Sima Jeha, MD
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Operator: Good afternoon, and welcome to "Childhood Leukemia and Lymphoma: Update on Treatment and Follow-up Care," a free telephone/webcast education program. It is now my pleasure to introduce your moderator, Ms. Lauren Berger. Thank you, Miss Berger. You may now begin.

Lauren Berger: Thank you and hello everyone. On behalf of the Leukemia & Lymphoma Society, we thank you for choosing to spend this hour with us today. We welcome you to "Childhood Leukemia & Lymphoma: Update on Treatment and Follow-up Care," featuring Dr. Sima Jeha. We thank her for sharing her time and expertise with us today, and for her dedication to serving families touched by cancer.

You all should have received information regarding today's program, either in the mail or via E-mail, including an agenda, a biography of our speaker, and an order form for the Leukemia & Lymphoma Society's materials. We encourage you to look through all the materials at your leisure if you have not already done so. You will also find an evaluation form for you to fill out for today's program. For nurses and social workers, you can receive one hour of continuing education credit.

After Dr. Jeha's presentation, we will take questions from our telephone and our web-based audience. Today, we have over 1,100 individuals registered for our program from across the United States, and several international participants from Canada, Australia, the United Kingdom, Mexico, Venezuela, Saudi Arabia and Denmark, and we welcome all of you.

If we're not able to get to your questions today, you can call the Leukemia & Lymphoma Society's Information Resource Center toll-free at 1-800-955-4572. This number is listed on many of the materials in your packet, and this number will connect you with an oncology professional who can answer your questions, help you obtain information, or order free material specific to your needs. The Information Resource Center's hours are 9 a.m. to 9 p.m. Eastern Time, Monday through Friday.

We are also audio taping and transcribing today's program for posting on the Leukemia & Lymphoma Society's website in several weeks. This provides you with an opportunity to read or listen again to today's program, especially to follow up on any terminology or therapies that you may have missed.

Before I turn the program over to Dr. Jeha, I would like to introduce the Leukemia & Lymphoma Society's President and CEO, John Walter, who is on the call today to welcome you and share a few words. John, thank you for joining us.

John Walter: Thank you, Lauren. I'd like to add my welcome to all the parents, patients, caregivers, and healthcare professionals on the call today. We are very fortunate to have as our presenter today Dr. Sima Jeha, who has dedicated her career to improving the lives of those with childhood cancers and their families. Dr. Jeha is an expert in childhood leukemia and lymphoma, and we appreciate her dedication to supporting the mission of the Leukemia & Lymphoma Society through her research and her work every day with children and their families. I wish to thank Dr. Jeha for taking the time out of her busy schedule to help further your understanding of childhood leukemia and lymphoma, as well as follow-up care.

The Leukemia & Lymphoma Society is committed to bringing you the most up-to-date information about blood cancers. We know it is important for you to stay current so that you can work with your healthcare team to determine the best options for the best outcomes. Our vision is that, one day, the great majority of people who have been diagnosed with a blood cancer will be cured, or they will manage their illness with good quality of life. Since its founding in 1949, LLS has invested more than $680 million for research specifically targeting blood cancers. We will continue to invest in research for cures, programs, and services that improve the quality of life for patients and families. We hope this teleconference will be helpful to you on your family's journey forward. Thank you and I'll turn the program back over to Lauren.

Lauren Berger: Thanks so much, John. I now have the pleasure of introducing Dr. Jeha. Dr. Jeha is the Director of Developmental Therapeutics in the Division of Leukemia and Lymphoma at St. Jude Children's Research Hospital in Memphis, Tennessee. Dr. Jeha's complete bio is included in your package, and I encourage you to read it. Dr. Jeha, thank you so much for being with us today, and I will now turn the program over to you.

Dr. Jeha: Laura, thank you very much for the kind introduction, and good morning, or good evening, everyone, depending on where you're calling from. I would like to thank the Leukemia & Lymphoma Society for giving me the opportunity to share this hour with you, and I also would like to thank them for forwarding me some of your questions, based on which I will tailor and guide my talk today. Then there will be time for questions at the end of the talk.

So, my talk today will be divided into several parts. I will start by mentioning briefly a word on causality of leukemia and lymphoma, then the diagnosis, then there will be a part on treatment. And finally, I will cover side effects of treatment. This will include the acute, or short-term, side effects that happen during treatment, and also the long-term side effects that can be seen or detected after we finish treatment.

Dr. Jeha:

One of the common questions that parents ask themselves when the diagnosis of leukemia or lymphoma—or actually any cancer—occurs, is whether this is inherited or whether it was caused by something that they could have foreseen or prevented. The research today has demonstrated that genetic abnormalities do play a key role in the development of cancer, including leukemia and lymphoma. Genetic abnormalities are common in both leukemia and lymphoma, and they serve as signatures that help in the diagnosis and the treatment of these diseases. With ongoing research in the human genome, there will be more signatures identified, and hopefully this will help more in learning about the causality and also about the biology of leukemia and lymphoma and finding new therapies. All this information is very useful and shows that genetics play a role in the causality of cancer.

Most of you know that constitutional chromosomal abnormalities are associated with an increased risk of leukemia and lymphoma. For instance, kids with Down's syndrome or Fanconi anemia tend to have a higher incidence of developing leukemia. Also, there are rare cases reported of clusters of leukemia within a family, and it is known that, in identical twins, the risk of developing leukemia in the identical twin if one of the twins develops it is higher than in the regular population, especially if the leukemia occurs in the first six years of life. Having said that, genetic changes do not necessarily mean that this is inherited, or that if a child has cancer, that it will mean that other family members, including the children of the patient in the future will develop cancer. Those associations are not quite identified, and there is no evidence for it to cause a lot of anxiety in cancer survivors, making them worry about marrying and having kids.

For instance, a genetic abnormality that's seen is neonatal blood spots that are present at birth; some of the children with those abnormalities end up developing leukemia, and others with that same abnormality end up not having leukemia. This is where the question comes about: "Is there a risk that is induced from environmental factors?" Might there be a predisposition in children that is accentuated by environmental factors? Those environmental factors could be anything from immune reactions to an infection, or exposure to some carcinogenic agents, whether this is a pesticide or even a prior chemotherapy agent.

In summary, there is an association between genetic predisposition and environmental factors that does play a role. There is a lot of research ongoing to really try not only to understand those associations, but to help prevent leukemia or detect it earlier in the future. However, to date, there is no evidence that the parents or the family could do anything to predict or to prevent the development of leukemia or lymphoma in their children.

Dr. Jeha: How is the diagnosis made? Many families get nervous about the diagnosis, because leukemia is basically a mimicker. Leukemia is a cell in the bone marrow which is where the blood cells are manufactured. The bone marrow is very active because our red cells are replaced every day. Because of the rapid division, one of the cells starts dividing, and if there is an abnormality, or loss of control, the division goes out of control, and then replaces the normal marrow. Subsequently, the red cells that give us energy, the white cells that protect us from infection, and the platelets that prevent bleeding, all decrease, and are replaced by the abnormal leukemia cells. This results in a variety of presentations, which can be anywhere from fatigue or pallor because the red cells are low; bleeding and bruising because the platelets are low; or fever because the white cells are low and there might be some infections. Some kids will present with increased lymph nodes, enlarged lymph nodes and fever, and, in some cases, they might be seen by their pediatrician with a prescription of antibiotics given. No improvement occurs, the patient is referred to a cancer center, and the family gets upset that the diagnosis was delayed one or two weeks. However, this is not unusual, because in most cases a small fever or enlarged nodes in children end up being a common infection. In very rare cases, it ends up being leukemia. A delay of one or two weeks many times is within normal, and it's okay. It's not considered missing the diagnosis, and it will not affect the long-term outcome. This is just to relieve the anxiety that some families feel once the diagnosis is made and they think they have been missing the symptoms. In reality, the symptoms can be very tricky sometimes, even for a doctor.

The main thing, especially for pediatricians or nurses listening in, is for the healthcare provider not to rush and give something like prednisone or other steroids, which are actually used in the treatment of leukemia, and can induce remission. Sometimes steroids are given because the diagnosis of juvenile rheumatoid arthritis is made because a child is having bone pain, and the symptoms improve because steroids are good for both juvenile rheumatoid arthritis, and for leukemia. But when it's leukemia, the symptoms will ultimately recur, and then it will be more difficult to treat a leukemia that has been treated with steroids just because it will be considered like a relapsed leukemia.

A short delay in diagnosis does not affect the outcome. What affects the outcome is when the kid is sick, or has high count and this missed, or when the wrong diagnosis is made and treatment with steroids is initiated.

Once the diagnosis is made, it's a very traumatic time for the family because most of the time, as I mentioned earlier, the diagnosis mimics infection, and the parents are expecting to go to the doctor and come back home and take care of business with the other kids and with other

Dr. Jeha: family problems and issues. When they are told it's leukemia, the whole life of the child, but also the family and the siblings, changes. It's an acute change with a lot of new information, new vocabulary, and a new life that starts for the next few months in the case of lymphoma and acute myelogenous leukemia, or AML. In the case of ALL, it can be up to three years. With non-Hodgkin's lymphoma, it can also be prolonged.

It's a sudden change in lifestyle that will take over about a year, plus or minus, of the family's life. It's very important to have resources, and it's good to have the Leukemia & Lymphoma Society and other resources like that to help families in their time of need. The main thing is to make sure to ask your doctors all the questions, ask the nurses all the questions. It's your right to really understand what's going on, the terminology, and the treatment to be given.

For AML, or acute myelogenous leukemia, the treatment is intensive chemotherapy, and it's given in either four or five courses, and different protocols can vary. It hasn't been really proven whether four or five are better. In some protocols, they give only four and it might be sufficient, but in most protocols, we still give five. Basically, the treatment finishes in about six months. But during those six months, the children are, most of the time, in the hospital, or have very low counts.

For Hodgkin's lymphoma, the treatment is mostly outpatient, and it depends on the stage of the lymphoma. It can be outpatient chemotherapy plus or minus radiation therapy. Most non-Hodgkin's lymphomas are very similar to ALL. It's like a spectrum of disease, with almost the same type of cells, and sometimes it's a gray zone about whether it's truly ALL or lymphoma, especially for T-cell leukemia and non-Hodgkin's lymphomas that are pretty similar sometimes and require very similar therapy.

Burkitt's lymphoma, or the mature B-cell lymphoma, is different in the sense that it requires very intense short-term therapy, similar really to the AML that I mentioned before.

For the most common leukemia in children, which is acute lymphoblastic leukemia, or ALL, or non-Hodgkin's lymphoma, the treatment is longer. For ALL, the duration of treatment is three years.

Many families, when they are diagnosed, are wondering what's the best treatment, where to go, what's the best place. The good news is that for childhood ALL, there are a variety of options that you can hear of when the child is enrolled or is offered therapy, but it can become confusing. The Children's Oncology Group contains many of the protocols that treat most of the children in the U.S. A lot of international collaborators also

Dr. Jeha: apply these protocols. The outcomes are very good, with the cure rates over 80 percent and approaching 90 percent in children with low risk (meaning good age group, low count, and good genetic changes in the leukemia).

Some institutions, like St. Jude and Dana Farber, have their own in-house protocols. If you look at the protocols and the outcomes, the difference is really in the 1 to 2 to 3 percentile. Most of them had excellent results with very similar backbones.

The reason we enroll children on a protocol is because enrolling the child will allow the investigator to collect data. When you are on a research protocol for leukemia, it doesn't mean that your child is a guinea pig and you are trying an investigational thing on them, because in frontline leukemia, the treatment is very standard. However, it gives us the right to collect data and to monitor. So, in a way, it's better for children to be on a protocol because, if there is a side effect or a toxicity, when we are monitoring several hundred of children, we are more likely to notice a recurrent pattern. If our survival curve or outcome is not better than on prior protocols, we find this unacceptable. Usually, most of the protocols have what we call a Data Safety and Monitoring Board, which are experts from an outside institution that monitor to make sure that the treatment is safe and effective. Protocols are really very well designed and they are monitored, many times, by external investigators to prevent bias. There is a lot on the NCI (National Cancer Institute) website, toward the value of having a protocol. And several publications on the NCI website credit the advances in childhood ALL to the fact that most children with ALL are actually enrolled on protocols versus the adults, whereas most of the adults are treated off protocols.

You might be hearing a lot now about how, in childhood ALL, the outcome is much better than in teenagers or adults. Whereas there are many factors that can create this difference, including the biology of the disease and the organ function, which gets worse with age and maybe affect the prognosis, many people also feel that the fact adults do not enroll on study and are not monitored as closely explains why advances are not made in adult ALL as much.

The summary is that the childhood protocols are different. They span over three years, including an induction phase of about one month followed by an intensive consolidation phase of about six months to one year, depending on the risk group, and then followed by two years of maintenance therapy, which is a milder form of treatment, but which is necessary to really get rid of the leukemia and not have it recur.
And if you look at the protocols, again, they are similar: They use drugs that have been available for 30 years now. But, with every protocol, we

Dr. Jeha: ask one or two questions in order to better improve the use of the medications that we have. Usually those questions are rational, like, we try to improve and sometimes we randomize, what we call randomize the patient, meaning if we don't know if a change in the chemotherapy will improve the outcome like we expect we treat half the patient on one arm and the other half on another arm.

Parents wonder, "Which arm should we go on?" and they wonder about the concept of randomization. Whenever you are offered a randomization by your doctor, this means that the doctor does not know which arm is better. And if we know which arm is better, ethically we need to stop the study immediately and treat the children on the arm that is better. Most of the time, we don't know which arm is better until the study closes, and then we apply the treatment in the better arm for the next protocol. And the next protocol will ask a new question. This is really the basis behind protocols.

Again, you need to discuss with your doctors what the other options are. When I discuss with patients, I tell them what's investigational in the protocol. There are things that are standard and there are things that are more experimental or investigational. The parts that are investigational, like randomization and research testing, are usually optional. Parents should have the right to say that they want to participate in the protocol but they will not participate in the research test. Not participating in an optional part of the study should not be taken against you. Do not feel that you owe it to the doctor or to the institution to enroll in those optional tests. It's your right to say, "I want to take the standard treatment." In this case, your child will be treated on the standard arm. But you will still be enrolled on the protocol, and your child will still be followed. As I mentioned earlier, they will still be monitored for toxicity and outcome. However, they will not necessarily participate in the research test if you are not convinced that this is in their best interest or if you feel that the research test will cause anxiety, pain, or whatever it is that will interfere with the quality of life. Most of the time, those optional tests tend not to interfere with the quality of life, and in that case, parents do not mind enrolling their kids on it. But again, still they remain optional irrespective of whether they do or do not interfere with the quality of life.

The other option, of course, is for the child not to enroll on the protocol at all. If the child refuses to enroll altogether--so remember, the options are you have the protocol, and there are the parts that are standard, and you have the optional research tests. If you enroll, you can go with the standard treatment plus or minus the optional tests. If you refuse even the standard treatment on the protocol, usually what you need to do is ask the investigator or your doctor, "What is the option?" Most of the time, the option would be the standard arm of the protocol. For instance, at St.

Dr. Jeha: Jude, if a patient refuses to enroll on a protocol for some reason, what I offer them will be the standard arm of the protocol, because this is the best treatment usually—the standard arm—that we know of. Ethically, we cannot offer less than the best treatment for the patient.

If you are not on a protocol, the disadvantages would be that the follow-up might not relate to the follow-up of the group. So, again, there might be some side effects that are missed because they are not collected the way we do collect them on an official protocol. Protocols are meant to protect you. You shouldn't be scared of them, but you should understand them.

It's hard, when the diagnosis hits the family, to tease out what's investigational and what's not. The consent form should be done slowly, and the parents should have time to think about it. At St. Jude, we have the parents sign two consents. The first one is induction, which is pretty straightforward standard therapy. When it comes time to optional randomization and the continuation, we have another consent at the end of induction. By that time, we feel that the family is more familiar with the leukemia, the diagnosis and the terminology, and can make a more informed decision with less stress and be less scared than at the beginning.

Once all the treatment is over after the three years, we usually do a spinal tap and a bone marrow just to make sure that there is no leukemia before we stop. Then we have a big party and we stop chemotherapy.

The follow-up depends at different centers and different groups, as to how they do it. Usually a follow-up of about three to four times a year the first year of therapy is enough. And just a follow-up for count history—this is a good exam—we don't need to do marrow. In the past, we did marrow after we stopped therapy. But now, we tend not to do that. The second year, twice a year is enough, and after that, yearly follow-up. At St. Jude we've always followed the patient yearly until adulthood. Now there is a nationwide move to follow those patients yearly for life.

The reason to do that is because we know that most children with ALL will be cured, and we want to make sure that they reach adulthood. In the same way we followed the side effects while they were on protocol and treated, we want to make sure that there are no side effects that happen after they stop the protocol, whether they are cardiac, or even psychological. It could be discrimination in health insurance or jobs, and we like to keep track of that. So now there is a national effort to keep following patients. Of course, it's optional, but I think this program is very popular and most of our patients are still followed for life. We have yearly events for them called the St. Jude Life, and we keep following them to make sure that they have a productive and healthy life.

Dr. Jeha: As I said, most of the treatment consists of drugs that have been discovered more than 30 years ago; however, now we are living in a very exciting era. First of all, we have the technology, from genomics to flow cytometry, to where we really understand the biology of leukemia much better than we did. And we have signatures, as I mentioned earlier, that allow us to target the leukemia, whether it's with immunotherapy or molecular therapy in addition to the chemotherapy. For instance, there is now rituximab, which is a monoclonal antibody that is used a lot in mature B-cell lymphoma in conjunction with chemotherapy. The good thing about rituximab (the immunotherapy) and the chemotherapy, is that they have different mechanisms of action, and the toxicity is not overlapping. So, you combine them and you have an additive effect without increasing the toxicity much, because the toxicity is different. It doesn't overlap.

Research is ongoing, first to discover or to develop more monoclonal antibodies other than against CD20. There are some against CD19, CD22, etc., which are all markers on the leukemia cell. These monoclonal antibodies are being manipulated to where they are attached to either cytotoxic agents or things that enhance cell kill. All these antibodies are in early phases and I hope most of your children will not need them, because, in order to develop new agents, they have to be used first in relapsed leukemia, then they are advanced to frontline if they prove to be safe and effective.

Other than the immunotherapy that I mentioned, there is cellular therapy, and now you might have heard about natural killer cells. The natural killer cell is part of the immune system, and it has been shown to play a key role in keeping the cancer in remission. Now there are ways to treat the patient with natural killer cells. Of course, the question remains now, because all those are still investigational approaches, how much the natural killer cell will add to the armamentarium of leukemia. Immunotherapy [and] cellular therapy both take advantage of the role the immune system plays in leukemia.

And we have molecular targets. One of the most successful stories about molecular targets in the treatment of leukemia is the story of the tyrosine kinase inhibitors; imatinib first and now dasatinib. And there are several others under development. Iimatinib, or Gleevec, targets the BCR-ABL, which is caused by the translocation of the Philadelphia chromosome, which is not very common in childhood leukemia but it infers a poor prognosis. Now we are combining the tyrosine kinase inhibitor, meaning imatinib or dasatinib, with combination chemotherapy. They are additive in effect, because they target different targets in the cell. They act in different mechanisms, and they don't have overlapping toxicity.

Dr. Jeha: There are a lot of publications already from both adult Philadelphia-positive and pediatric Philadelphia-positive leukemia, showing that since we added these tyrosine kinase inhibitors—those molecular-targeted agents—to combination chemotherapy, the outcome of Philadelphia-positive ALL has significantly improved. We are reaching a point to where this might change our approach to transplant, to where we might see that we can get away transplanting less patients than we did in the past.

This will bring me to the transplant: "When do we do it and why don't we do it? This is actually a large subject, but in summary, we transplant patients mostly when they have relapse after relapse, because once they relapse on the current protocol, especially if it's an early relapse or a relapse on therapy, the chances of them being cured and staying in long-term remission are small. So, we offer them transplant.

Transplant is offered in first remission only to the very high-risk patients. And those constitute less than 5 percent of all newly diagnosed patients with ALL. The question would be, "How do you identify those patients?" Those are identified by many ways, because there are different prognostic factors, including the white count, age, sometimes location, that impart a poor prognosis on the leukemia. One of the factors that has really helped us in the past years, to determine the risk and to tailor therapy, is the assessment of minimal residual disease. Minimal residual disease, or MRD, means measuring, either by flow cytometry or by PCR methods, molecular methods, the amount of leukemic cells that we cannot see in the microscope when we look at the marrow.

Sometimes I hear confusion from families about the use of MRD, because when we started using it (as I mentioned about the purpose of protocols earlier where we have some optional or research tests) the theory was that since there are so many prognostic factors (age, cytogenetics, response), we determined that probably measuring the response to therapy is the best way to assess all those prognostic factors taken together. Because ultimately, what you want is a good response to therapy. So, it was a hypothesis that children who cleared their leukemia fast, or are called good early responders, who achieve minimal residual disease that's undetectable early on in induction, would be more sensitive to chemo and have a better prognosis. When MRD started being tested, it was tested to prove the theory, so we were not sure if this was correct. And we were—many protocols were just collecting the data but not acting on it. But now more and more institutions are actually acting on this data. We are at St. Jude, and I know that COG and Dana Farber are too, because we documented that MRD is helpful in guiding the therapy.

In children who achieve MRD negativity early, which means they cleared the leukemia even by MRD determination, which is very sensitive, the

Dr. Jeha: prognosis is very good, and we don't need to be very aggressive with therapy. This way we prevent unnecessary side effects because we know they will do well, whereas the patients who have high levels of MRD need to move to an arm where we give them more intensive therapy.

In the newly diagnosed, MRD is helping us a lot at St. Jude, and I think at COG also, to determine what patient goes into transplant in first remission. If a patient does not achieve MRD negativity, at a certain time point or at a level which we determine is safe to prevent relapse at a specific time point, then we discuss transplant in first remission with the family.

But, as I mentioned earlier, MRD can actually help us decrease the intensity of therapy. And going back to the Philadelphia-positive chromosome, now that we are giving the tyrosine kinase inhibitor with chemo in children who have a rapid early response and are MRD-negative, we are starting to shy away from transplanting them in first remission despite the Philadelphia-positive chromosome because of their rapid response, especially if they don't have a sibling matched donor. This is, really, in a nutshell, where most of the standard protocols are now.

In addition to the new therapies I mentioned, immunotherapy and molecular therapy, there are also two new drugs that have recently been approved for leukemia. One of them is clofarabine, which is a new nucleoside analog, in the same family as cytarabine. Another one, which is also a nucleoside analog, is nelarabine. Clofarabine is active against ALL and is approved for relapsed ALL in childhood. It's also being used in AML in adults on an investigational basis.

Nelarabine was approved for T-cell relapse, and both clofarabine and nelarabine are being introduced into protocols, not only for relapsed leukemia, but also for high-risk leukemia in the frontline. This is where determining the risk is very important, because you can even add novel therapies to the kids who are at high risk of a relapse, because you want to really prevent that relapse. Whereas the kids who are standard risk, you don't need to do investigational therapy in them.

What are the risks of all the therapy that we give? I will go briefly over that and leave room for questions, and, this way, answer the questions about toxicity that you are most interested in.

Basically, there is the acute phase of toxicity, and the most important and dreadful one is infections. You can have opportunistic infections in immunocompromised patients, and if a patient has infection when their white count is zero, they have no immune system whatsoever. Any fever

Dr. Jeha: or deterioration in clinical status needs immediate attention and immediate initiation of antibiotics because you can go into septic shock within less than one hour.

This is why we advise all patients, when they are in induction or in phases of intensive therapy, to be less than one hour away from a very good medical center, and to call if the patient has fever, before even coming. If a patient who is near to a clinic calls St. Jude, we pull the chart, we have the antibiotics ready, and as soon as the patient arrives, cultures are drawn, and antibiotics are started immediately.

We have to remember that patients do not die only from leukemia. They can also die from toxicity. And preventing infection and treating them early is the best way to prevent death in remission, which is very devastating. The parents and family have a great role in identifying that there's a change in the clinical status of the kid and bringing them to attention immediately.

I will not go over hand-washing and all that stuff because I'm sure all of you are very familiar with the recommendations to prevent infection.

Other side effects of chemo are neurologic side effects. At St. Jude, we are not using cranial irradiation as a preventive measure. We only use it on patients who have a CNS, or central nervous system, relapse. However, we don't use it frontline because we are trying to minimize the effect of irradiation. Having said that, we have to remember that even intrathecal therapy and high-dose methotrexate can also cause some CNS or neurologic toxicity. The effect of these varies, and you can have some patients who develop seizures during treatment. If those happen, they need to be appropriately addressed, and the patient needs to be on an antiseizure medication that does not interfere with the chemotherapy. We have some good ones now that don't interact with the chemo.

Very rarely the neurologic sequelae are more severe, such as either weakness or paralysis; some of the time it reverses, sometimes not. But these are very rare cases, and, again, they can happen even with chemo or spinal taps. These need to be followed very closely by the investigator.

In most cases, neurologic toxicity, if it happens, is really low grade, and there are several studies being done on different protocols. For instance, at St. Jude, we follow the cognitive performance, including memory, and fine motor skills. We are trying to identify very subtle changes and see if we can do some modification or alteration or interfere to prevent them. For most cases, children who go through standard treatment for ALL go on to have a normal life, and even if they have a minor neurologic deficit that is detected only on testing, it's not severe enough to really interfere

Dr. Jeha: with their daily life. However, if you have a child at school who you think has some problem in attention or memory or behavior, you need to bring it to your doctor for follow-up on that.

With the current treatment of ALL, we are careful not to exceed the cumulative dose of anthracycline. Cardiac toxicity is very rare, and we monitor for it. We're very careful, but we don't see much of it, and we prevent it by not exceeding the safe cumulative dose.

In bone health, we still have to make some progress in a subtype of patients. Leukemia is a disease of the bone marrow, so by definition, when the patient's present, they might have some deficiencies already in their bone density; the bone density might be already low from the leukemia. With the chemo and the steroids, the bone density will only get worse. This is one problem they can have with bone. Another one, which is a more severe one, is avascular necrosis (AVN), which can lead to very severe pain and, in severe cases, necessitate hip replacement. Avascular necrosis is very uncommon in children less than 10 and is much more common in teenagers. The main causative agents are steroids, and there are a lot of studies to try to see whether we can diagnose it early [and] whether we can predict who will have it. There are a lot of studies about when it happens and what should we do.

I know you might really want to hear a lot of answers from me, but unfortunately nobody has the right answers for that. We do MRI here periodically as part of research on our protocol to see if we can detect AVN, but many places do not: They wait until the patient is symptomatic. Even when we detect it on the MRI, we are not sure what to do with it, and what's the best thing to do. Should we decrease the dex, stop the dex? Some people feel that once AVN happens, the damage is done, and whether you stop the steroids or not, it does not make any difference. Our incidence of AVN is similar to all protocols, so this is to tell you that different people follow their AVN, or treat them, or manage them differently. But, I think we all have very similar incidence. Again, it's most common in the teenager. A few cases require hip replacement, which makes it even harder because very few patients have this problem, which makes it more difficult to study and to compare methods because we don't have the numbers to do so.

However, those cases that develop this problem are devastating enough to be very frustrating, both for the family and for the physician. There is still a lot of research ongoing in this area, and hopefully one day we will succeed in, if not preventing it altogether, at least successfully diagnosing it, and knowing what to do once we diagnose it. Most cases cause pain, and with time, improve. Others require intervention. Intervention can be

Dr. Jeha: anywhere from core decompression of the joints, to relieve the pressure, to hip replacement.

In summary, it's a very interesting era for leukemia and lymphoma, because those diseases have made a lot of strides over the past 50 years. They were almost universally fatal in the 50s and 60s, now most children are cured, and what we worry about more are the long-term side effects. We still have those side effects to deal with, and we also have the few patients who have high-risk disease and who relapse. There's a lot of research ongoing with other approaches, whether it's new agents or new therapeutic approaches, such as immunotherapy or molecular therapy, to complement our current therapy and, hopefully, with the help of minimal residual disease, prevent relapse altogether. I will stop here to leave room for questions.

Lauren Berger: Thank you so much, Dr. Jeha, and we really appreciate the fact that you did answer many questions that were submitted prior to the program, so that's helpful. Now, for the interactive part of our session. Will the operator please give instructions so people can queue in with a question?

Operator: Thank you. To participate in the call by asking a question, please press star, then the number one, on your keypad. If you would like to withdraw your question, press the star, then the number two, on your keypad. If you are joining us by Web, simply click on the "Ask a Question," type your question, and then hit "Submit." We will take questions in the order they are received.

Be aware that, due to time constraints, we can only take one question per person. Once your initial question has been voiced, the operator will transfer you back into the audience line. Again, to participate in the call by asking a question, please dial star one on your keypad, or click on "Ask a Question," type your question, and then click "Submit."

Lauren Berger: Thank you, and please keep your questions general in nature. We'll take the first question from the telephone audience, please.

Operator: Thank you. Our first question comes from the line of Chiquita from Montana. Please proceed with your question, your mike is now live.

Question: Yes, I'm Chiquita from Missouri. But, anyway, my son, he's 18 years old. He was diagnosed two years ago with Hodgkin's lymphoma. The doctor didn't speak too much on Hodgkin's lymphoma. I just wanted to know, what is the survival rate for Hodgkin's lymphoma?

Dr. Jeha: Hodgkin's lymphoma, the survival rate, or the cure rate, even, is close to 90 percent. Most of the children with Hodgkin's do very well with chemotherapy plus or minus radiation therapy. Those who are refractory, or who relapse, are much more challenging, and might require more intensive therapy and transplant in some cases.

Lauren Berger: Thank you for your question. We'll take the next question from the Web. The question is, "My son has ALL low-risk pre-B, and is on AALL0331. He will finish treatment in June next year. What are your thoughts on end-of-treatment bone marrow biopsy to check for residual disease? My son's clinic said it is up to the physician as to whether this is done."

Dr. Jeha: At St. Jude, as I mentioned earlier, we do end-of-therapy evaluation, because most of the children have a line, and we really like to know before we remove the line, make sure that we have a final bone marrow before we stop. I will not say that it's wrong not to do it, but our practice at St. Jude is to do spinal tap and bone marrow at the end of therapy in all patients.

On the bone marrow, we don't do a biopsy, but we do an aspirate, and we check for minimal residual disease. Very, very rarely we see cases where the MRD is positive, and in that case we keep the line and we follow the MRD. But in most cases, I must say, the MRD is negative, and we end up removing the line. I wouldn't say that it has to be done in everyone, but our practice at St. Jude is to do it.

Lauren Berger: Thank you. We'll next--take the next question from the telephone audience, please.

Operator: Thank you. Our next question comes from the line of Diane from New Hampshire. Please proceed with your question. Your mike is now live.

Operator: Hi. My son was diagnosed with pre-B cell ALL in March of last year, 2009. I've always been curious about this, because he limped about six months prior to treatment, only when he ran and when he played; you know, when he was on his legs a lot. I've just been curious if limping that far in advance is any kind of signal that something was going wrong in his bone marrow?

Dr. Jeha: As I mentioned earlier, it could have been. I'm not sure about the whole six-month period. In many cases, we see kids who present with a history that has been going on for weeks, and in some cases, months. In kids, it's very hard to tell whether the bone pain is growing pain or from running, or whether part of it is from the leukemia itself. I don't want to say that any muscular pain from running should create alarm in the family, but one of the presentations of leukemia can be bone pain.

Lauren Berger: Thank you for your question. We'll take the next question from the Web. "My eight-year-old daughter had ALL and has been off treatment for two years. She's having memory and input/output processing problems, which are affecting her. Her oncologist does not believe these side effects are an issue and treats her as a normal child. We need to get help. What kind of doctor should we go to, and what suggestions can you make?"

Dr. Jeha: If you can go to a neurologist and have him advise for neuro/psych testing, this might guide you to at least quantitate and identify what the defects are, whether they are from chemo, or not. Sometimes it is hard to tell. It's similar to fertility. If kids are treated before reaching puberty, or even if they are women and are treated at any time, their fertility status is questionable. The only time that it is definitive is if they are boys, have reached puberty, and they do a sperm count. Most of the time with kids, it's hard to know later if the infertility was really induced by chemo, or they had a fertility problem already, or maybe it is a combination of both. It's the same for neurologic side effects or a neurologic problem. But, it might be attention deficit, or something that is easily treatable. I really suggest that you go to a neurologist and have neuro/psych testing and identify what the problems are. Whether they are from the chemo or not, usually the approach to treating them is the same.

Lauren Berger: Thank you. We'll take the next question from the telephone audience, please.

Operator: Thank you. Our next question comes from Mary from Oregon. Please proceed with your question. Your mike is now live.

Question: Yes. I was wondering how you see complementary and alternative medicine assisting with the standard protocol for children pre-puberty, specifically in terms of how massage is helpful, and integrating therapeutic touch for children who may have residual touch trauma from the invasive treatments?

Dr. Jeha: Yes, actually several centers have either hypnosis, or something similar, as part of things they offer the families, especially for children going to procedures where they use hypnosis, or imagery, etc. I am not against any alternative approach, whether it's a nutritional supplement or whether it's actually physical, such as massage, hypnosis, et cetera. What I always advise you to do is to discuss it openly with your physician, and I always ask my patients to discuss it openly with me.

The only reason is to make sure, if it's a nutritional or herbal supplement, that it's not something that might interfere with the chemo. Sometimes it can make the toxicity worse, and sometimes it can revert, or salvage the

Dr. Jeha: effect of the chemotherapy. An example is leucovorin, which is just folic acid, and it can really revert the effect of methotrexate. Discussing it with your physician will make sure that you're not giving something that can interact with the chemo and affect the outcome. The same for massage, or other things. You have to make sure that, for instance, the platelets are okay. Always discuss with your physician to make sure that it's safe, and if it is, then there is no problem adding it to the treatment.

Lauren Berger: Okay. We'll take a question from the Web, please. "If I suspect my child has AVN or osteonecrosis as a result of dexamethasone, is it reasonable to request an MRI, and what are the common signs that you see before diagnosing AVN?"

Dr. Jeha: Joint pain is very tricky in children with leukemia. Again, discuss it with your physician, and let them work it out. I would not expect that a family member or a patient can make the diagnosis, and many times we need extra testing because several things that the kids get can cause bone or musculoskeletal pain. The dexamethasone can cause muscular pain, and the withdrawal can sometimes cause musculoskeletal pain. Vincristine can cause pain and neuropathic pain, and also the pain could be from AVN. If your child has problems, you need to discuss it with the doctor. The first step would be to take a plain x-ray if AVN is suspected. Most of the time it will show on plain x-ray. If it's suspected and the plain x-ray doesn't show anything, then the next step would be MRIs if other causes of the musculoskeletal pain is ruled out.

Lauren Berger: Thank you so much for your question, and thank you so much to all of you for your questions. The Information Resource Center will be open at the Leukemia & Lymphoma Society following this program to answer any questions that you may have that were not answered during the call, and they will be happy to share questions with Dr. Jeha if your question was not answered on the call. In addition, they can provide you with information on clinical trials. As Dr. Jeha had mentioned, they can help you with a search, or provide any information, or answer questions. The Information Resource Center can be accessed at 800-955-4572.

Thank you, Dr. Jeha, so much. We're so grateful to you for donating your time today, and we thank you for all the work that you do in supporting families touched by cancer.

We hope that many of your questions were answered, and once again, please remember that the Information Resource Center is open to support you and answer questions. I encourage all of you to complete an evaluation form. Your feedback really helps us to plan future programs, and we read all evaluations.

Lauren Berger: On behalf of the Leukemia & Lymphoma Society, Dr. Jeha, we would like to thank you for sharing your time with us today. Good-bye, and we wish you well.

Operator: Ladies and gentlemen, this does conclude today's conference. You may disconnect your lines at this time, and we thank you all for your participation.