Pediatric ALL:
Update on Treatment and Follow-Up Care

October 23, 2013

Speakers: Susan R. Rheingold, MD | Cara L. Simon, PhD

someday is today | LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers

Slide 1 – Welcome and Introductions

OPERATOR:
Hello, everyone, welcome to *Pediatric ALL: Update on Treatment and Follow-Up Care*, a free telephone-web education program. It is my pleasure to introduce your moderator, Lauren Berger, of The Leukemia & Lymphoma Society.

LAUREN BERGER:
Thank you and hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. And our special thanks to Dr. Susan Rheingold and Dr. Cara Simon for sharing their time and expertise with us today. We are proud to offer this program in collaboration with Abrale and Alianza Latina of Latin America. We would like to acknowledge and thank Jazz Pharmaceuticals for their support of this program. Following the presentations, we will take questions from the audience.

Slide 2 – Pediatric ALL – Update on Treatment

LAUREN BERGER:
I am now so pleased to introduce Dr. Susan Rheingold, Medical Director, Oncology Outpatient Clinic, and Attending Physician at the Children's Hospital of Philadelphia, and Dr. Cara Simon, Pediatric Nurse Practitioner, Outpatient Leukemia-Lymphoma Program, at the Children's Hospital of Philadelphia in Philadelphia, Pennsylvania. On behalf of The Leukemia & Lymphoma Society, thank you so much for volunteering your time and your expertise today.

Dr. Rheingold, I'm now privileged to turn the program over to you.

DR. SUSAN RHEINGOLD:
Thank you very much, Lauren. And I'm thrilled that The Leukemia & Lymphoma Society has invited some pediatric acute lymphoblastic leukemia (ALL) specialists to talk with families, teachers, caregivers, about update on treatment, supportive care, and answer many of your questions that I'm sure you all have. I am the pediatric ALL specialist at the Children's Hospital of Philadelphia, and although I am sure many of you are very well-versed with leukemia, I decided I was going to start with a little bit of background about where we are.

Slide 3 – Types of Childhood Cancer
Childhood leukemia accounts for about a third of the types of cancer we treat in patients under the age of 15. ALL alone accounts for about a quarter, so in a sense it's kind of the bread and butter of pediatric oncologists. Over 3,000 children a year are diagnosed with ALL in the United States and, of course, more internationally.

Slide 4 – ALL Incidence and EFS (event-free survival)
If you look at this slide, bottom left, it shows that the incidence of lymphoid leukemia, or ALL, is increasing very, very slightly. But the good news is despite the fact that the amount of leukemia is increasing very, very slightly, the diagram on the right, shows that we are curing more and more patients with leukemia every year. And you can see the blue bars there for the children under 15, every decade or time period listed there, shows an improvement in event-free survival (EFS).

DR. SUSAN RHEINGOLD:

Slide 5 – Clinical Presentation of ALL
How do children with leukemia present? Many of you know this and fear these signs and symptoms. Very often they present due to the low blood counts because their leukemia is taking over their bone marrow. They start getting pale because they're anemic. They might have headaches, not have a lot of energy, might be taking more naps. Your platelets, which keep you from bleeding, are low, and that shows up as bruising, or maybe a child's gums are bleeding a little bit more when they brush their teeth.

The leukemia cells also like to go anywhere in your body where there's lymphoid organs, and your most common lymphoid organ is your lymph nodes. So children can have swollen glands and swollen lymph nodes. The leukemia will also infiltrate into the liver and the spleen. It can cause skin-type lesions. In boys, it can infiltrate into the testicles. And on the X-ray on the left, you see a diagram of a child who has leukemia but has a very large mass sitting on top of their heart, due to leukemic infiltrate into the lymph nodes there. Those children can present with trouble breathing or wheezing, looking almost like an asthmatic.

Slide 6 – Diagnostic Procedures
How do we officially diagnose a child or young adult with leukemia? We need to do a bone marrow aspirate and biopsy. A bone marrow aspirate, your bone marrow is where your leukemia is being made, as well as where usually all your healthy cells, your red blood cells, white blood cells and platelets are being made. So we need to look at that.

The first thing we do is we look at it under the microscope, that's called morphology. In the old days, doctors purely looked at it and that's how they determined whether—did it look like your child had lymphoblastic leukemia, did it look like your child had myeloid leukemia? Not really able to tell much more about the different subtypes.

But now we do something called *immunohistochemistry*, or you may hear it as *flow cytometry*, where we actually look for proteins on the outside of the leukemia cells to help us tell more specifically what subtype of leukemia it is. We look at the genetics of the leukemia cells, which are generally abnormal and not reflective of the genetics of all the rest of the cells in your body. So it's not the genetics you inherit from your mother and father, it's the genes of the leukemia cells that made them become cancer.

The other two tests are tests I'll touch on briefly, which are some of the new expanded tests that oncologists are doing on really a research level, to better understand leukemia cells. What proteins are they making extra, what genes are turned on, what genes are turned off, what genes are deleted? And this is helping us come up with some exciting new targets for what you hear referred to as *targeted therapy*. It's giving us a sense of what are the abnormalities that we could specifically turn on or turn off. And I'll give you some examples of where we have been very successful with that.

The other thing is, when the child first gets their bone aspirate and biopsy, we always do a spinal tap, looking to see if the child has leukemia in the spinal fluid as well. We all have terminologies for things in medicine—and it can get quite confusing—but CNS 1 means that there's no leukemia, when we look under the microscope at the spinal fluid. CNS 3 means there's clearly lots of leukemia. It's easy to spot in the spinal fluid. The child might even be symptomatic with things like headaches.

DR. SUSAN RHEINGOLD:
CNS 2 is a newer category that means that we rarely see a leukemia cell, so it's not completely negative, but we see one or two cells. For the most part, we treat these children currently as being negative, but we're investigating whether we need to be a little bit more aggressive with this population because are these the kids that go on to relapse in the CNS (central nervous system).

Slide 7 – NCI (National Cancer Institute)/Rome Risk Classification for ALL
When I first started my training many, many years ago, and learned about leukemia, if a child walked in the door with ALL, they fell in one of three categories. Anyone under the age of 1 was considered an infant. And infants need more intensive chemotherapy and are, unfortunately, not cured at the same rate as older children. If you were over 1, but under 10, and you had a white count when you walked in the door of the hospital of less than 50,000, you were considered standard risk, and that was the bulk of children. If you were over 10 and/or your white count was greater than 50,000 when you walked into the hospital, you were considered high risk.

Now, a lot of people take these as being bad. High risk sounds scary. High risk really has just come to mean that if we don't modify your therapy and get a little bit more aggressive, then you are at a higher risk of relapsing. But as you'll see, by some of my numbers coming up, the risk of relapse is very small in most populations of children with ALL, whether you're called standard risk, low risk, average risk, intermediate risk, high risk, or very high risk.

Slide 8 – Immunotyping/Flow
So as I said before, we use a machine to determine what proteins are on the outside of leukemia cells. And in the blue box with all the plus signs, that shows you all the things that would show you have AML and not ALL.

Now, what about B-cell ALL versus T-cell ALL? In this day and age, we treat them slightly differently. So it's important to know which subset you have. The B-cell ALLs are the things in the red boxes that are positive, and the T-cell ALLs are the proteins in the yellow boxes are positive. And that's what helps your doctor definitively tell you what kind of leukemia your child has.

Slide 9 – Childhood ALL Cytogenetics
I mentioned genetics of the leukemia cells. The majority of children and young adults are going to have B-cell ALL. It accounts for about 88%. Luckily, half of those patients have what we consider very good cytogenetics, meaning that their leukemia cells have genetic factors that say that they're probably going to be very responsive to chemo. An example of that is you normally have 46 chromosomes in your cells. The leukemia cells in children can have 50, 55, 56. And when it has that many chromosomes, that's actually a good sign to have extra chromosomes.

There can also be translocations, where two chromosomes split and then reconnect to one another. And there's an example of that in the yellow piece of the pie, TEL-AML or 12;21. That also traditionally has been associated with a good prognosis.

Our little bolt of lightning there I use to identify the types of leukemia that sometimes we can tell are going to be a little tougher to treat. So children who have less than 45 chromosomes in their leukemia

DR. SUSAN RHEINGOLD:
cells, we know don't do as well with standard therapy, and we may have to consider alternatives like bone marrow transplant.

The other group, the BCR-ABL or a translocation of chromosome 9 and 22, is referred to as the Philadelphia chromosome ALL. Traditionally as well, that was a subgroup of patients who we knew with regular chemotherapy didn't do as well and they went to transplant. But luckily, what we've identified, is an abnormality related to that chromosome translocation. It creates a protein that we now have a targeted drug to turn off. And just by adding that targeted drug to chemotherapy, these children are now cured at rates that are much closer to a typical child with ALL.

Slide 10 – Microarray/SNP (single nucleotide polymorphism)
Some of the fancier type stuff that is done—and it is certainly not done on every child—it's not going to impact currently how we treat your child today. We're using this kind of data to better understand subtypes of leukemia. It is something called *microarray* or *whole-genome single nuclear–type polymorphism*. In this patient, all these chromosomes have abnormalities. They have gene deletions or gene amplifications of the leukemia cells, and this particular example has a deletion of a gene called IKAROS. We've learned that these children, if they don't respond well to early chemotherapy, may also be tougher to treat. Perhaps, someday, we can discover a direct targeted therapy to treat that abnormality of IKAROS.

Slide 11 – Mapping the Human Genome
The next slide, don't get scared, it's just showing the many ways we now can look at a leukemia cell from a research side. Mapping the human genome was worth every penny because what we can do is we can tell genes that are overexpressed, genes that are underexpressed, what those genes do, how they're sequenced, how many copy numbers, and all that type of stuff is at the cutting edge of research now in leukemia, to try to help us determine who in the future might need bone marrow transplant earlier, who might benefit from a very targeted therapy, and be able to treat their leukemia with a simple pill, et cetera. But as I said, none of this right now is actively being used in any child who currently has leukemia.

Slide 12 – MRD (minimal residual disease): A Stronger Predictor of Outcome in ALL
An example of something that we are using, and something that was researched 10 years ago, was something called *minimal residual disease (MRD) testing*. And that, which was researched 10 years ago, is the basis for a lot of our risk determination and how we determine if you need more therapy or if you can possibly get away with less therapy if you have ALL.

What minimal residual disease testing is, or a lot of people refer to it as MRD, I can look under the microscope and tell you if maybe 1 in 100, maybe 1 in 200 cells look like a leukemia cell. In this MRD testing, a machine looks for those proteins on the outside of your child's leukemia cells and can tell you if there's 1 in 10,000 cells that are still leukemia cells, or 1 in 100,000 cells that are still leukemia cells.

When you look how children did at the end of their first month of therapy, based upon whether they had 1 in 10 leukemia cells, 1 in 100, 1 in 100,000—if you were negative, if you had less than 1 in 100,000—those children overall were cured 90% of the time. But children who still had 1 in 10 leukemia cells were

DR. SUSAN RHEINGOLD:
only cured about 50% of the time. What's important to realize when looking at this slide and all the grades in between is that all these children received similar therapy because we didn't know the importance of this at the point we were getting the data. It was just research labs.

Slide 13 – More Predictive With Time
Now we know that if your survival is going to be worse because you have minimal residual disease, we need to alter your therapy based upon it. And in this slide, these children's therapies were not altered. But in the current day, all therapy will be altered.

Slide 14 – MRD Trumps Cytogenetics
We looked at more particulars. We looked at minimal residual disease to see how it compared to the cytogenetics, the genetics of your leukemia. And what we showed is if you had good genetics of your leukemia but you still had minimal residual disease, you were going to do worse. So that minimal residual disease was actually more important than the genetics of the leukemia in some cases.

We also learned that B-cell leukemia, the minimal residual disease, it decreases much more quickly than in a child with T-cell leukemia. And so we've learned that we have to follow them differently for different subtypes, and this is also being done now for myeloid leukemia to truly understand how quickly a child is responding to therapy.

Slide 15 – COG (Children's Oncology Group) ALL Treatment Allocation
So all these data and all this stuff I've talked to you so far, shows how one investigational group, or the Children's Oncology Group (COG), allocates treatment. My three little risk groups that I had to memorize as a fellow is now much more complex. In the Children's Oncology Group, which is probably the largest pediatric treatment cancer group in the world and treats probably more children with leukemia than elsewhere in the world, they divide the T-cell leukemias from the B-cell leukemias now from the start. If a child starts on what is considered a standard-risk protocol, we take their cytogenetics, we take their minimal residual disease testing, and we determine whether in fact at the end of the first month, are they still standard risk or do we need to treat them with a little bit more therapy and up-risk them to high risk or very high risk, or is there targeted therapy. In the diagram is PH-positive, that's Philadelphia chromosome, and there is a targeted drug for it.

Same thing with T-cell ALL. Children are divided into low-, intermediate-, and high-risk therapy. So your doctors are doing this in a very organized fashion.

Slide 16 – B-ALL Post Induction Risk Groups
The next slide shows a complicated way that your oncologist would look at all the factors of your child's disease to determine at the end of their first month of therapy what their new risk should be, based upon minimal residual disease, genetics, how old they were when they came in the door, what their white cell count was.

The 5-year EFS represents the event-free survival, and that was predicted for each group. So you can see that the low-risk patients, these are the best of the best, had a cure rate greater than 95%. In a lot of worlds in cancer, that number's unheard of and it's considered those kids are practically cured.

DR. SUSAN RHEINGOLD:
The average-risk kids, 90%, 95%. High risk, which sounds scary, just means we're giving more chemo, but we're getting to almost the same number, 88% to 90% of kids are cured. The very high-risk group was any group that was less than 80%, so it includes children who might have a 40% chance of a survival and children who might have a 79% chance of survival. But their therapy within that is tailored appropriately.

Slide 17 – Therapy and Biology
So let's talk about the actual therapy. I list there some of the different groups that treat childhood cancer. So the Children's Oncology Group, as I said, is the national group that treats probably more children with cancer than anywhere else in the world and treats them on different clinical trials. Dana-Farber or Boston Children's also has a consortium for treating childhood leukemia, as does St. Jude, as well as TACL (Therapeutic Advances in Childhood Leukemia & Lymphoma), I listed as an example of a group of children's hospitals with leukemia expertise, who are focused on treating relapsed leukemia. Early-phase trials are new trials for those targeted therapies. We can't just put them in a newly diagnosed child because we know they do so well. First, we have to understand, what are the side effects of these drugs? What is the cure rate of these drugs, do they show any kind of improvement in outcome? So now we even have these specialty groups like TACL or POETIC (Pediatric Oncology Experimental Therapeutic Investigator Consortium) that just focus on children with relapsed leukemia, as does the Children's Oncology Group.

Slide 18 – Why Do Clinical Trials?
Over the decades, these clinical trial groups have continually increased survival in children with leukemia. So this slide, from the Children's Oncology Group and its predecessor, shows that way back in the late '60s and early '70s, when they first started treating children with leukemia with any type of medicine, they got up to about a 20% cure rate. But a lot of those children still relapsed and data showed that they were relapsing in their spinal fluid. But a lot of those children still relapsed and these children who were relapsing, were relapsing in their spinal fluid. And so that big jump from the white triangles to the yellow circles represented a group of families that agreed to go on a clinical trial, who were randomized to receive radiation to their child's brain and spine, or not, to see if that could prevent these CNS relapses. A very scary thing. If I was a family sitting in front of you and you told me about radiation, understandably I'd be scared. It increased children's survival by 40%—so from 20% to 60%.

Slide 19 – How Far Have We Come?
Since then, we've learned a lot better how to give chemotherapy through spinal taps, and we give a lot more spinal taps now than they did in the '70s. And so we've replaced a lot of the radiation with spinal taps and have continued for each generation to have more and more children cured from leukemia.

Slide 20 – Why Aren't the 15- to 21-Year-Olds Doing Better?
I happened to see some of the questions that people put in, and a lot of people are asking the very appropriate question about the teenagers and the young adults. So when this diagram was published, what they realized is when you look at the children under 15—most of them were enrolled in clinical trials—showed continual improvement. But the 15- to 19-year-olds kind of had hit a plateau in the '80s,

DR. SUSAN RHEINGOLD:
'90s, entering 2000. These patients kind of leveled off there. We weren't improving their survival. And one of the first things we did was we said well, where are they going, where are these patients being treated? And they were being split: they were being treated between pediatric oncology centers, adult oncology centers, and community oncologists, and no one was really investing in this subgroup.

In the past 10 years, the government and the oncology groups have really identified this as a group that we need improvement in.

Slide 21 – Best Therapy for Adolescents
In the next slide—these are studies from different countries—where they looked at adolescents treated in pediatric centers on pediatric protocols, and they compared them in the same exact countries to the same age patients, 15 to 21, treated in adult centers on adult protocols. And as you can see, everyone was shocked. Just by walking into a pediatric children's hospital and being treated on a pediatric trial or like a pediatric trial, you had a 20% higher rate of cure than if you walked into the adult hospital, which might be right next door. And that's when we realized that people 15 to 21, and now up to the age of 40, should really be treated like we treat pediatric patients.

I think the adults felt that the therapy was so intense that they weren't going to handle it. But a 20- and 30-year-old handles it just fine, that's very different from a 70- or 80-year-old who may have complex heart disease, high blood pressure, obesity, and other medical problems. And the real victory came, the last Children's Oncology Group trial that treated patients up to the age of 30. So if you happened to walk into an oncology center that was adult and pediatric, you could go on the Children's Oncology Group trial. And if you were over the age of 16, the 5-year event-free survival was 79%. So by using this risk stratification and saying older patients needed to be treated a little bit more aggressively, we have now worked in getting their cure rates of these teenage and young adults up to the rates that we might expect for a 10-, a 12-, and a 14-year-old.

Slide 22 – What Do Clinical Trials for ALL Ask?
Why do we do clinical trials? What do we ask? There are many different types of questions that can be asked in a clinical trial. One of the newer ones that we're delighted to be looking at is reduction in therapy. We found some of these patients who have very good outcomes don't need as much therapy to be cured, as maybe the patient next to them. And things like removing radiation from therapy, which can have a lot of late effects, are significant. So that's the first thing one may want to do in a clinical trial.

There's another section I call rearranging the deck chairs. We take different drugs, we try them oral, we try them IV, we try them in a different dose, we try them in a different order, and believe it or not, by fine-tuning that, we've also improved cure rates.

I think what a lot of people on the phone might be interested in is what about the new agents, the targeted agents? Are we seeing higher cure rates by adding in newer agents? Are they too toxic? Are they tolerable? A new agent is often tested initially all on its own, but when we mix it with the classic chemotherapy, do we have side effects that aren't good or at least side effects that we need to learn how to mitigate?

DR. SUSAN RHEINGOLD:

Slide 23 – Reduction in Therapy
So an example of a reduction in therapy, this is, on the left, the current trial for the low risk patients. These are the patients who we predict are going to have a 95% to 98% cure rate. We're not trying to show that one of these two arms is better. We're just trying to show that the arm on the left, which although is the same length of therapy, is a decrease in therapy overall. And if it's the same, well, then why don't we treat children with less therapy?

Slide 24 – Changing Drug or Dose
The survival curve on the right shows a study from probably about a decade ago, where we had shown in the Children's Oncology Group, that having something called a delayed intensification, so after you started your therapy, going ahead and giving a re-induction therapy, did that help? And we showed that one of those cured more children. So we said well, if one's good, is two better? And what we proved was that two versus one made no difference, so there was no reason to put children through all that extra therapy. Now, at least in the Children's Oncology Group protocol and most of Europe, they get one delayed intensification. That's kind of the standard.

Slide 25 – Dexamethasone vs Prednisone
Another example is we know dexamethasone is a stronger steroid than prednisone. Dexamethasone probably also penetrates the spinal fluid, and therefore decreases the likelihood a child will relapse with leukemia—that's the top of the slide there, which showed that the event-free survival was better for the children who got dexamethasone than prednisone. But the bottom half of that slide shows that the children who got dexamethasone were twice as likely to get a really serious side effect of therapy called avascular necrosis, where they got bone breakdown. It took kids and made teenagers unable to play sports any more, to have chronic pain, to possibly need a wheelchair in the worst scenario.

So what the Children's Oncology Group decided was to have that many children disabled didn't make sense. So if you're under the age of 10, you get treated with dexamethasone. If you're over the age of 10, when your risk of avascular necrosis is much higher, you get prednisone. So not only are we tailoring the best therapy, but we're again looking for the least side effects.

Slide 26 – Adding New Agents
What about adding new agents? This is the part probably that a lot of you are very interested in. We certainly have newer chemotherapy agents, and I gave two examples there, clofarabine and nelarabine.

Nelarabine is a very specific targeted drug for T-cell leukemia. We now have these drugs in up-front trials, meaning newly diagnosed children, if a family agrees that they want to go on trial, are getting randomized to therapy with or without the newer drug, to see if the newer drug, in addition to the regular chemo, will actually cure more children.

The next group is targeted agents. Imatinib is the name of that first drug ever that was designed to hit a genetic abnormality in leukemia. So that Philadelphia chromosome ALL was creating a protein that was telling the cells to divide and replicate more and more and more, and this turned it off. It's a simple pill. You take it with your chemotherapy. There are certain types of leukemia where all you do is take this pill. Dasatinib is the next generation of that.

DR. SUSAN RHEINGOLD:
Another example of a targeted agent is many people have an MLL (Myeloid/Lymphoid, or Mixed-Lineage, Leukemia)—it's a different gene on the 11th chromosome. That's an abnormality, and lestaurtinib was the first drug to try to tackle that abnormality.

The last group is something called immunotherapy. We have a working immune system, but the immune system often doesn't see the leukemia as foreign. So what we do is we work in different ways to harvest our own immune system to attack the leukemia cells, and I'll give you some examples of that.

Slide 27 – VHR (very high-risk) ALL - Schema
The very high-risk ALL patients are the ones we said had less than 80% survival. So what we're doing for them is we are taking all of those patients, and a third of them are being treated in what's called a *control arm*. That's the best therapy we know exists to date. Then there's two *experimental arms*. We're adding therapy, in the separate square boxes for each group, CPM/ETOP—which are two drugs, cyclophosphamide and etoposide, that we use in every patient who relapses. But we don't necessarily use the etoposide in everyone in first therapy. We are studying whether these kids who are at higher risk of relapse, if we treat them with some of the good relapse leukemia drugs, will we prevent them from relapsing in the first place?

In the red circle, CLOF, is the clofarabine. What if we give clofarabine-cyclophosphamide and etoposide, will we cure even more children up front?

Slide 28 – New Drug for T-Cell ALL
In the T-cell ALL trial at the Children's Oncology Group, the higher risk children are being randomized to receive nelarabine or not. So half the patients are getting it, half the patients are not. The trial's been open long enough that we know that the side effects are really no different between the two groups, but it's going to take quite a few more years to determine if there is a significant difference in survival between the two groups.

Slide 29 – Targeted Leukemia Therapy
What about targeted therapy? I gave you a diagram of a leukemic cell and all the different things that you could target. You can target proteins on the outside of it. You can target the drug transporters that spew the chemo back out and make leukemia cells resistant to chemotherapy. You can target the immune system. You can target how the cell processes the information, and you can turn off its ability to reproduce on the internal side.

Slide 30 – New Drug Targets
This slide shows all the different targets that have been identified and drugs that have been created both by hospitals, academic centers, and pharma, to target some of these internal pathways. This is extremely complex. A lot of these drugs are actually now FDA-approved to target these abnormalities going on inside a leukemia cell to keep the leukemia cells growing and dividing, and we want to turn that off.

DR. SUSAN RHEINGOLD:

Slide 31 – The First Molecularly Targeted Drug
As I told you, the classic example in the very first drug, which actually had Leukemia & Lymphoma Society-funded research, shows how chromosome 9 and chromosome 22 *translocated*, meaning they split and they reattached. When they reattached, they created a new gene called BCR-ABL. That gene sent a message to the cells to grow, grow, grow, grow. The drug attached to that BCR-ABL red section and turned it off.

Slide 32 – Targeted Therapy: The Way of the Future
On the left-hand side, the blue curve at the very bottom, was the Philadelphia-positive ALL children historically. The yellow line on top shows when you simply added this one drug to their chemotherapy, we increased their survival from 30% to 70%. And on the right, the slide shows when they broke down the children who got transplants and those who didn't. It showed that you did not need a bone marrow transplant anymore if you responded nicely to the therapy—all by adding one drug. So we love targeted therapy.

Slide 33 – ADVL114: Temsirolimus
Another example that also was funded by The Leukemia & Lymphoma Society research is a drug I do research on, and this is a trial of a drug called temsirolimus. Meaningless to you, but it regulates the part of the cell that says hey, this is a good environment, grow. Versus we're in the Sahara desert, don't reproduce, bad time to move forward. We're taking that and we're studying that drug on a regular chemotherapy backbone to see if it's tolerated and, therefore, will it cure more children.

Slide 34 – Monoclonal Antibodies
I talked about immune therapy and antibodies. There are all kinds of proteins on the outside of the leukemia cells. B-cells, T-cells, normal and leukemia cells have these proteins, and they're called CDs (clusters of differentiation). They're named CD-1, CD-2, CD-3. We have come up with antibodies to these proteins, so therefore an antibody sees that protein as foreign, attaches to it, and delivers a killer gift to the leukemia cell. So it could deliver something that's a poison to the cell. It could deliver a signal that causes the body's normal cells to come and attack it. These drugs are very, very promising. Many of them are approved and are increasing the cure rates of all different types of cancer, when we're studying them, because it's a delivery package that doesn't tend to have a lot of side effects, but delivers it.

Slide 35 – Mode of Action of BiTE Antibody Blinatumomab
A really new example, that a lot of people are hearing a lot of buzz about, that I've included, is something called blinatumomab. I do not name these things, a pharmaceutical company names them. But this is an example of how they created an antibody that attaches both to your leukemia cells and your normal T-cells. Your T-cells are the things that go out and they might fight when you have an infection. What this does is that it brings the T-cells near the leukemia cells to kill them, by connecting it, by that little green and red connector. Children who have not been responsive to prior therapy or resistant to classic chemotherapy are being put into remission using this type of antibody.

DR. SUSAN RHEINGOLD:

Slide 36 – What Is CART-19 Immunotherapy?
Another type of immune therapy that's in the news a lot and also is being funded, in part by The Leukemia & Lymphoma Society, is CART-19 or CAR immunotherapy. CD-19 is the protein on the outside of the leukemia cell. Here what they do is they take the child's T-cells out, and they engineer them in the laboratory to become cancer-killing cells. Then you put them back into the child and these engineered cells expand and go out and attack the leukemia cells. So as you see in the bottom diagram, imagine those yellow cells are your normal body T-cells and the orange cells are the leukemia cells, and it kills them.

What's nice about this is that those T-cells hang around. The longest patient—a year and a half later, we still can find those engineered T-cells. So without getting any more medicine or any more therapy, if another leukemia cells pops up somewhere, those T-cells are still there to fight infection, the way someone who received a chickenpox vaccine would be able to fight chickenpox if exposed.

Slide 37 – Clinical Update of Pediatric and Adult ALL Patients Treated With CART-19
So the data that we've talked about thus far is five children who have received this, they've been refractory, they don't respond to therapy any more. Chemo—their leukemia cells laugh at it. Many of these children have had bone marrow transplants and relapsed after. Four out of the five children went back into remission, and three are alive and well up to now, one year and a half out. Interestingly, one relapsed with a leukemia that didn't have that target protein on the leukemia any more. Same thing with the adults. We've seen similar responses with adult ALL and the adult form of leukemia, CLL, chronic lymphoblastic leukemia, as well.

So those are some of the really interesting and exciting new therapies for thinking about different ways of attacking children's leukemia when it comes back and when it gets resistant to classic chemotherapy.

Slide 38 – Take Home Message
So from the therapy side of things, the take-home message is we are curing more and more children with ALL. Changing around, adding more conventional chemotherapy is probably not going to make much more of a difference in the next several decades. Targeted therapy, on the other hand, is much more specific and often it's less toxic. So today's experimental therapy, these new targeted drugs, is likely going to be tomorrow's cure. I think for those of you who have adolescents and young adults or work with adolescents and young adults, the bottom line is, and the National Cancer Treatment Guidelines, recommend that anybody up to the age of 40 should be treated like children when it comes to ALL. They should be treated on pediatric-based protocols with the chemotherapy. A lot of the adult centers have adopted this and provide that therapy, so we've taken some huge strides in curing more of a population that traditionally was a little hard to cure.

This concludes my presentation. We're going to have an open question section at the end, but I am going to turn this over to Dr. Cara Simon, who's going to talk about the side effects of therapy.

Slide 39 – Side Effects of Therapy
Good afternoon. I'd like to thank The Leukemia & Lymphoma Society for sponsoring this program. I'm going to switch gears slightly and talk about the side effects of the chemotherapy.

DR. CARA SIMON:

Slide 40 – Side Effects of Treatment
So, side effects of chemotherapy can occur after chemotherapy, after radiation therapy, or even after some of the supportive care therapy. The severity of the side effects is going to depend on the type of cancer that we're treating, the location of the cancer, and the age of the child at the time of therapy, and the side effects can encompass all the body's systems.

Slide 41 – LLS Has Top Notch Resources
When I talk about the side effects, I'm going to talk about some treatment, but some of the treatment is going to vary from institution to institution. Each institution has their own guidelines, which are all evidence-based, but may differ depending on what part of the country or what part of the world that you're in. However, The Leukemia & Lymphoma Society and the CureSearch for Children's Cancer are both good resources for side effect treatment.

Slide 42 – Most Common Side Effects of ALL Treatment
The most common side effects of ALL treatment are hair loss, bone marrow suppression, impairment of the immune system, central nervous system complications, musculoskeletal complications, gastrointestinal complications, growth and development, and pain.

As I said earlier, the severity of the side effects are going to vary from child to child. Often I'll have a parent say, "My child's not having very many side effects, does that mean the chemotherapy is not working?" It doesn't necessarily mean that the chemotherapy is not working. The side effects are going to vary depending on the child.

Slide 43 – Hair Loss
So I think one of the side effects that affect people most, especially as the children get older and become adolescents, is hair loss, which can also be called *alopecia*. The chemotherapy can cause complete loss of hair or thinning of the hair, although usually with ALL, during the intensive phase of therapy, most children will completely lose their hair. It typically starts about 14 days after treatment is started. However, by the time the kids are in maintenance, the hair usually comes back, and you may see some minor thinning of the hair around vincristine treatments during maintenance, but for the most part the hair will come back during maintenance.

Slide 44 – Side Effects of Treatment
Bone marrow suppression is the most common dose-limiting component of cancer therapy. It's one of the few side effects that we hold treatment for. Most side effects of the ALL treatment, we will treat the side effects, but continue chemotherapy. However, with bone marrow suppression, we often will hold chemotherapy. Your bone marrow, as Dr. Rheingold mentioned, is the area where your red blood cells, your white blood cells, and your platelets are formed.

Slide 45 – Bone Marrow Suppression (Anemia)
So bone marrow suppression can cause anemia or a low red blood cell count. Your red blood cells are responsible for carrying oxygen throughout the body. If your red blood cell count is low, your body is not getting enough oxygen.

DR. CARA SIMON:
Some of the symptoms you may see with anemia are shortness of breath, headache, feeling more tired or fatigued, needing to nap, fast heart rate, or pale skin. In younger children, one sign often will be that they're not eating well because if they're 2 or 3, they don't normally—they won't tell you "I have a headache" or "I feel more tired," but you may notice that their appetite had dwindled.

Treatment for anemia would be red blood cell transfusion. The level of anemia in which you transfuse will vary from site to site, but one thing to remember is if the child is symptomatic, regardless of the number, you always transfuse.

Slide 46 – Bone Marrow Suppression (Thrombocytopenia)
Thrombocytopenia or a low platelet count is another sign of bone marrow suppression. Your platelets are the part of your blood that help to form the clot when you cut yourself. If your platelet count is low, then you have a risk of bleeding. Often this will be gingival bleeding, like gum bleeding or nose bleeding. You can get a lot of bruises, or black or tarry stools if there's bleeding in the GI tract. Or petechiae, which will look like little red spots. And treatment for thrombocytopenia or low platelet count is platelet transfusion.

Slide 47 – Bone Marrow Suppression (Neutropenia)
Neutropenia is a third symptom of bone marrow suppression, and it is when your neutrophils or your absolute neutrophil count is low. Your neutrophils are a type of white blood cell that are responsible for fighting infections, so if your neutrophil count is low or you have neutropenia, then you're not able to fight infection. Your body has no defense against infection.

We classify neutropenia as mild, moderate, or severe. It is often asymptomatic. However, the child may develop fever. If the child has fever and is neutropenic with an absolute neutrophil count less than 500, it's considered a medical emergency, and the child should be taken immediately to the emergency room or to the clinic and will most likely be admitted for IV antibiotics until it's found that the child does not have an infection. The lower your neutrophil count is, the more at risk you are for severe infection, and the longer that you have neutropenia, the more at risk you are for severe infection.

Slide 48 – Side Effects of Treatment
Another side effect of treatment is impairment of the immune system. This increases your risk for infection, and we know that we can treat some infections prophylactically or preventatively with antibiotics such as with PCP [*Pneumocystis* pneumonia], we know that we can prevent PCP by giving either Bactrim™, which is the most commonly used drug, or if you don't tolerate Bactrim, we can use other drugs, such as pentamidine or atovaquone.

We typically hold routine immunizations during chemotherapy—not necessarily because the immunizations are harmful, although live vaccines as varicella and measles should not be given because you can actually—if your immune system is not working properly, you can actually develop disease from the immunization. But if your immune system is not working correctly, you also will not respond to the immunizations as well as you should. So we typically will hold all immunizations until after therapy is complete, either 6 months or a year after therapy, to allow the immune system time to recover. However, we do recommend that anyone receiving chemotherapy receive a yearly influenza vaccine, and it needs to be the inactivated injection, not the nasal spray.

DR. CARA SIMON:

Slide 49 – Central Nervous System
Central nervous system complications can include cognitive deficits, behavioral changes, neuropathic pain, or a flat-footed gait. So with cognitive deficits, that is an issue that a lot of parents are concerned about because of intrathecal chemotherapy especially. Is this going to affect my child's ability to learn? There have been a lot of studies done, looking at cognitive outcomes in children with leukemia. However, most of them have very small numbers, so it's hard to make huge generalizations based on these small numbers. Most of them do, however, report about a 20% to 40% incidence of cognitive problems in the school-age children. And most of them report that the younger the child is, the more likely they are to develop problems.

The high-risk protocol in COG currently has a sub-study in it looking at cognitive outcomes in children with leukemia between the ages of 6 and 11. You also will see behavioral changes, especially when the child is on steroids. For the parents that are out there, I'm sure this is hitting very close to home for you when your child is on steroids. They often have personality changes, they may be more aggressive, and this appears to happen more in younger children than in the older children.

And then with drugs like vincristine, they can also sometimes get neuropathic pain or a flat-footed gait, which can be improved by medication specifically for neuropathic pain, such as Neurontin®, or through physical therapy.

Rarely with ALL, you can have children develop seizures, strokes, or change in mental status. These are usually related to the intrathecal methotrexate and usually occur about 9 to 11 days after the intrathecal is given. Typically you hold the intrathecal medication until the symptoms have resolved, and then often when the intrathecals are resumed, you resume intrathecal cytarabine—or the studies that say that if you do resume intrathecal methotrexate, it's suggested that you give leucovorin 48 hours after, although there's no evidence that that is helpful.

Slide 50 – Musculoskeletal Concerns
Musculoskeletal side effects that you can have are steroid myopathy or muscle pain. You can develop weakness, especially in the lower extremities. Osteonecrosis or osteopenia. An increased risk of bone fractures. Pain at bone marrow site. Most people recommend that, especially adolescents receiving ALL therapy, receive calcium and vitamin D supplements to help decrease the risk of osteonecrosis or osteopenia.

If you develop osteonecrosis, most children will develop it during maintenance therapy. The current recommendations in the COG studies are if you develop osteonecrosis in maintenance, that you hold the steroid that they are receiving—whether it be dexamethasone, or if they're older, prednisone—for at least 6 months or until symptoms significantly improve or normalize. And osteonecrosis is diagnosed by MRI.

The current high-risk ALL study has a sub-study in it that is a prospective study, looking for the incidence and natural history of osteonecrosis. It includes screening MRIs and pain assessment questionnaires that are given at the end of consolidation, the beginning of maintenance, and the end of treatment, so that we can find out more information about osteonecrosis. Osteonecrosis is one of the side effects that does not totally resolve once therapy is complete and can often impact quality of life.

DR. CARA SIMON:

Slide 51 – Gastrointestinal
Gastrointestinal side effects are mucositis, which can be mouth sores in the lining of the mouth, or it can be where it actually looks like the lining of the mouth has been scraped off—it sometimes isn't actual individual sores. Mucositis can actually occur all throughout the GI tract. We usually talk about it in the mouth because that's where we can see it, but you have the same mucosal lining throughout your GI tract, and the mucositis can occur throughout the GI tract. Sometimes when someone has mucositis in their mouth, they may also present with diarrhea, and the diarrhea can be caused from the mucositis in the rectum.

They can have nausea and vomiting, diarrhea or constipation, perirectal cellulitis, chemical or reactive hepatitis, pancreatitis, or veno-occlusive disease. For the mucositis, nausea, vomiting, diarrhea, constipation, and the perirectal cellulitis, we treat those with symptomatic treatments. There's a variety of different mouthwashes that can be used for both keeping the mouth clean and for pain, and also oral pain medicines, such as oxycodone or even in severe cases, IV pain medication. For nausea and vomiting, antiemetics. Always make sure that not only does the child have Zofran® or another strong antiemetic, but also other antiemetics, in case one is not enough. Parents should have medicines for a good bowel regimen.

With chemical reactive hepatitis, pancreatitis or veno-occlusive disease, the medications that were the causative factor would be held.

Slide 52 – Side Effects of Treatment
So cancer chemotherapy can also affect your growth and development, and it should be monitored throughout treatment. Early on in treatment, when the chemotherapy is more intensive, children may not gain weight at the rate that they should, and that needs to be monitored. If their weight is too low, then you need to think about intervening with NG (nasogastic) feeds or even with oral supplements.

The other thing that we often see with ALL is weight gain related to the steroids. Parents should be encouraged to offer healthy snacks, although I always explain to parents, we tell you to offer healthy snacks, but the steroids are going to make them crave things that are spicy and salty. Try and give them things that are spicy and salty in limitation, and the best thing is to encourage a healthy diet.

If the parent is going to give any kind of herbal supplement or any kind of natural homeopathic—herbal or vitamin, they should clear that through their oncologist first. It's not that oncologists don't want those medications used, but many of those will interfere with the medications and either block the medications from being absorbed or they may be toxic to the liver as well as the medications being toxic to the liver.

Another side effect can be pain, and the pain can be either acute or chronic. If they have active leukemia, they can have pain in their extremities and their long bones related to pressure in the marrow. The best thing—the first thing—is to treat the underlying cause of the pain and then also to give adequate pain medications. Often parents are afraid to give stronger pain medications because they're afraid of their child becoming addicted to the pain medication and that's really not a worry. You want to treat the pain, and you can use both pharmacologic and nonpharmacologic treatment of pain.

DR. CARA SIMON:

Slide 53 – Psychosocial Effects (Fear)
Some of the psychosocial effects are fear: fear of the unknown, fear of treatment and procedures. Sometimes parents will feel guilty for not realizing how sick their child was, or the siblings may feel guilty that they're healthy and their sibling has gotten sick. Or the parent may feel that they did something that caused this. The Leukemia & Lymphoma Society has a lot of information for caring for the caregivers on their website.

Slide 54 – Psychosocial Effects (Anger)
Parents may feel angry, and this is a normal reaction. Children may have expressed more anger than normal, and this could be a side effect of the steroids. And depression, feeling sad or blue, is a normal reaction to the diagnosis for both the parent and the child. Also, there may be changes in the family routine that bring about feelings of social isolation and loss.

Slide 55 – Quality of Life (QOL)
So I'm just going to talk briefly about quality of life. There have been a lot of studies, numerous studies done on treatment of ALL and how it affects the quality of life. And the studies all pretty much agree that quality of life is definitely impaired during treatment. It's impaired by the side effects; it's impaired by the isolation that can occur. It, however, can be affected after therapy, if they have prolonged side effects. When they've looked at children and adolescents with ALL, they've shown that when they've compared them to children without leukemia, that they have decreased quality of life scores.

Slide 56 – Survivorship
So as Dr. Rheingold said, the majority of these children are going to be survivors. So survivors should be followed annually, even years off therapy. Most survivorship programs will follow children with leukemia into adulthood or will be affiliated with adult centers who follow adult survivors. Late effects need to be screened. They need to be screened for cardiovascular late effects, growth and development, school performance, liver and renal function, and radiation field if they had radiation, such as cranial radiation, to treat central nervous system disease.

This concludes my portion of the presentation, and I'm going to turn it back over to Lauren with The Leukemia & Lymphoma Society for the question-and-answer section.

Slide 57 – Question-and-Answer Session

LAUREN BERGER:
Thank you so much, Dr. Rheingold and Dr. Simon, for your very clear and your informative presentations. As you just mentioned, it is time for the question and answer portion of our program. We'll take the first question from the web audience, please, and that's from Wendy, and she asks, "Can you please talk about skin rashes similar to eczema after ALL treatment? Also some muscle twitches at night, and sometimes just drifting off to sleep."

DR. CARA SIMON:
I have seen some children, it's been reported in the literature, after completion of maintenance therapy with mercaptopurine and methotrexate, of having skin rashes. Typically they resolve on their own, about 6 to 8 weeks after therapy, so it's not a long-term problem.

Then as far as the muscle twitches at night, that can occur during therapy. It's difficult to say what they may be from without knowing at what point on therapy. If it's a time period when they're on the steroids, children on the steroids don't rest as well and sleep as well, so that may be causing some twitching.

And then the third part of the question was post-treatment, when do post-treatment energy levels resume? That often is dependent upon the child. But most children within a few months of coming off therapy will be back to their normal level of energy. Most children during maintenance chemotherapy will be almost back to their normal level of energy and able to participate in school activities and sports as they did before.

LAUREN BERGER:
Thank you for your question, Wendy. We'll take a question from the Spanish audience, and this one is from Lilliana, and she asks, "Please define a relapse and also what is the chance of a relapse?"

DR. SUSAN RHEINGOLD:
So for all those children that aren't cured, those are generally children who relapse. So relapse means that after we have done a bone marrow and don't see leukemia in your marrow any more, we start seeing leukemia again. Officially, the definition of leukemia is greater than 25% bone marrow cells. But if a child has gone down to none and suddenly we're seeing 5 or 10 or 15%, we would consider that a relapse.

The number of children who relapse is small, so if 95% to 98% of a subgroup is cured, that means less than 5% of that group are going to relapse. The good news is very few children, probably only about 1% to 2% of children on ALL therapy, will actually die from side effects of the therapy or things completely unrelated to the therapy. Overall now in the United States do about 15% of children with all types of ALL relapse.

LAUREN BERGER:
Thank you for that question, Lilliana. We'll take the next question from the web audience, and this one is from Kimber. Kimber asks, "How do you know which type of ALL you have? All we were told is, 'It's ALL.'"

DR. SUSAN RHEINGOLD:
I'm sure if you went back to your doctor, your doctor would be able to tell you if it was B or T ALL, based upon that testing that they do when you're first diagnosed. As well, some of the trials, if you consented to go on a trial, it may say at the top of the consent document, for children with B ALL or T ALL. So the only way to really find out is to ask the doctor or look through any consents you may have signed for therapy.

LAUREN BERGER:
Thank you for your question, Kimber. We'll take the next question from the web audience, and this one is from Claire. Claire asks, "Can you please discuss the sibling risk of a child with ALL?"

DR. SUSAN RHEINGOLD:
That's an excellent question. The sibling risk is almost nonexistent. The one area of concern is identical twins, less than 5 years of age. So if identical twins, if one is young and develops leukemia, the risk that the other identical twin is slightly higher, but certainly far from guaranteed. I, in my entire career, have seen one pair of patients, Down syndrome identical twins—and that's two risk factors because children with Down syndrome are more likely to have ALL.

But if you have a child who's 2 and a child who's 14, it's really not of a concern. We don't test and we don't screen other siblings on a regular basis for leukemia. That being said, there is a very, very rare family cancer syndrome, also called Li-Fraumeni, where most everyone in the family has increased risk of developing cancer and needs to see a hereditary cancer specialist for that. But those patients, it's a very, very small and very unique group that is generally identified when you give a family history, when your child is first diagnosed. But for the most part, the risk to a sibling is negligible.

LAUREN BERGER:
Thank you for that question, Claire. We'll take the next question from the web audience. "You spoke earlier about minimal residual disease. How does 1 day matter when measuring the 8-day minimal residual disease? That is, if a person got it at 6 days, how useful is that measurement?"

DR. SUSAN RHEINGOLD:
We actually don't know the answer to that. We know that the majority of day 8 bone marrow are drawn on day 8, although the study would permit you to draw it on day 7 or day 9. But that day 8 is not nearly as important as the day 29, when you're much further into therapy. The day 8 just gives us a sense of how quickly do you respond. By day 8, if you've managed to completely clear your leukemia by a peripheral blood test, that's a sign that you're probably going to need less therapy, than someone who at day 29 still has some disease available. So the specifics of obtaining it on day 6, day 7, day 8 versus day 9 is unknown. The Children's Oncology Group will only consider the ones valid if you haven't actually gotten any of your chemotherapy for day 8 yet.

LAUREN BERGER:
Very good, thank you for that question. We'll take the next question from the Spanish audience, and this one is from Essie. Essie asks, "Can you please talk a little bit more about ALL in infants? Are there issues and treatments that are different than for children of an older age?"

DR. SUSAN RHEINGOLD:
Yes. Children with infant ALL very often have a genetic abnormality in their leukemia cell involving that MLL gene, and that is probably something that they were predisposed to, even in utero, that we could have predicted that they might develop leukemia with this. We know that this is a more aggressive form of leukemia, for whatever reason. When we treat these children with standard therapy that we would use to treat a 1-year-old, their outcome is very poor. And we know that the children under 3 months of age, even with more intensive therapy, their outcome is poor.

We also know that children of that age, regardless of whether they have cancer or not, are more at risk for infection and side effects, so they have to be treated very differently. They have to be given things to help their immune system. Sometimes they're treated with more preventative antibiotics. The children are

DR. SUSAN RHEINGOLD:
often in diapers and get a lot of bad skin breakdown. They can have trouble eating, and they can lose a lot of weight. So these children, have a 1-2 effect of a much more aggressive leukemia that takes more therapy to treat it, but they get much more side effects and they get much more ill from the chemotherapy than the older kids.

They are very actively working on ways to target the MLL gene, to focus just for that population. The current Children's Oncology Group trials for infants include a drug that targets that, but it's not a very specific target. It's kind of a loose target, so it probably will not make a difference in outcome, but it will help us understand if we did target it, did we help or not.

LAUREN BERGER:
Thank you for that question from Essie. We'll take the next question from the telephone audience, please.

OPERATOR:
The next question comes from Kristin in Massachusetts. Your line is now open.

KRISTIN:
Yes, hi. First I just want to say thank you so much for doing this. We all really appreciate it. It's very helpful. I just kind of wanted to ask a question about the cognitive outcome. Just wondering if there was somewhere where I could read more on cognitive outcomes, and also if there would be a test specific to ALL patients after treatments, that they could take and you could see if potentially there are any signs, disabilities, when it comes to school.

DR. CARA SIMON:
So for cognitive evaluations, there's not a specific evaluation for children who have ALL. But often if the parents come to us and they report that they're concerned or the teacher at school is concerned, then we will refer them for a neuro-psych evaluation. In the neuro-psych evaluation, they will do the full scale of cognitive evaluations, looking at all the different areas of learning. These can also be done through the school district. If you're at a center, at a large enough center where they have neuro-psychological therapists, then you can get the testing done at your center. But if you're not, then the school district is a good place to get that testing done. Then based on those results, the psychologist can come up with a treatment plan—or really an education plan—for the child, that can then be taken back to the school, to say "this is how Johnny needs to learn math, so that he can do well." It doesn't mean that he's going to do poorly in math and he's not going to be able to do well, it's that he may need a different strategy to help him learn than someone else in the classroom or the majority of the students in the classroom. Does that answer your question?

LAUREN BERGER:
At The Leukemia & Lymphoma Society, several of our chapters implement programs called Staying Connected, facilitating the learning experience during and after cancer treatment—as well as our fact sheets on long-term and late effects. So I'll give you the information to call the Information Resource Center at the end of this program, and you may be able to get some more information about this.

LAUREN BERGER:
We'll take the next question from the web audience, please, and this question is from Steve. Steve asks, "What should guide a parent's decision-making to accept standard treatment or to pursue a study treatment?"

DR. SUSAN RHEINGOLD:
I think that's a very, very personal choice. The trials, if they're open, are always offered to families. I think some families hear that this is the standard therapy, but you could get more and are the type of people that are well, if there's any chance we can get more, we want it. And there's other families that are no way, we know this cures 90% of the children, so we don't want to add any other risks. I think your doctors can guide you and answer questions, but I feel like for families, it's really an internal question. How do you view life, what are the kinds of things that you would find acceptable? If an arm has to have some hospitalizations, but another arm didn't, would that work with your family? Do you have five other children at home, so that would be a challenge? All those kind of issues are very acceptable to take into account.

The only reassuring thing we see about clinical trials is that each generation improves on outcome. Do understand that the questions we're asking are questions that are vetted. They're not driven by pharmaceutical companies, they're driven by top oncology minds, who focus on that pediatric disease. The government reviews these studies, and scientific committees review these studies. It can take 2 to 3 years easily to design and get one of these studies approved, so it's not light thinking.

So at least have the comfort that these are very well thought-through clinical trials. But your participation in it is completely your comfort with being randomized and understanding that your fate is up to a computer as to which arm you may end up on. If you feel like you couldn't tolerate one of those arms, then please, don't get randomized. We'll treat you with your best therapy, and we'll treat you just like the children who went on the study.

LAUREN BERGER:
Thank you, Steve. We'll take the next question from the telephone audience, please.

OPERATOR:
The next question comes from Jenny in Missouri. Your line is now open.

JENNY:
Yes, I was wondering if you could talk a little bit more about, I guess the difference between when a child has a bone marrow transplant. Is that a better outcome than the radiation or the chemotherapy? If you could go into detail about that a little bit more.

DR. SUSAN RHEINGOLD:
That's an excellent question because I didn't really touch a lot upon bone marrow transplants. The side effects of bone marrow transplant are very toxic, so a child that goes through bone marrow transplant for ALL will get total body irradiation. That does definitely increase some of the risk factors, the cognitive factor, et cetera. It will also make a child sterile. So when you compare it to chemotherapy, although chemotherapy might be a longer process, the risk of side effects and the risk of dying during the therapy

DR. SUSAN RHEINGOLD:
are not as great. That's why oncologists reserve transplant for the kids that have really proven to us that they're not going to have those 80% to 90% survivals if we just use chemo alone, with or without radiation. It's really a small percentage of children, less than 10% of children really now, or at least in the future trials, that will receive radiation.

So transplant is rarely the first recommendation, unless your child falls into a group that puts them at a tremendous risk of relapsing with chemo alone. Those patients will still need chemotherapy to get them into remission. So we have learned going into a transplant, with active leukemia, will not be successful. In fact, it's probably somewhere around less than 0.1% leukemia, where you should go into a transplant, although that data is being looked at.

So transplant, because of its late effects, because of its side effects, because of the risks of a child actually dying during transplant, is much higher than regular chemo, it's really reserved for the patients we know who are not responding the way we like, certainly for the children who relapse, who didn't respond to the chemotherapy the way we would like the first time.

LAUREN BERGER:
Thank you for your question, Jenny. We'll take the next question from the web audience, and we've received several questions on this topic. This one is from Patricia, who says, "I have a 21-year-old daughter who is a survivor of childhood leukemia, ALL, in 1998. She was treated on a standard-risk, standard protocol at Children's Oncology Group at that time. I'm curious, this far out of treatment—actually the Pediatric Oncology Group—I am curious this far out of treatment, if there are ongoing risks which she should be aware of?" And there are several questions, in their early 20s, and people ask those things.

DR. CARA SIMON:
Ongoing risks can be two things. It could be risk of recurrence of leukemia, and this far out, the risk of recurrence of leukemia would be very low. But as far as risk of side effects, a lot of that depends on the treatment and the drugs and the amount of the different drugs that they received. That's why we recommend that adults, even though it's been 10, 15 years since you received your leukemia treatment, that you follow in a long-term survivor program.

Studies that have been done, looking at long-term survivors and their health, have shown that long-term survivors of pediatric cancers have higher rates of other illnesses, such as heart disease or diabetes. In the long-term survivor program, the Children's Oncology Group has come up with long-term survivorship guidelines so that you can even be followed at your general practitioner's office if you are not near a major center. Then they can follow the guidelines as to what different testing, such as echocardiograms or pulmonary function tests or neuro-cognitive testing, that you should get done based upon the drugs that you received during treatment and the amount of the drugs you received during treatment.

For most children with ALL, they may have some neuro-cognitive deficits, if they were in the period in which they received a lot of steroids, so they may have some avascular necrosis or some osteopenia. In the current trials for leukemia, they get anthracycline therapy. They don't get a very high dose. But we still monitor echocardiograms about every 5 years to monitor heart function, but a lot of it is going to depend on the drugs that they received and the cumulative dosing of the different drugs that they received.

LAUREN BERGER:
Thank you for your question, Patricia. We'll take the next question from the telephone audience, please.

OPERATOR:
Our next question comes from Deborah in Pennsylvania. Your line is now open.

DEBORAH:
Hi. I was wondering about the long-term side effects of mercaptopurine and methotrexate and asparaginase. If you've had anaphylaxis, is Erwinia just as good?

DR. CARA SIMON:
So, long-term side effects of mercaptopurine and methotrexate, the things that they monitor long-term with those drugs are looking at liver functions. Both of the drugs are metabolized to the liver, and it's not uncommon during treatment that we see bumps in liver function with treatment of those drugs. That is also followed post-treatment, to make sure that those levels return to normal.

For asparaginase, I can answer and then Dr. Rheingold can add anything that I missed. If you have an allergic reaction to PEG-asparaginase, the recommendation is that you get Erwinia asparaginase. They're formulated in different ways. What we typically think of PEG-asparaginase is an E. coli-based asparaginase, and the Erwinia asparaginase is an Erwinia-based asparaginase, so there's not cross-reactivity between the two. We do recommend, because asparaginase is a very valuable drug in the treatment of leukemia, that if you react to PEG-asparaginase, that you do substitute the Erwinia asparaginase in its place.

LAUREN BERGER:
Thanks, Deborah, for that question. We'll take the next question from the web audience, and this one's from Jennifer. She asks, "Have you seen with small children that they lose bladder control or don't recognize when they need to go potty? Every bathroom trip for my child with ALL seems to be an emergency."

DR. SUSAN RHEINGOLD:
That's interesting, because I recently had a patient who had that issue. Interestingly, when I talked with the family, this child never had the issue at school and never had the issue at night. It was only during the day. I did send the child to a urologist to get a whole work-up evaluation, which found nothing. So that's not a typical side effect. The only thing I would consider doing is if you notice that it happens more when the child's on the steroid or right after the steroid pulses, the child could be having an issue with high sugars. The steroids are causing temporary diabetes, causing the sugar to be high, and when the sugar is high, it forces or it really makes a lot of urine. So like people with newly diagnosed diabetes, they're going to the bathroom a ton. Your doctor can do a very simple test if it seems to be related at that time, to look at kind of how much hemoglobin has too much sugar attached to it, which reflects kind of what's been going on over the past couple of weeks. Or, 4 or 5 days into the steroid pulse, they can check a urine and see how much sugar is in the urine itself.

LAUREN BERGER:
Thank you for the question, Jennifer. We'll take the next question from the telephone audience, please.

OPERATOR:
The next question comes from Anne from California. Your line is now open.

ANNE:
I think my question was answered. It was about the cognitive problem as a result of chemo or radiation. I wondered if that disappeared after treatment was over, or if it was a long-term problem.

DR. CARA SIMON:
The cognitive deficits, unfortunately, are a long-term problem. And with radiation especially, they have shown that the further out you get from the radiation, you continue to have, over time, changes in your cognitive function. It's unfortunately a side effect. However, it's not usually severe in most children. So it's usually something that can be worked around through the schools.

LAUREN BERGER:
Thank you for your question, Anne. We'll take the next question from the web audience, and this one is from Lee. He said, "My son finished treatment for ALL 6 months ago and had urinary retention following vincristine. He still struggles to release urine voluntarily and cannot empty his bladder fully. Do you have any information on this type of side effect and the prognosis?"

DR. SUSAN RHEINGOLD:
Typically the vincristine, which can affect the nerves, we see improvement with time off of the therapy. More common manifestation than the bladder manifestation is children who are clumsier, or have trouble with some of their coordination movement due to the vincristine affecting the nerves and their reflexes in their lower extremities. Generally we do see that get better with time. I still think it would probably help to see a urologist, to see if there's anything in the urodynamic world that could help the child. Or there could have been other side effects that might actually be leading to this—if the child ever had issues with bleeding from the bladder, that can sometimes cause a stiff bladder during their therapy. But I would hope things would get better, and I would have you get evaluated by a urologic specialist to see if there's anything that could be started that might help the child now.

LAUREN BERGER:
Thank you for the question, Lee. We'll take the next question from the telephone audience, please.

OPERATOR:
The next question comes from Erica in New York. Your line is now open.

ERICA:
Thank you for an excellent presentation, doctors. I wanted to ask whether you could briefly address fertility complications potentially after chemotherapy for pediatric—after the treatment of pediatric leukemia?

DR. CARA SIMON:
Fertility complications after pediatric leukemia, for most children who receive—who have leukemia and receive standard treatment, they don't typically have any fertility problems. Children that are—in studies, they've looked at females who are prepubertal, they have even less complications. However, if someone is needing to go to transplant because they have relapse therapy, then they will have issues with fertility as they get older.

DR. SUSAN RHEINGOLD:
There's also a subgroup of boys who have leukemia in their testicles, and if you need to radiate the testicles as well, that will of course affect sperm function. But for by far the majority of children undergoing ALL therapy, we would expect their fertility to be that of the normal population.

LAUREN BERGER:
Thank you, Erica, for your question. We'll take the next question from the web audience, please, and this one's from Ann Marie. Ann Marie asks, "What are your recommendations for children who were treated at a hospital that does not have a survivorship program?"

DR. CARA SIMON:
So my recommendation for children treated at a hospital that they do not have a survivorship program is to go to the COG—the CureSearch website. On the CureSearch website you can find the survivorship guidelines, and then the parents could download those guidelines and take them to their pediatrician and have their pediatrician follow those guidelines.

DR. SUSAN RHEINGOLD:
The other—sometimes there might be a location an hour or two away that does have a comprehensive survivorship clinic, and as usually they only see the patients once a year, you may be able to arrange a once-a-year visit to that location. Maybe a relative lives in a city you're going to anyway, and you can get evaluated. The clinic itself will get your records from your treating institution, so that's an alternative if you're only an hour or two from a site that has a comprehensive survivorship program.

LAUREN BERGER:
Thank you for your question, Ann Marie. Our Information Resource Center can also help you find that website and also additional places for survivorship information and support.

Slide 58 - Resources
Thank you for that question, and thank you all for all of your questions. If we were not able to get to the question that you wanted to ask, please do call our Information Specialists at 800-955-4572, or you can email us at infocenter@lls.org. Our specialists can provide you with information about pediatric ALL research, clinical trials, other questions you may have about treatment, questions about financial assistance for treatment, and anything else that you would like to ask. I'd also like to mention our partnership and our friends at The MAX Foundation. The MAX Foundation helps patients with blood cancer, including ALL, who live in any country of the world and who need support services. You can contact The MAX Foundation at www.themaxfoundation.org.

LAUREN BERGER:
Please help me thank Drs. Rheingold and Simon. We are so grateful that they have volunteered their time with us today.

On behalf of The Leukemia & Lymphoma Society, Abrale, Alianza Latina, Dr. Rheingold and Dr. Simon, thank you for sharing your time with us today. Goodbye, and we wish you well.

END