review the flyer in your packet, go to www.LLS.org/chat or contact an Information Specialist at The Leukemia & Lymphoma Society.

Dr. Litzow, thank you again for volunteering your time with us today.

On behalf of The Leukemia & Lymphoma Society, thank you all for joining us for this program. Goodbye and we wish you well.

[END]