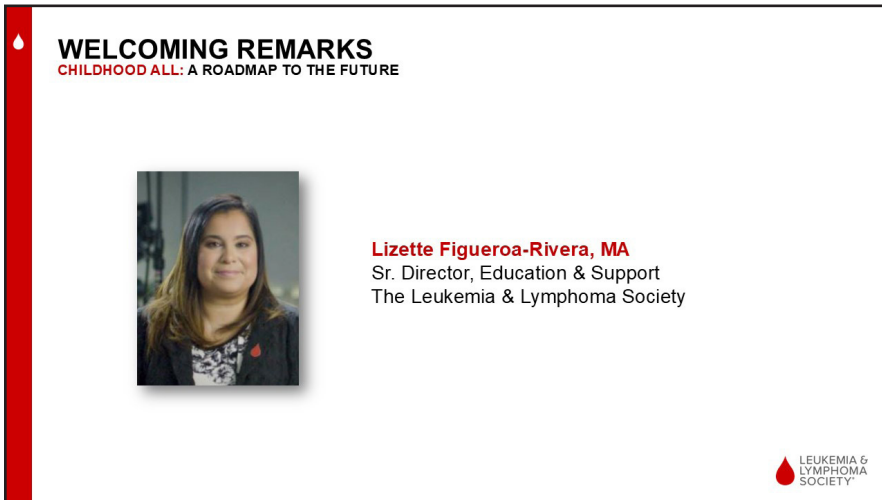




Slide 1: CHILDHOOD ALL: A ROADMAP TO THE FUTURE

Operator:

Greetings and welcome to Childhood ALL: A Roadmap to the Future. It is now my pleasure to introduce your moderator, Lizette Figueroa-Rivera. Thank you, Lizette. Please begin.



Slide 2: Welcoming Remarks

Lizette Figueroa-Rivera:

Hello everyone. On behalf of The Leukemia & Lymphoma Society (LLS), I'd like to welcome all of you. For many patients and families, coping with a blood cancer diagnosis can be complicated, stressful, and overwhelming. With so much information available online from so many different sources, it can be challenging to know what is accurate or up to date. LLS is the leader in free information and comprehensive support for blood cancer patients, families, caregivers, and healthcare professionals from diagnosis and treatment to remission, survivorship, and ongoing wellness.

Acute lymphoblastic leukemia (ALL) is the most common blood cancer in pediatric patients. There has been enormous progress in ALL treatment in recent years which is reflected by the increase in the 5-year overall survival from 57% in the 1970s to up to 96% in most recent studies. Now, LLS is dedicated to transforming treatment and care for kids with blood cancer through our Dare to Dream Project. Dare to Dream will help us better treat pediatric cancers and create

safer, less toxic, and more effective outcomes by matching kids’ treatments to their unique biology through funding groundbreaking research, driving advocacy efforts, and expanding free education and support services. Let us be here for you and your family as we continue to work to ensure kids can live out possibilities beyond cancer.

It is my pleasure to introduce Dr. Stephen Hunger, Chief of the Division of Oncology and Director of the Center for Childhood Cancer Research at the Children’s Hospital of Philadelphia. He’s also a Professor of Pediatrics at the University of Pennsylvania, Perelman School of Medicine in Philadelphia, Pennsylvania. Dr. Hunger, I’m privileged to turn the program over to you.

**Childhood Acute Lymphoblastic Leukemia (ALL):
A Roadmap to the Future**
June 2024
Stephen P. Hunger, M.D.
Jeffrey E. Perelman Distinguished Chair in Pediatrics
Chief, Division of Pediatric Oncology
Director, Center for Childhood Cancer Research
Children’s Hospital of Philadelphia
Professor of Pediatrics
Associate Director (Pediatric Cancer), Abramson Cancer Center
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania, USA




Slide 3: Childhood Acute Lymphoblastic Leukemia (ALL): A Roadmap to the Future

Dr. Stephen Hunger:

Thank you very much, Lizette. I want to thank you and The Leukemia & Lymphoma Society for inviting me to speak today. I think this is a great opportunity to try to help patients and families understand more about acute lymphoblastic leukemia and its treatments.

Disclosures

- Stock ownership
 - Amgen
- Honoraria/Consulting fees
 - Amgen, Jazz, Novartis, Servier



Slide 4: Disclosures

My disclosures are as listed on this slide.

Learning Objectives

- Advances in treatments for ALL in children
- Side-effect management
- Advocating for your child's needs with the healthcare team

Slide 5: Learning Objectives

This is a summary of the learning objectives and outline that I'm going to cover today talking about advances in treatment for children with ALL, side effects management, and advocating for your child's needs with the healthcare team.

Acute Lymphoblastic Leukemia (ALL)

- ALL is the most common pediatric cancer, accounting for about 25% of all cancers that occur in children
- About 6000 total ALL cases/year in US
 - Half occur in children and adolescents <20 years old
 - Incidence peaks at 2-4 years of age, with incidence of 80 cases/million at that age
- ALL was incurable until the early 1960s
- Long-term survival rates for children with ALL now approach 90%
 - Survival is inferior for adolescents and young adults (AYA) and gets progressively worse for older patients

Hunger and Mullighan, *N Engl J Med*, 373: 1541-52, 2015

Slide 6: Acute Lymphoblastic Leukemia (ALL)

Acute lymphoblastic leukemia or ALL was the most common pediatric cancer and accounts for about a quarter of all cancers that occur in children. Across the United States, about 6,000 persons will be diagnosed with ALL. Each year, in about half of those occur in children and adolescents less than 20 years of age. The most common age for diagnosis of ALL is between 2 and 4 years of age and starts to decrease in the teenage years. I think the important perspective is that ALL was really incurable until the early to mid-1960s.

If you step back and think about that, that really means there are essentially no people who have survived 60 years after a diagnosis of ALL. Now, our long-term survival rates are now approaching 90% or slightly higher than 90%. That's taking a look at all patients. It's not quite as good for adolescents and young adults, which I'll refer to as AYA patients in times during this presentation. It gets progressively worse for persons as you get older than 20 years of age. Also important to point out is that infants less than 1 year old, the diagnosis do not have anywhere near as good as outcome as older children.

Children's Oncology Group ALL Trials

- Only US National Cancer Institute (NCI) sponsored pediatric cooperative group
- ~220 members institutions in US, CA, AUS, and NZ
 - 90-95% of enrolled patients reside in US
- About 2000 newly diagnosed ALL patients/year enroll in COG ALL trials
- About two-thirds of US ALL cases among those 0-19.99 years old enroll in a COG ALL trial
 - ~70% of those 0-14.99 years old
 - ~50% of those 15-19.99 years old

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 Hunger, *J Clin Oncol*, 30: 1663-69, 2012

Slide 7: Children's Oncology Group ALL Trials

Now, a lot of the data I will talk about today come from the Children's Oncology Group (COG) ALL trials and I'm sure many of the patients and families on the phone may be enrolled or have children who are enrolled in COG ALL trials. The COG is the only US National Cancer Institute-sponsored pediatric cooperative groups. It has about 220 member institutions located in the United States, Canada, Australia, and New Zealand. Somewhere in the range of 90 to 95 patients who enroll in clinical trials of the Children's Oncology Group reside in the United States.

There are about 2,000 newly diagnosed ALL patients a year who enroll in COG ALL trials. This represents about two-thirds of cases of ALL that occur in the USA each year, among those less than 20 years of age, about 70% of those 15 years old and younger, and about half of those 15 to 20 years of age.

Clinical Trial Terminology

- Remission: <5% ALL cells in the bone marrow based on morphology (microscope) with no leukemia outside the bone marrow (extramedullary)
 - CR1=first remission; CR2=second remission; etc.
- Molecular remission: <0.01% MRD in the bone marrow
- Event-free survival (EFS): percentage of patients alive and in remission without having relapsed at a given timepoint (usually at 3 or 5 years)
- Overall survival (OS): percentage of patients alive at a given time point (they may have relapsed and may or may not be in remission)


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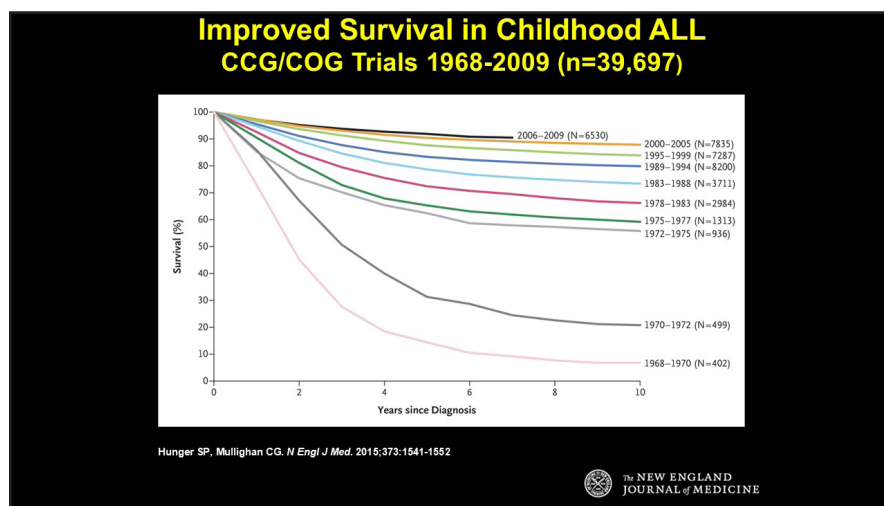
Slide 8: Clinical Trial Terminology

Just a little clinical trial terminology to start with, first the definition of remission. Remission means when you look at the bone marrow under the microscope, there are less than 5% leukemia cells and there's no leukemia outside of the bone marrow. We refer to leukemia outside of bone marrow and you may hear the term extramedullary disease. Extramedullary disease generally refers to leukemia in the testicles or the central nervous system or in masses outside of the bone marrow. When we talk about a patient in remission, we refer to first complete remission or CR1, second complete remission or CR2, etc.

Now, I'm sure a lot of you have heard about molecular remission. This is generally defined as less than 0.01% minimal residual disease or MRD in the bone marrow. There are several technologies that are used most commonly. These can detect down to one leukemia cell and 10,000 to 100,000 normal cells. There are some newer technologies that you may hear referred to as next-generation sequencing or high throughput sequencing that can detect down to one leukemia cell in a million normal cells.

When we talk about clinical trials which you'll often hear referred to as event-free survival or EFS. These are the percentage of patients who are alive and in remission without having relapsed at a given time point. When we look at the physicians and researchers, when we look at the outcome of clinical trials, we're generally looking at something like 3 or 5 years.

Overall survival is the percentage of patients alive at a given time point, but they may have relapsed and may or may not be in remission. Overall survival will generally be less than event-free survival.



Slide 9: Improved Survival in Childhood ALL CCG/COG Trials 1968-2009 (n=39,697)

Now, if we look at the improvements in outcome over time, these are what we call Kaplan-Meier curves that show survival rates over time. You can see they generally plateau when you look somewhere in the range of 3 to 5 years, meaning most of the patients who will have an adverse event, have it happen within that time. In here, we see a steady improvement in outcome. In the late 1960s, we were down in the range of 10% or less long-term survival.

More recently, we're at 90% or slightly above 90% at 5-year survival rates which I think is a remarkable improvement over time, but it also says that we still have work to do because if your child or your family member is not one of those who survived, then this curve doesn't mean as much to you.

Chemotherapy Agents Used in Childhood ALL: Year of FDA Approval

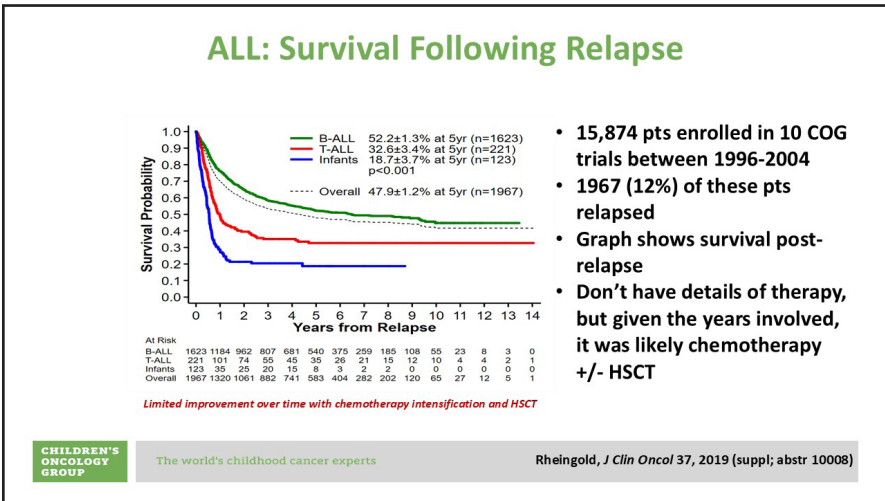
Agent	Year Approved by FDA
6-Mercaptopurine	1953
Methotrexate	1953
Prednisone	1955
Dexamethasone	1958
Cyclophosphamide	1959
Vincristine	1964
Cytarabine	1969
L' Asparaginase	1978
Daunorubicin	1979

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Slide 10: Chemotherapy Agents Used in Childhood ALL: Year of FDA Approval

Now, most of those improvements have come from using chemotherapy drugs that we actually have had around for quite a while. I think one of the important things to realize is there are now newer drugs that are available, and I'm going to talk about some of them, but most, if a child walks into my hospital today, or one of the hospitals where any of you live, this is a list of the common drugs used to treat ALL. As you can see, they were approved by the Food and Drug Administration (FDA) in the 1950s, '60s, and '70s. All of these drugs were in widespread use in clinical trials by the mid-to-late 1970s.

All the improvements you saw after that really came about through using drugs we've had available for a while in a better and more effective way, not necessarily through having better and more effective drugs available to us. Now, that is starting to change, but we have not yet seen the long-term outcome of that.



Slide 11: ALL: Survival Following Relapse

I think the other important thing to emphasize is that if and when patients relapse, the outcome is not as good for treatment after relapse. This is a study, so there were over 15,000 children enrolled in one of 10 children's oncology group trials between 1996 and 2004. Almost 2,000 of them, about 12% of them relapsed.

If you look at survival from the time of relapse, overall, it's slightly less than 50%, and it's higher for children with B-lineage ALL than for T-lineage ALL, and much higher than for infants. We don't know the details of therapy for these patients, but it was likely given the time period that the therapy post-relapse was chemotherapy with or without a stem cell transplant.

Major Questions in Pediatric ALL Therapy in 2024

- How do we increase cure rates for those not cured today?
 - 10-12% of children with ALL will relapse
 - Only about half of children who relapse are cured
- How do we optimize therapy for ultra low risk ALL?
 - Subgroups of children with ALL with >95% EFS and >98% OS can be identified
 - How do we treat them to have the fewest short- and long-term side effects?
- How do we improve cure rates for children with ALL diagnosed in low and middle income countries worldwide, where most children live?

Slide 12: Major Questions in Pediatric ALL Therapy in 2024

As I sit back and say, what do I think the major questions are in pediatric ALL therapy today? I really see 3 broad questions.

The first is how do we increase cure rates for those who are not cured today? 10% to 12% of children with ALL will relapse, and as I just showed you, only about half of those who relapse are cured. One big focus is how do we do better for those children? The other side of the coin is that gratifyingly and somewhat remarkably, we have a group we can identify within the first month of therapy who will have what I call ultra-low risk ALL, meaning they can be identified prospectively, and they will have an event-free survival over 95% and overall survival over 98%.

In fact, one recent clinical trial we conducted for this low-risk group had a 100% survival at 5 years among 600 children. That's a remarkable and a wonderful thing, but once we find the children that we're almost certain to cure, we also want to ask how do we treat them to have the fewest short and long-term side effects? If a child is diagnosed at the most common age between 2 and 4, and they end therapy when they're 4 to 6 years of age, a 5-year-old in the United States today has 76 additional years of expected life.

We have to think of those who we cure. It's important how they'll do 10 and 20 years from today, but to me, it's even more important how they will do 40, 50, and 60 years from today. How can we optimize therapy today to make them lead long, healthy, and productive lives?

Then the third question is that most children who are diagnosed with ALL aren't fortunate enough to live in a high-income country like the United States or Canada, or those in Western Europe. Now, there are certainly economic disparities in all of those countries, but there are many more resource challenges in areas of Africa, Asia, South America, etc, where cure rates for ALL often are quite a bit lower than they are where we live. We also have to think how can we improve outcome for those children?

ALL: Risk Factors and Treatment Stratification

- Clinical
 - Age, initial white blood cell count (WBC), central nervous system (CNS) status
- Immunophenotype
 - Children: 85% B-ALL and 15% T-ALL
- Treatment response
 - Assessed by minimal residual disease (MRD) levels at end induction (EOI) and end consolidation (EOC)
 - COG uses multi-parameter flow cytometry (flow) to measure MRD
 - Emerging more sensitive technologies assess MRD by Next Generation Sequencing (NGS) or High Throughput Sequencing (HTS)
- Sentinel genetic lesions
 - Chromosome number (ploidy) and structural rearrangements, particularly chromosome translocations
- COG risk stratification systems use a combination of clinical features, immunophenotype, MRD and sentinel genetic lesions to classify patients into different risk groups
 - Different treatment backbones for different groups
 - Different randomized questions in different groups
 - Identify small high-risk patient subsets to test precision medicine therapies

Slide 13: ALL: Risk Factors and Treatment Stratification

Now, what we have learned over many years is that ALL is not the same in every child. Even though the leukemia may look the same under the microscope, there are very big differences that come about through initial things. The way we do this is we try to identify what we call risk factors, which might identify children or subsets of children who are at higher or lower risk of relapse and try to adjust therapy based on the risk of relapse. The risk factors we look at first are things we really know right when you're first diagnosed. How old is the patient, how high is the white blood cell count, and are there leukemia cells in the spinal fluid? We also look at what we call the immunophenotype. ALL cells can be derived either from B-lineage lymphocytes, which is about 85% of childhood ALL, or for T-lineage lymphocytes, which is about 15%. Historically, these have had very different outcomes, although I'll show you in a couple slides that that's changed quite a bit.

The other thing that helps predict outcome is how do you respond to treatment? Actually, I think to parents, this is sometimes the most obvious thing that if the leukemia cells die quickly when you start chemotherapy, that's probably better than if the leukemia cells die slowly. We've learned over time that really we can assess this using sensitive technologies called minimal residual disease or MRD. We look both at the end of induction, which is after 4 weeks of therapy, and also, in some cases, at the end of consolidation, which is after 12 to 14 weeks of therapy.

Most US centers and the Children's Oncology Group clinical trials use a technology called flow cytometry that can measure disease somewhere down to one in 10,000 to one in 100,000 cells. There are newer technologies that have been developed that are readily available commercially, that we call often next-generation sequencing or NGS, or high-throughput sequencing or HTS, they can go down more to the level of one in a million cells. We're still trying to learn how and when to use that more sensitive technology.

Then the other thing is that the leukemia cells themselves have acquired a series of genetic changes or mutations, that is what causes leukemia. These are not present in most cases in the normal body cells. They're what we call acquired or somatic lesions, but some are associated with a better than usual outcome and others with a worse than the usual outcome. Some actually can guide therapy in selection of what we call targeted therapies. These play a big role in treatment allocation.

Within the Children's Oncology Group clinical trials and within our everyday practice, we use a combination of the clinical features, the immunophenotype, the MRD measurements, and the genetics to classify leukemia patients into different risk groups. They're generally different treatment backbones for the different groups. In clinical trials, different questions are asked in different groups. It also allows us to identify small subgroups of patients who may be at higher risk of treatment failure, and there may be what we call precision medicine or targeted therapies we can test in these children.

Clinical Risk Groups in Childhood B-ALL: NCI Criteria

- **Standard risk: ~65% patients**
 - Age 1.00-9.99 years and initial white blood count <50,000
 - Current 5-year EFS ~92%, OS ~97%
- **High risk: ~35% patients**
 - All others
 - Current 5-year EFS ~75%, OS ~85% for non-infants
 - Achieved with more intensive therapy
 - Outcome still poor for infants < 1 year old
 - ~3% of patients; generally treated on different trials
- **NCI risk criteria do not apply to T-ALL**
 - All treated with more intensive therapy similar to that for HR B-ALL

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Hunger and Mullighan, *N Engl J Med*, 373: 1541-52, 2015

Slide 14: Clinical Risk Groups in Childhood B-ALL: NCI Criteria

Now, the simplest risk groups use only what we know shortly after the patient walks in the door. These are the so-called National Cancer Institute or NCI criteria that were established in the mid-1980s. Using this, about two-thirds of children with B-lineage ALL fall into the standard risk group. They're between 1 in 10 years of age and have an initial white blood cell count less than 50,000. For this subgroup of patients, the event-free survival at 5 years is about 92%, and the overall survival is about 97%.

High-risk patients are about a third of patients. The rest, either they're 10 years of age or older, or they're any age with a white blood cell count over 50,000. These patients, about 75%, have about a 75% event-free survival with current therapies and about 85% overall survival for non-infants. It's also achieved with more intensive therapy, and unfortunately outcome is still poor for infants less than a year of age. It's only about 3% of children with ALL, and they're generally treated on different trials and with different regimens than older children.

These risk groups do not apply to children with T-cell ALL, the age in the white blood cell count are not anywhere near as important in that subgroup. They're all treated more intensively with therapy similar to that we use for high-risk B-lineage ALL.

Survival Improvements 1990-2010: COG Trials T-ALL vs. B-ALL

Immunophenotype	5-year OS%: 1990-94	5-year OS%: 2006-10	Reduction in death rate
B-ALL	84.9 +/- 0.5 (n=5068)	91.7 +/- 0.4% (n=7397)	45.0%
T-ALL	70.7 +/- 1.7% (n=748)	90.6 +/- 1.7% (n=676)	67.9%

Overall Survival difference for B-ALL vs. T-ALL

1990-94: 14.2%

2006-09: 1.1%

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Hunger, *J Clin Oncol*, 30: 1663-69, 2012
Raetz, *Pediatr Blood Cancer*, 65: e27057 (S222), 2018

Slide 15: Survival Improvements 1990-2010: COG Trials T-ALL vs. B-ALL

One of the very nice things we've seen over the past 20, 25 years is that children with T-lineage ALL now do much

better than they used to. If we look back and compare survival differences in the early 1990s between B- and T-lineage ALL, those with B-lineage ALL had a 14% better survival rate than those with T-cell ALL. If we look in the more recent era, that's only a 1% difference. T-cell ALL is really not the same poor prognostic factor that it used to be, but we do know that we have to treat the patients more intensively.

"New" Treatments for Childhood ALL

- "Targeted" or precision medicine therapies
 - Tyrosine kinase inhibitors (TKIs) such as imatinib and dasatinib
 - Directly inhibit mutant proteins fundamental to ALL development
 - Standard of care in Philadelphia chromosome positive (Ph⁺) ALL
 - Currently being tested in Philadelphia chromosome like (Ph-like) ALL
- Immunotherapies
 - Blinatumomab
 - Inotuzumab
 - Chimeric antigen receptor (CAR) T-cells

Slide 16: "New" Treatments for Childhood ALL

Now, there are a number of new treatments for childhood ALL that I'm going to spend some time talking about. The first category are what we call targeted or precision medicine therapies, and common one of these are drugs called tyrosine kinase inhibitors or TKIs. Two, you may have heard about are imatinib and dasatinib, and it's somewhat oversimplified, but you can think of standard chemotherapy as killing cells that grow fast. They've somewhat non-discriminately killed cells that grow fast. The side effects are focused on the effect of this chemotherapy on the cells that grow fast. Their hair cells grow fast, their hair could fall out with chemotherapy. The cells that line the inside of your mouth and your intestine grow fast, so you can get mouth sores from chemotherapy. The idea of targeted therapies is they preferentially kill leukemia cells because they're directed at what's wrong in the leukemia cells rather than just non-discriminately killing cells. These TKIs can directly inhibit the mutant proteins that are essential to the development of ALL, their standard of care, and a subtype called Philadelphia chromosome-positive or Ph⁺ ALL, which is about 3% to 5% of children with ALL. They're currently being tested in a similar subset that we call Philadelphia chromosome-like or Ph-like ALL.

Then the other big development of the last 10 to 15 years has been the advent of immunotherapies for ALL. These have really changed opportunities for treatments and improved cure rates initially in children with relapsed ALL, but now starting to be tested in children with newly diagnosed ALL. Now, I'm going to touch briefly on 3 of these called blinatumomab, inotuzumab, and chimeric antigen receptor or CAR T-cells.

Newly Diagnosed ALL: Current COG ALL Trials

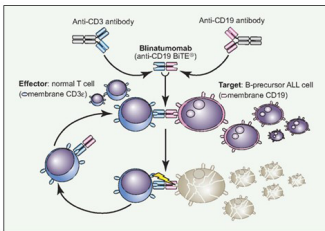
- AALL1731: Standard Risk B-ALL
- AALL1732: High Risk B-ALL
- AALL1631: Ph+ and Ph-like ALL

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Slide 17: Newly Diagnosed ALL: Current COG ALL Trials

Several of these are now being tested in trials for children with newly diagnosed ALL.

Blinatumomab



Adapted from Brown, Blood, 131: 1497–98, 2018

- Bi-specific T-cell engaging (BiTE) antibody that links CD3+ T-cells to CD19+ cells, enabling killing of the CD19+ cells by the patient's own cytotoxic T-cells
- Given by continuous 28-day infusion
- Side effect profile very different from cytotoxic chemotherapy
 - Causes lymphopenia but little anemia, thrombocytopenia or neutropenia
 - Very low incidence of serious infections
 - Unique CNS toxicities including hallucinations and seizures
- Improves EFS and OS in relapsed ALL


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Slide 18: Blinatumomab

Blinatumomab is a so-called bi-specific T-cell-engaging antibody or BITE. What this means is antibodies can bind to different proteins, and this is, if you will, a 2-sided antibody. One side binds cells in your body called CD3-positive cells, which are your normal T-cells, and one side binds to CD19-positive cells. CD19 is expressed on the surface of almost all B-lineage leukemia cells. This is given as an infusion and what it does is it links and brings the T-cells directly to the leukemia cells and the T-cells are able to kill the leukemia cells. The killing is not done by the drug, the killing is done by the body's own normal T-cells.

Currently, this drug is given by a continuous 28-day infusion, so if your child receives it, they often will spend the first 3 to 7 days in the hospital getting the infusion going properly and then receive it as an outpatient using a backpack. The side effects are very different than what we see with standard chemotherapy. They don't cause low blood counts in general and they don't cause infections in general, but there can be some unique central nervous system toxicities that include hallucinations and sometimes seizures. This drug clearly improves both event-free survival and overall survival and relapsed ALL, so it's become a standard part of therapy for children with relapsed ALL.

COG AALL1731: Blinatumomab in Newly Diagnosed ALL

- NCI standard risk B-ALL
 - All patients receive an identical “3-drug” (dexamethasone, calaspargase, vincristine + intrathecal chemotherapy) induction for 28 days and are then assigned to different risk groups
- The major study question is to determine if adding two 4-week cycles of blinatumomab to standard therapy improves EFS
 - Blinatumomab given by 4-week continuous infusion
 - Start in the hospital and continue at home
- Separate treatment approaches for children with Down syndrome and ALL due to higher rates of toxicity in these children

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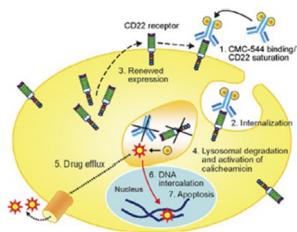
Study Chairs: Sumit Gupta and Rachael Rau

Slide 19: COG AALL1731: Blinatumomab in Newly Diagnosed ALL

If something works after ALL relapses, well, then the first thing you say is, “Why wait until they relapse? Let’s try it with newly diagnosed patients.” The COG is now conducting a clinical trial testing blinatumomab in children with newly diagnosed ALL, trying to see if adding extra cycles of blinatumomab will improve cure rates.

Also, children with Down syndrome, although I’m not talking about them in detail today, children with Down syndrome have an increased risk of developing ALL and also have many more side effects from ALL therapy. We’re particularly interested in seeing if blinatumomab can replace some parts of chemotherapy in children with Down syndrome who have ALL.

Inotuzumab Ozogamicin (InO)

Thota and Advani, *Eur J Haematol*, 98: 425-34, 2017

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Slide 20: Inotuzumab Ozogamicin (InO)

Now, a second drug I want to talk about is inotuzumab. It’s called inotuzumab ozogamicin. We call it INO because that’s otherwise a hard name to say. This is another immunotherapy, but it’s a different kind and you can almost think of it as a targeted weapon or a targeted missile. A protein called CD22 is expressed on B-cells, and what this drug is, it’s an antibody that recognizes CD22 coupled to a chemotherapy agent. The CD22 binds to the leukemia, the antibody binds to CD22 on the leukemia cells, and the chemotherapy agent is taken into the cells and then does its work there. Now you’re not having chemotherapy floating through the blood and affecting all tissues, it’s only getting into the leukemia cells.

This is given by a 1-hour infusion, usually once a week for 3 weeks. You usually get it on, let’s say Monday this week,

Monday next week, and Monday the following week, have a week off, and then that's the end of the cycle. It's been shown to improve outcomes in adults and in children with relapsed ALL, and so again, logically is now being tested in children with newly diagnosed ALL.

COG AALL1732: Inotuzumab in Newly Diagnosed ALL

- NCI high risk B-ALL
 - All patients receive a "4-drug" (dexamethasone if <10, prednisone if ≥10; calaspargase; vincristine + intrathecal chemotherapy) induction for 28 days and are then assigned to different risk groups
- The major study question is to determine if inotuzumab improves EFS compared to chemotherapy alone
 - Inotuzumab arm replaces one cycle of chemotherapy (delayed intensification part 2) with inotuzumab and adds a 2nd cycle
 - Inotuzumab given by 1-hour infusion weekly x 3

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Study Chairs: Jennifer McNeer and Maureen O'Brien

Slide 21: COG AALL1732: Inotuzumab in Newly Diagnosed ALL

The Children's Oncology Group is conducting a trial testing inotuzumab in patients with newly diagnosed higher-risk ALL, in this case, replacing one part of chemotherapy plus an additional cycle.

COG AALL1631: Chemotherapy + Imatinib in Ph+ ALL

- Patients with Ph⁺ or Ph-like ALL with an "ABL class fusion" enter 2-4 weeks after diagnosis
- Receive chemotherapy + imatinib
- Testing two different chemotherapy backbones to determine if one is better than the other
 - "EsPhALL" regimen from Europe
 - "COG" HR B-ALL backbone
 - Less toxic and preferred if cure rates are the same

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Study Chairs: Lewis Silverman and Andrea Blondi

Slide 22: COG AALL1631: Chemotherapy + Imatinib in Ph+ ALL

We are also conducting trials testing targeted therapy, so there's a current clinical trial testing chemotherapy plus imatinib in patients with Philadelphia chromosome-positive ALL. This clinical trial is testing 2 different chemotherapy regimens, both with imatinib, the one developed in Europe called the EsPhALL regimen and one developed in the US called the COG regimen. Patients are randomly assigned to one or the other with the goal of seeing which one is better. Our hope is that the COG regimen is at least as good, if not better, because it's less toxic. We hope that will be the outcome of that clinical trial, but we don't know that yet.

Chimeric Antigen Receptor (CAR) T-cells

- CAR T-cells are generated by stably transducing patient T-cells with a construct that leads to expression of a genetically modified T-cell receptor on the surface of T-cells
- Recognizes an antigen on the leukemia cell surface (CD19) and contains a co-activation domain (4-1BB for tisagenlecleucel) and the CD3 zeta domain that mediates target cell killing

Si Lim, *Pediatr Blood Cancer*, 68:e29123, 2021

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Slide 23: Chimeric Antigen Receptor (CAR) T-cells

Then CAR T cells. CAR T cells are generated by genetically engineering a patient’s own T cells. The T cells of a patient are removed from their body by a process called pheresis where they’re collected, and then they go to a laboratory where the T cells are genetically engineered to recognize and kill leukemia cells that express a particular antigen, primarily CD19.

ORIGINAL ARTICLE

Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

S.L. Maude, T.W. Laetsch, J. Buechner, S. Rivera, M. Boyer, H. Bittencourt, P. Bader, M.E. Yamani, H.E. Stolnicki, C.D. Myers, M. Qorri, S. Du Manoir, H. Hiramatsu, K. Schick, K.L. Davis, P.L. Martin, E.R. Nemecok, G.A. Yanik, C. Peters, A. Banochel, N. Bosslet, F. Mechinaud, A. Barabasi, J. Krueger, C.H. June, B.L. Levine, P. Wood, T. Trause, M. Leung, K.T. Muenier, C. Zhang, K. Sen, D. Lebowitz, M.A. Pulsipher, and S.A. Grupp

- ELIANA was the first global, multicenter CAR T cell trial
- Treated patients had relapsed/refractory (r/r) ALL with a mean of 3 prior therapies (range 1-8) and 61% with prior HSCT
- CR + CRi (within 3 months) 82% (65/79 infused; 95% CI, 72-90)
- 98% (64/65) of responses were MRD-negative
- Duration of remission among responders
 - 60% at 12 months
- Event-free survival among infused patients
 - 50% (95% CI, 35% to 64%) at 12 months
- Overall survival among infused patients
 - 76% (95% CI, 63% to 86%) at 12 months
- **Results led to FDA approval of tisagenlecleucel in r/r ALL on 8/30/17**

Maude, *N Engl J Med*, 378: 439-48, 2018

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Slide 24: First Global Multicenter CAR T-cell Trial

These were developed first, we’re now looking at about a dozen years ago, we started to see the efficacy of this. The first clinical trial that tested this was a clinical trial that used multiple sites all through the world. It treated patients who had relapsed and refractory ALLs. ALL had come back many times in the initial trial. The average number of treatment regimens patients had was 3. About 60% of patients had relapsed after a prior stem cell transplant.

The question was, what is the remission rate with this therapy? It was found that almost 100%, so 98% of patients went into remission and were minimal residual disease negative. About half of those patients continue to be long-term survivors without other therapy. This group led to the approval of this drug, which is called tisagenlecleucel. Because tisagenlecleucel is hard to say, the commercial name for the drug is KYMRIA[®], which more people have seen or known about.

CAR T-cells: Bridge to Transplant or Definitive Therapy?

- CD19-redirected CAR T-cells approved for relapsed/refractory ALL
 - CD22 CAR and CD19+ CD22 CAR under active clinical investigation
- >90% attain a complete remission (CR), almost always MRD-negative
- What should you do next?
- In early CAR T-cell trials, most (2/3-3/4) patients had relapsed after prior HSCT and many patients who entered CR did not receive subsequent therapy
 - Clearly see a long-term plateau in survival, showing that CAR T-cells can be a curative therapy by itself
 - However, no clear guidelines on who “needs” HSCT post CAR and who might be cured with no further therapy
 - Substantial institutional variation
 - Prognostic biomarkers needed to help identify who should or should not undergo HSCT

Si Lim, *Pediatr Blood Cancer*, 68:e29123, 2021

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Slide 25: CAR T-cells: Bridge to Transplant or Definitive Therapy?

This is another therapy that's clearly effective in children with relapsed and refractory ALL, but we don't yet know the optimal way to use it. We know that if you take patients with relapsed ALL, the vast majority of them, over 90%, will go into remission and they almost always will become MRD negative. Then the question is what to do next? One option would be to perform a stem cell transplant, and that's what often happens.

The other option would be to see if this works by itself. When you look, you see that without further treatment, some subset, perhaps 40 to 50% will be long-term survivors without further therapy but today we don't really know who those 40 to 50% of patients are. Many children receive transplant because it can be hard to get them back into remission. What we need are tests or predictors, what we call biomarkers, to say which patients really need a transplant and which might be cured without a transplant. That's some of the active research going on today.

Learning Objectives

- Advances in treatments for ALL in children
- Side-effect management
- Advocating for your child's needs with the healthcare team

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Slide 26: Learning Objectives

I'm going to switch gears now and talk a little bit about side effects and their management because I know those are very important to patients and families.

Acute Side Effects of ALL Therapy: Common

- General
 - Low blood counts and mucositis
 - Need for transfusions of red blood cells (rbc) or platelets
 - Infection risk: hospitalization and IV antibiotics for fever and neutropenia (F+N)
 - Nausea and vomiting: risk is drug-specific
- Corticosteroids
 - Appetite changes and weight gain, hyperglycemia, mood changes
- Vincristine
 - Neuropathy, constipation
- Asparaginase products
 - Allergy or hypersensitivity reactions
 - May need to change to a different product (erwinia asparaginase)
- Hair loss: related to specific drugs

Slide 27: Acute Side Effects of ALL Therapy: Common

Obviously, I can't cover all the side effects, but when we look at the common side effects that occur in many to most patients. The biggest one that's medically important are low blood counts and mouth sores. This leads to a need for transfusion of red blood cells or platelets. It increases the risk of infection, which leads to hospitalizations for the so-called fever and neutropenia and/or treatment of established infections. Nausea and vomiting is another side effect. This is really drug-specific. Some chemotherapy agents can cause a lot of nausea and vomiting. Others cause very little nausea and vomiting.

When we look at specific drugs, corticosteroids, by this I mean prednisone or dexamethasone can cause appetite changes, weight gain, high blood sugar, and significant mood changes.

Vincristine, which is given intravenously can cause what is referred to as neuropathy, numbness and tingling, almost like hitting your funny bone and also constipation that can be quite severe at times.

Asparaginase products can cause allergy or hypersensitivity reactions and may cause you to need to switch to a different class of this drug-related drug called Erwinia Asparaginases.

Then hair loss is again related to specific drugs. Some drugs very clearly cause hair loss, others cause very little hair loss.

Acute Side Effects of ALL Therapy: Uncommon but Can be Severe

- IV and intrathecal methotrexate
 - Stroke-like symptoms, seizures
- Asparaginase products
 - Bleeding or clotting (stroke or superior sagittal venous thrombosis)
 - Pancreatitis
- Anthracyclines
 - Heart muscle damage (cardiomyopathy); very rare with doses used for newly diagnosed ALL

Slide 28: Acute Side Effects of ALL Therapy: Uncommon but Can be Severe

Now, there are other acute side effects that are uncommon but could be severe. One is that patients who are treated for ALL receive intravenous and intrathecal or into the spinal fluid, methotrexate. These in a subset of patients can cause stroke-like symptoms. Sometimes transient, in other cases unfortunately permanent or seizures.

The asparaginase products, which I mentioned, can cause bleeding or clotting. This can come across as stroke-like symptoms if they occur in the brain. They also can cause pancreatitis, which can be quite severe.

The anthracycline's class of medications can damage the heart muscle, causing what we refer to as cardiomyopathy. Now, the risk of this is related to the total dose you receive in your lifetime and the doses we receive for newly diagnosed ALL therapy today are very unlikely to cause cardiomyopathy. That is why we monitor children with echocardiograms periodically.

Side Effects: Prevention and Minimization

- Most centers have "supportive care" recommendations
- Infections
 - Bactrim/Septa or pentamidine to prevent a rare pneumonia (PJP)
 - Centers may give prophylactic antibiotics or antifungal medications during specific phases of therapy
- Constipation
 - Stool softeners and laxatives during phases with vincristine
- Antiemetics to prevent or treat nausea and vomiting
 - Substantial patient to patient variability so make sure your treatment team knows what side effects your child has

Slide 29: Side Effects: Prevention and Minimization

I think in terms of prevention and minimization of side effects, all centers have what they generally refer to as supportive care recommendations and these are often a little bit different at each center so I don't want to talk about what is the standard, and I think it's best to work with your physicians and their care teams to find out the approach. There are some that are standard.

Children with ALL receive a medication called Bactrim™ or SEPTRA® orally, or receive a medication called pentamidine, either inhaled like an asthma medicine or through an IV to prevent a rare leukemia called PJP (*Pneumocystis jirovecii pneumonia*). Centers may also give preventative antibiotic or antifungal medications during specific phases of therapy. I mentioned the constipation before, and often patients are started on stool softeners and laxatives during phases that contain significant vincristine.

Most patients will receive at one time or another, antiemetics to prevent or treat nausea and vomiting. There is substantial patient variability with nausea and vomiting so it's very important that you give feedback to your physician and care team about how your son or daughter is doing with that.

“Normal” Life During ALL Therapy

- Different centers have different recommendations
- At our center we encourage school/preschool attendance and participation in normal childhood activities whenever possible for children with newly diagnosed ALL
 - Sport participation may depend on phase of therapy, especially for teenagers and contact sports
- 90% of children will be long term survivors and we want them to have as normal a childhood as possible

Slide 30: “Normal” Life During ALL Therapy

Now, I think the other question is how normal should life be during ALL therapy? Different centers have different recommendations.

At our center, we encourage school and preschool attendance and participation in normal childhood activities whenever possible for children with newly diagnosed ALL. Participation in sports may depend on the phase of therapy and particularly for teenagers contact sports, can he play football may depend on where they are in therapy and how likely they are to have low blood counts.

I think stepping back, if we expect that 90% of children will be long-term survivors, we want them to have as normal a childhood as possible.

Long-Term Side Effects of ALL Therapy

- Risk depends on treatment received
- Much higher if undergo stem cell transplant (SCT) or need treatment for relapsed ALL
- Fertility issues
 - Uncommon unless have SCT or treatment for relapse
- Birth defects in children
 - No significant increased risk
- Learning and school performance
 - Higher risk with cranial irradiation or age <6 at initial diagnosis
 - Many centers offer formal neurocognitive evaluations after therapy completion

Slide 31: Long-Term Side Effects of ALL Therapy

Now there are long-term side effects of ALL therapy that may occur and the risk depends on the treatment received. Long-term side effects are much higher if a child is treated with a stem cell transplant or needs treatment for relapsed ALL.



Common questions patients ask regarding fertility, which is uncommon to have fertility problems unless one undergoes a stem cell transplant or treatment for relapse.

There are plenty of data that chemotherapy does not cause birth defects in future children other than you can't get chemotherapy immediately approximate to fathering or having a child.

One of the big issues is learning and school performance. Impact of this is higher if you receive radiation, which we do less and less today, or if the child is less than 6 years old at initial diagnosis. Many centers offer formal neurocognitive evaluations after the completion of therapy to identify if there are any gaps and whether any special accommodations might be needed.

Learning Objectives

- Advances in treatments for ALL in children
- Side-effect management
- **Advocating for your child's needs with the healthcare team**

Slide 32: Learning Objectives


The last bit, I just want to talk briefly about advocating for your child's needs with the healthcare team.

Stakeholder Informed Priority Setting for Pediatric ALL Research

What: Investigator developed a patient/parent piloted survey

Purpose: To systematically capture parent and patient lived-experiences, perspectives, and preferences to better incorporate patient and parent voice into clinical trial design

Who: Partnership between Kellee Parker (pediatric oncologist), Lindsay Jibb (PhD RN researcher), Sarah Alexander (pediatric oncologist, chair of COG ALL cancer control group), Lisa Jacola (neuropsychologist, ALL-behavioral science liaison) and Kim Buff (ALL patient advocate/founder of Momcology®)



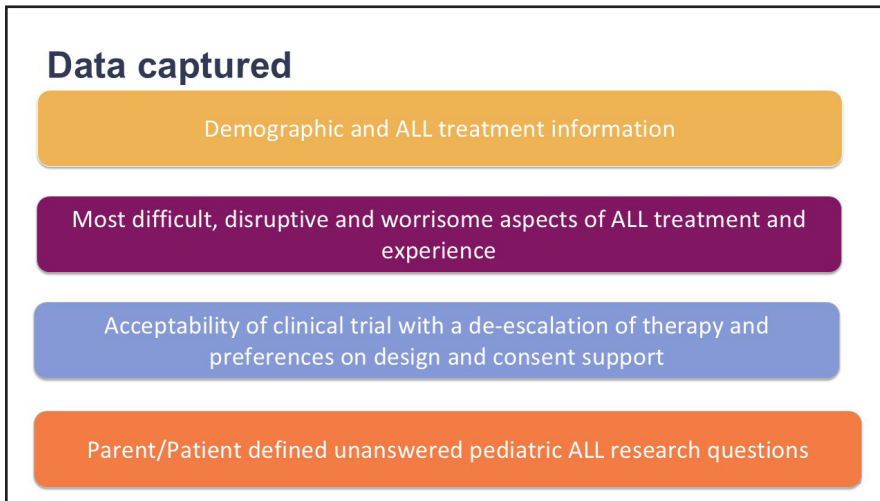
Your questions will help guide pediatric ALL in a way that is influenced by the people affected most by the disease and set an agenda for researchers and funders to focus on.

Slide 33: Stakeholder Informed Priority Setting for Pediatric ALL Research

These next slides were graciously given to me by a physician Kellee Parker from Utah, who is working with the Oncology group to try to understand the patient and parent's point of view of what is important to learn in ALL therapy.

They have been conducting surveys to really capture parent and patient lived experiences, perspective and preferences to help incorporate those into clinical trials. I think this is a very important effort because one of the things

we want to understand are what are the things that are the biggest negative impact to you as a patient or you as a parent related to ALL therapy and how can we better address that?



Data captured

- Demographic and ALL treatment information
- Most difficult, disruptive and worrisome aspects of ALL treatment and experience
- Acceptability of clinical trial with a de-escalation of therapy and preferences on design and consent support
- Parent/Patient defined unanswered pediatric ALL research questions

Slide 34: Data captured

This group has been conducting surveys that includes understanding the demographics and the treatment that the patient is receiving, asking about what you see as the most difficult, disruptive, and worrisome aspects of ALL treatment and experience, understanding what clinical trial questions you will feel acceptable in terms of trying to take away some parts of therapy, and really, what do you find that there are unanswered questions?



Dissemination, Utilization & Other Future Plans

- Results presented Children's Oncology Group Spring Meeting to inform development and design of future ALL clinical trials
- Momcology® webinar to share results back with the contributing community
- Future conference presentations and open access publications
- Stakeholder engagement symposium
- Continue to refine process to increase diversity of participants & apply to other disease groups

Slide 35: Dissemination, Utilization & Other Future Plans

These data are not yet available. They were presented at a recent Children's Oncology Group meeting. I found them very interesting when I saw them, but I'm not able to share them with you. Momcology® will be setting up a webinar to share the results back with the contributing community. They plan to make this an open access availability. I think that this is a very important effort for us to understand what patients and families feel.

Data for this study is not yet published
Please reach out to study team for questions!
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Elham Hashemi (Elham.Hashemi@sickkids.ca)

Slide 36: Data for Study

With that, I’m going to stop here and would be happy to answer questions that you might have, which I believe you can do either online or by calling.



ASK A QUESTION
CHILDHOOD ALL: A ROADMAP TO THE FUTURE

Ask a question by **phone**:
Press star (*) then the number 1 on your keypad.

Ask a question by **web**:
Click “Ask a question”
Type your question
Click “Submit”

Due to time constraints, we can only take one question per person. Once you’ve asked your question, the operator will transfer you back into the audience line.



Slide 37: ASK A QUESTION

Lizette:

Thank you so much Dr. Hunger, for all this great information. As you said, it is time for our question-and-answer portion of our program.

We’ll take the first question from our web audience. Doctor, the question is: Is there any information for high-risk maintenance? They change the standard-risk patient to steroid pulses every 3 months. Do they plan on changing high-risk to steroid pulses every 3 months as well?

Dr. Hunger:

Yes. The answer to that is yes. I think to me, this is very important and it somehow exhibits how we learn from our colleagues. The major study groups in Western Europe have never given vincristine and steroids during maintenance, whereas in the United States, we have. The outcomes are pretty similar between the 2 groups. Really, we’ve been able to step back from that to every 3 months for maintenance steroids and vincristine pulses, which I think is very

important because at least from patients I hear from, having a 5-year-old who takes 5 to 7 days of prednisone or dexamethasone every month can be like living a nightmare. There are some long-term side effects as well. We thankfully have backed off on that, and I view that as a major step forward.

Lizette:

The next question Doctor: If a patient with ALL had seizures while on chemo, do they end up continuing to have seizures after they're done with treatment?

Dr. Hunger:

That's a great question. It's an uncommon side effect, but it does happen in the range of 5% of children with ALL. Generally related to methotrexate, either given intravenously or through lumbar puncture, intrathecally. It's not related to the oral methotrexate that one takes during maintenance therapy. Most of the time, these are self-limited seizures, meaning, they're related to the drug itself and you don't get a seizure disorder with it. There are a subset of children who may have brain injuries sufficient that they do have long-term seizure issues.

You also have to remember that there are children without leukemia who develop seizure disorders, and some of the prime times to develop it are between 2 and 4 years of age. It may be that some children who have seizures during ALL therapy, it's not really due to the therapy. They were going to get them anyway and it's just at the same time. I think to answer the question, most children who have a seizure with treatment during ALL will not have additional seizures later.

Lizette:

The next question, Doctor: What's the recommended amount of sun exposure my daughter should have daily as she continues in maintenance phase? We use sunscreen, SPF 50, and keep her head and neck covered with a hat.

Dr. Hunger:

The chemotherapy agents, particularly those you take during maintenance, can make you more susceptible to sunburning, so we do recommend caution. The way I try to look at it in a practical way is to use sunscreen and certainly, if it's high heat, direct sun, think of using a hat as you do. What we don't want you to do is cover them head to toe in clothing or prevent them from going out in the sun. I think what you're talking about doing is very reasonable. The other thing, particularly with teenagers where it may be more common, is we try to discourage what I'll call recreational tanning, lying out to get a nice suntan.

Lizette:

The next question: Is there any data about permanent B-cell aplasia after CAR T-cell treatment yet? Is there a chance B-cells won't ever come back?

Dr. Hunger:

That's a very good question. I didn't go into that aspect of it, but the CD19 that the CAR T cells are directed against is also expressed on normal B cells. One of the ways we look at the efficacy of CAR T-cell therapy is we actually want to see that you don't have any normal B cells for a period of at least 6 months, because that tells us that the CAR T cells are killing cells they see with CD19.

What we see and we have a large group of children at CHOP who have been treated with CAR T cells, we do see long-lasting B-cell aplasia, the first patient we treated is now over 12 years after CAR T-cell therapy, and we see ongoing B-cell aplasia to that length of time. Even when the B cells come back, they don't always work normally. We will see patients whose B cells have recovered, but they don't make immunoglobulin normally.

I think these are questions we don't know the answer to yet, but we can certainly say that there are some patients who at least for a dozen years do not make normal B cells and need to have ongoing immunoglobulin replacement. There are other patients who recover their normal B cells in a period of 6 to 12 months or 6 months to 18 months after

the CAR T-cell therapy and start to make immunoglobulin and don't have any problems.

Lizette:

The next question: From my understanding NGS, which is next-generation sequencing testing, has been done in trials. Do you see it in the future being the standard or do you foresee that decreasing the rate of relapse?

Dr. Hunger:

The NGS technology, I think, it certainly is used in some clinical trials. It's also being used in some settings in routine patient care, although more commonly for patients who have relapsed than newly diagnosed patients. It has some advantages in that it is more sensitive, meaning it can detect lower levels of leukemia cells. It is, if you will, easier to standardize. Although, right now, there's only one company in the US that does this. Everybody who gets it, gets it sent to the same company. It's not done in laboratories at individual hospitals.

The other challenge with this technology is the turnaround time is in the range of 10 to 14 days after you send the sample off. At some points in therapy, like the end of the first month, we are using the result to change the therapy right away. Right now, next-generation or NGS sequencing wouldn't allow us to do that because we'd have to wait 2 weeks to get the answer. I think the flow cytometry has a big advantage in that it's generally available within a day or so. There are pros and cons. I think if I had that crystal ball, I think we will use HTS (high throughput sequencing), MRD more and more commonly, but till it can get a faster turnaround, I don't think it will totally replace today's technologies.

Lizette:

The next question: Is there CAR T-cell or immunotherapy treatment for T-cell ALL?

Dr. Hunger:

Great question. There are experimental therapies being developed and tested that are immunotherapy directed at T-cell ALL. Without going into the technology, it's a bigger problem. It's a bigger technical problem than B-lineage ALL, but there are some CAR T cells against T-cell ALL clinical trials that are ongoing and will be developed. Just the mechanics of the treatment make it very likely that that will be a treatment that if it's successful, which we don't know yet, but we certainly hope, it will probably need to be coupled with a bone marrow transplant.

Lizette:

We'll take the next question from our telephone audience please.

Operator:

Our question comes from Brittany. Brittany, your line is now open.

Brittany:

I just am curious if there's any research on the holistic side in addition to the medical treatment of specifically like B-cell ALL?

Dr. Hunger:

That's an important question. We have a program at CHOP or we have an integrative oncology program. I think there's 2 aspects to programs like that. One is what I'll call all focused on decreasing or ameliorating side effects. Many of the side effects of therapy, can you make them fewer in number or cause fewer problems? There are a lot of attempts to do that using things, such as massage therapy, acupuncture, herbal supplements.

The other question is, are there integrative medicine or holistic therapies that can improve cure rates and be a

different way of treating patients? I think that's a tougher challenge to find something that might change treatment as much as we might like it. The one thing I always say is I think it's very important to tell your doctor what medicines or other things you want to try, and I'll give a couple examples.

One is that methotrexate works by interfering with the metabolism of vitamin B or the B vitamins. Certain holistic medicines or vitamins you might give have very high doses of the B vitamin folic acid, which is the same thing as leucovorin or similar to leucovorin that we use to rescue you for methotrexate. At the same time you're getting methotrexate, if you give vitamins or supplements that have very high concentration of folic acid, it might be interfering with the activity of methotrexate.

The other is, many, many years ago, probably 30 years ago, I took care of a child whose family was giving the child some herbal Chinese remedies, which we didn't know about. The family didn't speak a lot of English and we probably didn't have good communication about him. That child developed near-fatal liver toxicity because the herbal remedies combined with the chemotherapy to cause very severe liver toxicity.

I think for those reasons, if you want to try what used to be called complementary and alternative medicines, now generally are referred to as integrative medicines, I think you just want to make sure that the treatment center knows what you're giving. When parents talk to us about that, we generally ask our pharmacists to take a look at it. Most of the time, the pharmacists say, "I'm not sure it's going to work, but it's probably not going to hurt, so it's fine to give." Sometimes the pharmacists say, "No, no, this is going to interact in a bad way. This would not be safe to give." I hope that answers your questions.

Lizette:

Our next question: Are there any advancements for AVN avascular necrosis?

Dr. Hunger:

Yes, that's a good question. I find AVN to be a very challenging side effect to deal with. For those who don't know, avascular necrosis is caused in significant part because of steroids but probably other things, such as asparaginase in combination with steroids, and can cause injury to the large bones and joints, most commonly the hips and shoulders, but also knees, feet, wrists, elbows. This can be anywhere from a minor annoyance to a severe toxicity.

I have unfortunately had the experience of having a patient who became an opioid teenager, became opioid dependent because of this pain and had some major problems related to opioid addiction. Others, it leads to hip replacement surgeries or joint replacement surgeries. We have learned that how much steroids we give and how they're timed can make a big difference. It's not intuitively obvious why this is, but we found that if we give steroids 3 weeks in a row, it's much worse than if it's a week of steroids, a week holiday, and then another week of steroids. You wouldn't think that would make that big a difference, but it actually did.

I think we have learned how to decrease the risk of avascular necrosis. We know the groups at highest risk are teenagers and girls more than boys. There are some surgical developments that have varying levels of success, but I would say, we still aren't good enough at treating AVN when it occurs. I find it frustrating to treat, and I know it's orders of magnitude, more frustrating to have it than it is to treat it.

Lizette:

Our last question today: Can cognitive side effects be reversed or improved with time?

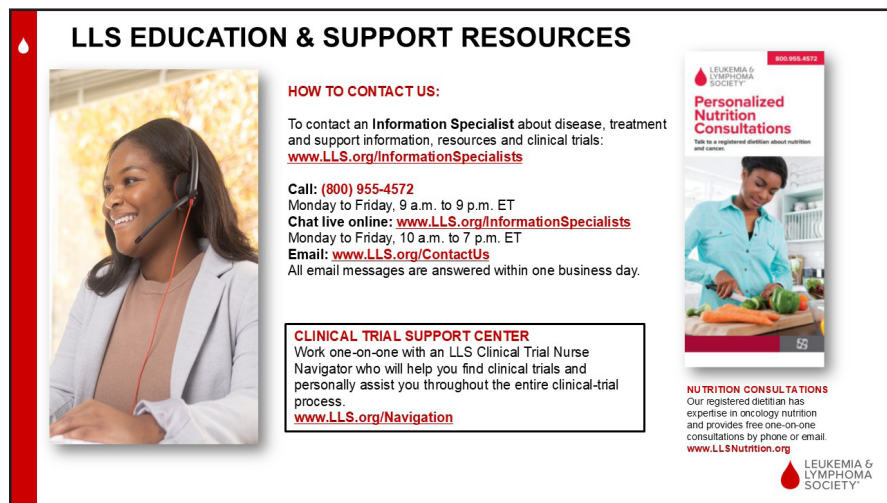
Dr. Hunger:

Another great question. I think there is some level of truth to what adults refer to as chemo fog. While you're getting chemotherapy, there can be some short-term side effects that get better with time. That's one of the reasons we want to look at long-term follow up of neurocognitive outcomes. Generally, I think they become most informative by starting to look at it when a patient is 3 to 6 months after completion of therapy, so that you don't have any confounding of still

taking chemotherapy. Oftentimes, what you see during therapy will get better over time when you stop therapy.

There are other neurocognitive deficits that can be persistent. These are generally things like attending what are called executive function tasks. Memorizing, you give somebody a list of 10 numbers and ask them to repeat it back, that there can be problems with things like this. A lot of the advantages of getting formal neurocognitive treatment to me is that if you recognize a deficit, you can often find ways to overcome it with accommodations at schools. IEPs or individualized educational plans or people can learn what their strengths are and what their weaknesses are.

I think this happens in children without leukemia too. I bet you some of you listening today have a sibling of a patient who has problems with school and has learned some ways to overcome them. I would strongly encourage you to talk to your center, particularly if you're concerned about your child's school performance, about getting formal neurocognitive testing done. The schools can do some testing in school, but it's probably not as detailed as what your center can do. You can use those to develop the best learning environment for your child or yourself. Now that often will involve an IEP.



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Slide 38: LLS EDUCATION & SUPPORT RESOURCES

Lizette:

Thank you so much, Dr. Hunger, for volunteering your time and your expertise with us today. I know we weren't able to get to all of your questions today or if you need more information or resources, you may speak to an LLS Information Specialist at 1-800-955-4572 from 9:00 AM to 9:00 PM Eastern Time, Monday through Friday, or reach us by email at LLS.org/ContactUs.

You may also reach out to one of our Clinical Trial Nurse Navigators at our Clinical Trial Support Center by visiting LLS.org/Navigation or call an Information Specialist. If you haven't already done so, please make an appointment with one of our Nutrition Educators. They are registered dietitians that can answer questions for patients and caregivers with any type of cancer.

LLS EDUCATION & SUPPORT RESOURCES



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Online Chats are free, live sessions, moderated by oncology social workers. To register for one of the chats below, or for more information, please visit www.LLS.org/Chat



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Patient Podcast

The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit www.TheBloodline.org



Slide 39: LLS EDUCATION & SUPPORT RESOURCES

They are free consults, and you may contact them by visiting LLSNutrition.org, or you may call toll-free at 877-467-1936.

LLS EDUCATION & SUPPORT RESOURCES



Help With Finances

The Leukemia & Lymphoma Society (LLS) offers financial assistance* to help individuals with blood cancers.

The LLS Patient Aid Program provides financial assistance to blood cancer patients in active treatment. Eligible patients will receive a \$500 stipend. Visit www.LLS.org/PatientAid

The Urgent Need Program, established in partnership with MyLife's Line, helps pediatric and young adult blood cancer patients, or adult blood cancer patients who are enrolled in clinical trials, with acute financial need. The program provides a \$500 grant to assist with non-medical expenses, including utilities, rent, mortgage, food, lodging, dental care, child care, elder care, and other essential needs. Visit www.LLS.org/urgent

The Susan Long Pay-It-Forward Patient Travel Assistance Program provides blood cancer patients a \$500 grant to assist with transportation and lodging-related expenses. Visit www.LLS.org/Travel

The Co-Pay Assistance Program offers financial support toward the cost of insurance co-payments and/or insurance premiums for prescription drugs. Visit www.LLS.org/CoPay

*Eligibility for LLS Lending Assistance Program is subject to credit review and approval. Assistance is available for U.S. residents and U.S. citizens.

The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancers:

www.LLS.org/Finances



To order free materials: www.LLS.org/Booklets



Slide 40: LLS EDUCATION & SUPPORT RESOURCES

As a reminder, you can download and print the slides, as well as view today's program from our website at LLS.org/Programs.



Slide 41: THANK YOU

Dr. Hunger, thank you again for volunteering your time with us today. On behalf of The Leukemia & Lymphoma Society, thank you all for joining us.

Goodbye, and we wish you well.