TRANSCRIPT

The Pediatric Treatment Approach to Adult Acute Lymphocytic Leukemia: Perspectives for Oncology Nurses

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Slide 1: Adult ALL: Perspectives for Nurses

Carson Jacobi:
My name is Carson Jacobi and I'm the Vice President of National Education Programs for The Leukemia & Lymphoma Society.

We welcome you to the program, *The Pediatric Treatment Approach to Adult Acute Lymphocytic Leukemia: Perspectives for Oncology Nurses*, featuring Dr. Barton Kamen and Katherine Breitenbach. We thank them both for sharing their time and expertise with us today and for their dedication to serving families touched by cancer.

We would also like to acknowledge and thank Enzon Pharmaceuticals Inc. for their support of today's program.

Before I turn the program over to our first speaker, I would like to remind you that The Leukemia & Lymphoma Society is committed to bringing you the most up-to-date information about blood cancers, so you can stay current in your field and help patients get the best options for the best outcomes. And our vision is that one day the great majority of people who have been diagnosed with a blood cancer will be cured, or they will manage their illness with a good quality of life.

And since our founding in 1949, The Leukemia & Lymphoma Society has invested more than $600 million for research, specifically targeting blood cancers. And we will continue to invest in research for cures and programs and services that improve the quality of life for patients and their families. And we hope that this teleconference will be helpful to you with your work in support of patients.

I now have the pleasure of introducing our speakers and then we will start the program.

Slide 2. Treating Young Adults and Adults

First speaker is Dr. Barton Kamen. Dr. Kamen is the Executive Vice President and Chief Medical Officer of The Leukemia & Lymphoma Society as well as the Professor of Pediatrics and Pharmacology at The Cancer Institute of New Jersey at Robert Wood Johnson Medical School. Dr. Kamen has been a recipient of a Scholar Award from The Leukemia & Lymphoma Society, in addition to several other acknowledgments. And please read further his bio that is included in

your materials

Also joining Dr. Kamen we have Katherine Breitenbach and she is a Clinical Research Nurse in the Section of Hematology/Oncology at the University of Chicago Medical Center. In her current position she coordinates the care of patients with acute lymphocytic leukemia, acute myelogenous leukemia and also APL, and maintains protocol adherence for patients on clinical trials and works closely with the bone marrow transplant program to ensure continuity of care for patients.

Dr. Kamen, I'd like to turn the program over to you. Thank you so much for joining us.

Dr. Barton Kamen:
An absolute pleasure to be here. And I thank you and I thank everybody for listening as we discuss issues of why treat young adults like children. And I especially want to thank Kate for joining us. I've been in oncology for 30 years and how and what to do are easy to establish, but I know very well that it's the nurses who do all the work.

I'm going to talk to you a little bit about how these drugs came to be. I hopefully will be setting up Kate very well for her talk and she's the major speaker. And you should all leave with a better appreciation of why we do what we do. And I leave you with a great appreciation for how you do it all because I have an access to central line and probably two or three years right now. You all are the front line and the better you do and the more you know, the better off we are.

So we're going to discuss treating young adults with leukemia and I'm going to try to convince you you need to treat them as if they are children.

Slide 3. Disclosure of Conflicts of Interest

I have no conflicts of interest. That's the mandatory slide to show you.

Slide 4. What is ALL?

And what is leukemia, is our first slide of substance. It's actually the most common pediatric malignancy.

If you don't have the slides, I will try to give you the highlights of all of them.

In fact, it's about the only malignancy, common malignancy, in which children outnumber adults. It's been estimated that there will be about 5,500 cases of acute lymphoblastic leukemia this year in the country and probably 3,000 to 3,500 of them will be in patients less than 20 years old. It is clearly a disease of young people.

Slide 5. Blood Cell Formation

To remind you of where leukemia comes from on the next slide we have a picture of blood cell

formation titled hematopoiesis. And you can see that wonderful stem cell in the middle, giving rise to monocytes and eosinophils, neutrophils, basophils and the red cells. And in the upper right corner you can see the B cells. Those are the cells that make antibodies. About 80 percent of acute lymphoblastic leukemia is a derangement in that B cell.

This slide will also serve to remind you about the common side effects of chemotherapy because while we think of cancer as an unregulated growth of these B cells, if you look around the slide you see lots of normal cells. And I'll remind you that every day you make and break somewhere between 200 and 300 billion of these cells, because you turn over naturally 1 percent of your red cells every day, and when you look up at the white cells, especially the neutrophil line, you make and break about 10 percent every day, similarly with the platelets. So this slide reminds us where the malignancy is coming from, but it also reminds us why drugs that kill cells also make us pancytopenic because we're going to be destroying all these normal cells.

Slide 6. Timeline of Cure

The next slide shows the good news and forms the basis of why we're going to be talking about being aggressive with our adult patients. You can see here the time line for the five year EFS, event-free survival. And you can see in the last 50 years we've gone from curing about 10 percent of the children to curing 80 to 85 percent. It's estimated now that with transplants and salvage therapy, that nearly 90 percent of children diagnosed with leukemia will be alive at five years. And you notice on the slide it says pediatrics, that is. The major problem is that the adults and young adults aren't doing so well.

Slide 7. Outcomes on Clinical Trials

Probably the most important slide for this whole session is right here and it's entitled Outcomes of Patients Treated on Either Pediatric or Adult Clinical Trials. And you can see four western countries, the United States, the Dutch, the Swedes, United Kingdom. And you can see a decade from the late 80s up until the millennium. And you can see where groups have treated patients 16 to 20, 15 to 20, and all you have to do is look at the last two columns. When these young adults are treated on pediatric trials, the five year survival rate is on the order of 70 percent. And when they're treated on adult trials, it's more like 35 percent. Remarkably, there was actually a paper published in the last few months by the French, when they noted that in one generation of leukemia trials, when they were also treating these young adults who were at 35 percent, one generation of trial they switched to treating the young adults like kids and they jumped from 35 percent to 60 percent. So it's clear that it's something that the pediatric trials have that will make a big difference in this young age population. The question is, what is it? Are we doing anything different?

Slide 8. Timeline of Cure

Well, the next slide is same slide I just showed you on the survival curve, and it shows that methotrexate and mercaptopurine, drugs you're familiar with, were around since 1950. Actually

methotrexate was like 1948. Vincristine, prednisone and asparaginase were all developed before 1960. The major recognition in treating patients with leukemia was what was called total therapy and we realized in the late 60s, early 70s, that there could be central nervous system disease and we needed to do prophylaxis either with spinal taps or cranial radiation. And this remarkable improvement in the cure rate was affected by no other really new drugs. Kate's going to talk a little bit about daunorubicin, an anthracycline, and I'll come back to that in a little bit. But the remarkable improvements have been in how to use these drugs better. And in the last decade, knowing more about the leukemia.

Slide 9. Personalizing Treatment

So basically as I just said to you, the drugs are all 40, now close to 60 years old. How we use them to treat patients is called personalizing or the tailoring the medicine. The patients are different and it's clear from our analysis of people getting vincristine and steroids and asparaginase, that one of the major factors is, did all the medicine get in. All the cure rates, all the curative plans in the world don't mean anything unless the medicine gets delivered. And we all know how hard it is to give neurotoxic medicines and medicines that don't make you feel well, on the right schedule.

Slide 10. Induction Therapy

With this brief introduction I'm actually now going to go through a couple of the drugs from a historical point of view and put things in perspective to make Kate's job a little bit easier.

Slide 11. Vincristine

Here is the first slide and the drug I want to talk about is vincristine. It's actually from Madagascar, it's the rosy periwinkle. It actually grows all over the world. When it was initially made by Lilly, I actually talked to one of the Lilly chemists and they told me that five acres of this plant, appropriately extracted, would be enough vincristine for the entire world, for one year of leukemia therapy. That speaks to the potency.

Slide 12. Vincristine Side Effects

The side effects of this drug are shown right here. And those of you in the audience have known this, will say to me Dr. Kamen, it's neurotoxicity, it's constipation, because the bowels will get an ileus, and it's the neuropathy, it's the pain and the tingling. Well, from an interesting historical point of view, I will remind you that the Indians in the Andes mountains were actually using periwinkle, vincristine look-alikes, because in fact they knew that with an overdose put on their poison arrow tips, they were such a potent neurotoxin they could bring animals down. So vincristine was actually found because it was a neurotoxin, when used in very, very large doses.

This slide showing vincristine side effects. I purposely put the question mark rare, on the right hand column, when I talk about numbness and tingling and trouble urinating because the bladder

and jaw pain. Almost everybody, if you press them, will talk about the jaw pain. They talk about being tired. They actually have numbness and paresthesias. And I think vincristine is almost as bad as platinum for causing these neuropathies.

We have very little antidote for this. We do know that lowering the dose, sometimes as little as 10 percent, makes a difference. In recent years and currently in the Pediatric Oncology Group, they're actually using moderately high doses of an amino acid called glutamine. And I've personally had some results in eliminating some of the neurotoxicities with glutamine. And I wish I could tell you what the mechanism was, but can't.

The importance of vincristine is that vincristine and a steroid alone, and I'll be covering the steroids in a bit, will make a remission in nearly 60 percent of the cases of certainly kids with leukemia. It's never been replaced and it's too important to replace right now in induction therapy. And I'll cover these terms again for you in a bit.

Slide 13. L-Asparaginase

The other major drug that was somewhat found by accident and we've never replaced, although we now have different longer-acting forms, is an enzyme called asparaginase. The three dimensional X-ray picture is shown on the left hand side, and the amino acid asparagine is shown on the right hand side. This enzyme asparaginase merely takes off the amino group and if you have the slides, it's that NH2 group in the lower left hand side of the picture, and the enzyme turns asparagine into aspartic acid. The importance of that is that the leukemia cells are deficient in their ability to make asparagine. So it's one of the essential amino acids. So literally within minutes of getting this enzyme, your blood levels of asparagine are non-detectable, and we're in effect starving the leukemia cells because they can't make this amino acid. In fact, a gentleman named Broome who's still alive and practicing medicine on Long Island, the North Shore, discovered this in about 1956 when he found that guinea pig serum was very good at killing lymphoma cells and the guinea pig serum was loaded with asparaginase. We don't use guinea pig serum for this drug. We in fact use it from bacterial sources and the enzyme, it's a fairly large protein, so those of you might expect, if you've been in the clinic for a long time, when you get a foreign protein you can make an antibody.

Slide 14. L-Asparaginase Side Effects

So one of the major problems with asparaginase is an anaphylactic reaction as an extreme. But certainly there are allergic reactions.

The other side effects you see, and I know Kate will cover them in greater detail, are hyperglycemia, pancreatitis, clotting or bleeding, and azotemia. Again, if you start with the azotemia, when the enzyme clips the asparagine to aspartic acid, it releases ammonia. And there have been clearly cases of hyperaminemia associated with it. Since it's really stopping protein synthesis, it decreases the synthesis in the liver of clotting factors. And that's why you can either get clotting or bleeding. It stops both anti-thrombin III as well as the clotting factors. And for

reasons I don't completely understand, you also can develop pancreatitis and diabetes.

Slide 15. Steroids

The third drug to make a remission most of the time is a steroid. And you see hydrocortisone on the left hand side of this picture. The one on the right is prednisone. It's a synthetic version of hydrocortisone. You all should remember that steroids are incredibly powerful in autoimmune disease. That's why we use them. If I give anybody listening to me here even 20 milligrams of a steroid, and then I looked at the lymphocyte count within four hours of taking the dose of steroids, you would be lymphopenic. It's incredibly powerful at eliminating lymphocytes. That's why we've been using the drug.

We've known this, also since the 1950s, there were papers in 1954 and 1955, before we had synthetic steroids, using ACTH, adrenocorticotropic-releasing factor, we knew that those patients getting injections of ACTH in the 50s could have such a bump in their steroid production that it had been reported in the Italian pediatric literature that some kids with leukemia had decreases in their lymphoblasts. So it wasn't hard to realize that steroids would become a powerful induction therapy.

Slide 16. Steroid Side Effects

You also realize that steroids can have all these side effects, as listed on the slide, anywhere from mood changes, night terrors, headaches, dizziness, sweating, heartburn. Again the list is long and I know Kate's slides have very long ones.

To put this in perspective about why we see these, and certainly the cushingoid changes, the average adult makes about 10 or only 12 milligrams per square meter per day of hydrocortisone. So if the average adult is 1.7 square meters, we do fine making only 25 or 30 milligrams of hydrocortisone. Prednisone is about five times the potency, so when you're giving somebody 60 milligrams of prednisone, you're giving them the equivalent of 300 milligrams of hydrocortisone. That's about ten times what the body makes in any given day. And that's why we see these exaggerated steroid effects.

Again, vincristine and steroids are so potent at making remissions, we've really never found a way to substitute them.

Slide 17. Continuation Therapy

The next phase of therapy, after an induction is made and vincristine, prednisone and asparaginase, certainly in the standard risk child with leukemia, will make a remission in excess of 95 percent of the time. If you stop treating patients, you will relapse. We know that when we've made a remission and then we did nothing, that within six or eight weeks we know the leukemia has come back. So by trial and error over the last 40 years, we know that continuation therapy is important. In the old days it was known as maintenance therapy.

Slide 18. Folic Acid and Methotrexate

And I'm just going to tell you about two drugs used in maintenance therapy because in fact they're both 60 years old. We have large familiarity with both of them and they've never been replaced.

One of the first drugs ever used to treat leukemia was an antifolate. You see the picture of folic acid, that's what's in your vitamin pill. And you can see the picture below it, it's methotrexate. A cousin of methotrexate was actually reported in the New England Journal in making a remission in about 6 or 7 out of 16 to 17 kids, at what we now call the Dana-Farber Cancer Center because Sidney Farber used a cousin of methotrexate, called aminopterin, and he gave about a half a milligram every day for two weeks and he made remissions. The reason is that folic acid is a vitamin. Without it we can't make DNA, RNA and many neurotransmitters and a lot of other amino acids. But it's a vitamin by definition, is a vital amine, that's the Latin. Without it you die. Your cells need it. And methotrexate and other antifolates are in fact look-alikes for folic acid, so they interfere with everything that folic acid is supposed to do.

Slide 19. Methotrexate Side Effects

So when you think about it, the side effects of methotrexate would be fairly predictable. Remember your skin, for example, turns over very quickly. You replace your intestinal lining about once a week. You replace all your skin once a month. So if methotrexate, or the vitamins important for skin growth, that methotrexate, if you give it, could cause mucositis and skin rashes. And you see the word stomatitis in the middle for the side effects.

I purposely put the blahs, the malaise, zoned out, impotent high up. Because we know from the arthritis literature, and the patients with leukemia actually don't take much more methotrexate than some of the arthritis patients, is at least half the patients with arthritis at some point will not want to take methotrexate because they feel zoned out, they feel the blahs, they really get fatigued. We think that's due to the fact that methotrexate interferes with folate metabolism and folate is important in amino acid homocystine, which is important for both vascular and as a neurotransmitter. So that when methotrexate is in and folate goes down, homocystine goes up, and it's actually a fairly potent neurotoxin. And that's why we think the adults don't like to take it. The extreme of that would be the encephalopathy, which usually only see with high dose. But in the clinic on an everyday basis, you'd expect at least half your patients not to want to take methotrexate because they just don't feel well with it.

Slide 20. 6-Mercaptopurine

The next important drug in maintenance therapy is actually Purinethol®, 6-mercaptopurine. This drug was developed by Gertrude Elion and George Hitchings in about 1950. And for those of you, I should remind if you don't think you can do anything without a doctoral degree, in Dr. Elion it's

an honorary degree, she's the woman with George Hitchings, who is the senior chemist, responsible for mercaptopurine, allopurinol, acyclovir, AZT and 6-thioguanine. And they won the Nobel Prize for that work in 1988. And Dr. Elion actually only had a masters degree. They were building this drug about the same time we were learning about the double helix. We didn't know really how important nucleic acids were. We were just figuring out it was part of the genetic code. But 6-mercaptopurine looks like adenosine and inosine. It interferes with DNA synthesis because it's a DNA building block look-alike. As such it's going to be very important.

Slide 21. 6-Mercaptopurine Side Effects

Interestingly, it's very rapidly taken up by the liver, so in addition to the usual, I'm going to lower my white counts because the cells are rapidly growing and I'm going to get ulcers on the skin, it actually causes a fair bit of hepatic dysfunction, especially when you add in it with steroids and methotrexate.

The look-alike of 6-mercaptopurine, and Kate may talk about it a little bit, is actually 6-thioguanine, 6TG, which is actually much more potent in causing hepatic dysfunction. In fact, there's a reasonable incidence of hepato-veno-occlusive disease with that. We don't usually use that much 6-thioguanine in standard ALL therapy, so I really did not talk about it much here.

Slide 22. Future?

On the next slide I actually have the future and hopefully I've set Kate up well. And before I tell you about the future, I will admit that I did not cover the anthracyclines, daunorubicin and doxorubicin, which I know Kate will do. And certainly in high risk leukemias, it's become the fourth drug that's often used during initial therapy.

If I come back to the substance of this slide, the future. Sadly the first line shows while waiting for the magic bullet, we do not yet have magic bullets for ALL patients, like we have Gleevec® for CML. We don't really have targeted therapy. Our 80 percent cure rate to 85 percent cure rate in children, is based upon incremental, very good clinical trials over the last 20 or 30 years, where we've learned to use drugs that are again 40 and 50 years old.

It is clear, and I'll give you some examples, that we now really do have pharmacogenetics and pharmacodynamic parameters for most of the drugs that we just discussed. And we need to know how to use these drugs correctly, and we can do that and we can do that now.

So for example, 6-mercaptopurine is metabolized by an enzyme called thiopurine methyltransferase. And about 88 percent of the world has adequate levels of thiopurine methyltransferase. And about 11 percent of patients have an intermediate level. And about 1 in 200 people are missing this enzyme called thiopurine methyltransferase. If you do not have this enzyme, and you're 1 in 200, you will need 1/10th to probably 1/50th of the dose of 6-mercaptopurine because the body is missing the ability to eliminate the drug. That's important. Again, instead of taking 50 milligrams a day or 75 milligrams a day of this drug orally, a patient

may only have to take 5 or 10 milligrams a week. We need to know that because if you take the full doses, the drug will be toxic.

Similarly we now know, especially from the arthritis literature, that there are at least four or five enzymes that are critical in determining whether methotrexate is very toxic and we can get mucositis or we can get the blahs and the malaise. So when patients are having trouble taking these therapies, we can actually measure these enzymes now and we can tailor the therapy.

Steroids, there are now known polymorphisms that we will be able to predict who's going to have the avascular necrosis, the bony disease or the osteoporosis that we see in many of the children. Fortunately the older adults are spared, but I'll remind you how important it is in that 16 to 18 year old group, somewhere up close to three-quarters, well, about 15 percent of the children will have severe avascular necrosis of either a knee or a hip. And three-quarters of them will actually come to have a joint replacement. Wouldn't it be nice to be able to do a genetic test to see if I can predict who may be at risk and to see if there are ways to avoid some of that side effect.

So I believe that is my last side. And with that, hopefully I've given you a taste of the history and where we've been with treating people with acute lymphoblastic leukemia. And most importantly, I showed you that the same medicines that cure 80 percent of the young adults should be able to cure a lot more of the 16 to 30 year old group. But it's really, really important that the drugs get in. And that's why I'm going to turn it over to Kate because she is the one who has had the experience using these medicines. I spend my career figuring how to use them.

So Kate, it's all yours.

Slide 23. ALL in AYA's

Katherine Breitenbach:

Thank you, Dr. Kamen. Hello, everyone, and thank you for listening today. As mentioned earlier, I work in clinical research at the University of Chicago and my main population of interest is acute lymphocytic leukemia, the majority of which I see are adolescents and young adults. So when I refer throughout this talk to AYA, I'm speaking in reference to that population and that's adolescents and young adults who range in age from 16 to 30 years.

Slide 24. Disclosure of Conflicts of Interest

Before we begin, this presentation is presented without conflict of interest or any commercial bias.

Slide 25. Objectives

And just to give you an idea of directions of this talk, we'll be examining data from clinical trials using pediatric treatment for ALL in the adolescent and adult patient populations, we'll review the

therapeutic treatment options for ALL, and apply knowledge of administration and drug interactions to ALL treatments, and develop a plan for side effect management to maximize the safety and quality of life and compliance of therapy.

Slide 26. New Leukemia Cases and Deaths

The incidence of ALL is relatively rare. You can see from this table, the data from 2008 shows roughly 5,400 new cases of ALL in the past year. And I always have to remind myself of the rarity of this illness. I'm sure that there are people listening who just see one or two cases of this disease in their oncology practices each year. I manage roughly 20 to 30 patients with this diagnosis, so I often forget this fact, that it is not very common.

Slide 27. ALL: Prognostic Factors

There are several prognostic factors for ALL that can help predict outcome of the disease and we'll go into each of these in a little more detail. I just want to highlight that age may be the most significant factor pertaining to survival outcomes for this illness.

Slide 28: Incidence by Age

And you can see from this graph that the incidence of ALL varies by age. And as Dr. Kamen mentioned, the majority of these diagnoses are in young children. ALL is mainly a disease of childhood. And you can see that the frequency of cases occur most in those 1 to 4 years of age and then decreases as we move along the age curve with relatively few cases occurring in middle age, and then it can increase later in life.

Slide 29: Childhood vs. Adult Outcomes

The outcomes of ALL in terms of age are significantly different. When adults are compared to children, we can see that 2 to 10 year olds have greater than a 95 percent remission rate, with the overall survival, as Dr. Kamen mentioned, at 80 to 90 percent. These are very high numbers for leukemia and when compared to their adult counterparts, older patients, too, have a promising remission rate, however not as high as children. But their overall disease-free survival falls short, with only 35 to 40 percent achieving a leukemia-free survival.

Slide 30. Cytogenetics

In fact, looking specifically at the cytogenetics of the disease, AYAs have a lower incidence of favorable cytogenetics. This data is looking at cytogenetics at disease presentation, and highlighted in the dark blue, you can see that favorable cytogenetics such as hyperploidy, translocation 12;21 and trisomy 4, 10 and 17 occur with greater frequency in children, roughly a quarter of all cases. And then poor, unfavorable cytogenetics such as the translocation 9;22 or the presence of a Philadelphia chromosome occur with greater frequency in adults. AYAs have only a 5 to 7 percent incidence of the Philadelphia chromosome, so it's not as high as listed in this table.

However, that incidence increases more with age.

Slide 31. Leukocyte Count at Presentation

An increased white blood cell count at diagnosis is also associated with worse outcomes. And this may indicate a decreased CR rate. The patient may require multiple inductions to achieve a remission. There is a decreased remission duration and overall survival as well as an increased risk of CNS relapse. And in fact, we're seeing a shift towards relapse in the CNS. And this extreme leukocytosis at presentation might play more of a role in patients with the B-cell lineage ALL.

Currently we have a 20 year old gentleman, he's 20 years old now, he presented two years ago with a white blood cell count over 100,000. And luckily went into a remission after induction, but had an isolated CNS relapse six months into his maintenance therapy and never achieved a great response when we tried to reinduce him, but did respond to a salvage regimen that we gave him with VP16 and ifosfamide. And fortunately, he went on to be transplanted. Unfortunately, recently he had a disease recurrence and we're at the point where we're trying to get this man into remission.

So that gives you an example of that shift towards CNS relapse and one example we've seen.

Slide 32. Childhood vs. Adult Disease

The biology of adult and pediatric ALL also differs. You can see on this slide that the incidence of T-cell ALL occurs more frequently in adults and this slide also shows you what we discussed before, the incidence of PH-positive ALL is significantly greater in adults than children by ten-fold.

Slide 33. Immunophenotyping

This slide just depicts the differing immunophenotyping of both B- and T-cell lineage. You can see the varying CD markers on the cells, distinguishing the different types within B-cell and T-cell ALL.

Slide 34. MRD is a Prognostic Variable

When we're doing bone marrow biopsies and checking for minimal residual disease at different time points, one of the things that we're looking for is the presence of these markers on flow cytometry in the cells of the marrow.

So, looking at outcomes after induction therapy; in adult hematology we perform our remission bone marrow biopsy on day 29. Dr. Kamen can speak more to this, but I know on the pediatric side, some institutions are checking for minimal residual disease on day 8 as an indicator of slow early-responders. The induction regimen that we use is designed in such a way that patients only

really receive two days of therapy, so a day 8 bone marrow biopsy is not so informative for us. We do one at day 14 which looks for hypocellularity and gives us some idea of response in terms of minimal residual disease, but it's not always an accurate predictor of induction failures.

MRD present on day 29 is a predictor of poor prognosis and a decreased remission duration.

Slide 35. Factors Influencing Treatment

I really like this diagram on this slide. It puts together everything we've discussed in the past several slides in terms of what influences diagnosis in terms of the varying biological markers, clinical characteristics, and it highlights the risk stratification, as well as the progression through therapy with either remission or relapse or cure. So you can go back and look at that in a little more detail, but I like how that really lays it all out for us.

Slide 36. Mortality: 2001-2004

As was mentioned, ALL is relatively uncommon in young adults. However, you can see from this graph, the incidence of mortality is heightened in the young adults aged 15 to 24, when they're compared to other age groups. You can see that large spike. And the incidence of mortality is fairly high for some of the other groups, but really is the largest in 15 to 24 year olds on this slide, and we'll discuss some of the reasons for this in the upcoming slides.

Slide 37. AYA's: Low Trial Participation

This next graph depicts the number of patients with ALL enrolled on clinical trials that submitted tissue samples in the year 2003-2004. You can see age is on the X axis. And there's a relatively high incidence of enrollment in children less than 5 years of age, probably due mostly to their parent ascent to clinical trials. However, if you follow the curve along, the participation really decreases with age and there's a large drop-off at age 18 and older.

Up until recently young adults and adolescents who were seen and treated by an adult hematologist received very different therapies than their counterparts that were seen and treated by pediatric hematologists. The pattern of referral for themselves and out in the community varied and therefore the treatment varies a lot for this patient population.

Young adults that were treated by adult practitioners were receiving treatment regimens for adults up to the age of 60 years old. And this treatment was really designed to be tolerable by a large age spectrum.

Slide 38. CCG vs. CALGB Analysis

Seeing adults with ALL have such poor outcomes, and this same age population treated by pediatricians having greater survival data, led to the question and hypothesis of this research trial done by Dr. Wendy Stock and colleagues, is this really the best and most appropriate treatment

for adolescents and young adults, treating them with an adult regimen?

The retrospective comparison examined 124 charts from the Cancer and Leukemia Group B Cooperative and 197 charts from the Children's Cancer Group, looking specifically at the presenting cytogenetic and molecular features, the type of treatment and doses planned, as well as the remission rate and the clinical outcome.

And these charts were examined from 1988 to 2001.

Slide 39. Survival Differences

So you can see with the survival curve, that the analysis is really striking and the event-free survival varies greatly with 16 to 20 year olds treated on an adult regimen, having only a 34 percent event-free survival at seven years, compared to 63 percent survival in their pediatric counterparts.

Slide 40. Outcome: Phenotype and Genotype

And the demographic data for this trial, paying greater attention to the numbers in parentheses, those are the percentage of patients in the different groups, but you can see from this data table that the groups are relatively similar, being mainly male, Caucasian, presenting with precursor B ALL. Roughly a quarter of each group had a high white blood cell count at diagnosis and a relatively small percentage had unfavorable cytogenetics. The difference, you can see, from median age group on the Children's Cooperative Group of 16 versus 19, so on the older end of the spectrum for patients treated by adult hematologists.

Slide 41. Age-Adapted Therapy

There have been similar studies with comparative results that have been published in other countries. That's what this slide is showing, the U.S. trial by Stock and colleagues is listed on the top. The French FRALLE and LALA Trial was just recently published with similar results. And additionally you can see the British, Dutch and Italian groups have done similar research, with generally the same age patient population and similar results at five years.

Slide 42. Why Pediatric Approach is Better

So this research tells us that AYAs do better with a pediatric approach, but why is this? A lot is attributed to the protocol design and dose intensity of the drugs used in the pediatric setting. Additionally, the treatment setting itself can impact outcomes. Pediatricians have a much different treatment approach than their more lenient adult hematologist counterparts. More frequently parents are present in the pediatric setting and bring their children to clinic and treatment appointments. They are able to grasp the severity of the diagnosis, where this can tend to fall apart for our young adults.

Often in the adult setting we see patients that we like to refer to as emancipated adolescents. These are young adults that no longer live with their parents, they live on their own and they assume the full responsibility for their medical care and present us with some unique challenges in working with them.

Additionally, the type of therapy plays a role. Pediatric regimens give much more frequent, non-myelosuppressive therapy. The therapy duration is longer and prophylactic CNS treatment is up front. On some of the past adult regimens, prophylactic intrathecal therapy into the CNS was not administered until day 29 of induction.

Slide 43. Past Pediatric Studies

So we've already touched on this a bit, but in terms of treating adolescents and young adults, we've learned quite a lot from the past pediatric studies. We know that a prolonged intensive consolidation treatment can improve event-free survival, risk-stratifying patients according to biological and clinical markers, as well as response-tailored therapy to their disease is important. The use of dexamethasone in pulses we've found can reduce the side effects and may be more efficacious than using just prednisone. As well as implementing this prolonged maintenance phase or duration therapy at the end of treatment over two to three years after consolidation is also important.

Slide 44. AYA's: Unique Population

Adolescents and young adults are such a unique population and we've really only begun to tease them out as a specific group to examine how to treat them individually. And due to this lack of specific examination as well as their low participation in clinical trials, we've seen in that graph earlier, we really don't understand or know enough about their cancer biology to know how to treat them best.

And as we've briefly touched on, they have some differing physiologic and psychological issues that can play a role in their treatment as well.

Slide 45. Treatment: Children vs. Adults

So this slide just reiterates the specific difference of treatment regimens for those less than 21 years of age, treated on pediatric protocols, and those greater than 16 years of age treated on adult protocols. We already know that the pediatric-treated patients receive more doses of this non-myelosuppressive therapy: that's vincristine, asparaginase, glucocorticoids. They also receive earlier and more frequent CNS treatment and a continued maintenance therapy. Adults have a much more abbreviated treatment plan and they get less of these non-myelosuppressive drugs, but more myelosuppressive chemotherapy.

Slide 46. CALGB 10403

So I added this slide just to visually show you what our treatment regimen looks like. At University of Chicago, we're part of the CALGB Cooperative. We have a current ongoing trial that's examining these issues that we've discussed. It enrolled 16 to 30 year olds on this treatment schema. And you can see that the therapy is quite long. I'm not going to go into a lot of depth, but there's three intensified consolidation cycles, each lasting roughly eight weeks in length, and then there's a maintenance phase at the end of treatment that lasts two years for females and three years for males.

Slide 47. Cytarabine (ARA-C)

Next I'd like to just go through each of the drugs that we use in our treatment regimen and I'll spend a little more time on those of particular interest.

The first drug, and I lumped these in categories of myelosuppressive drugs versus non-myelosuppressive drugs, so we'll start with the first drug, cytarabine or ARA-C. This drug can be administered intravenously or subcutaneously. It's the first of our myelosuppressive drugs. And the main thing I want to point out with this drug is the occurrence of what's termed ARA-C syndrome. For those of you who have seen a patient develop this, you know this is a diffuse drug rash that can be very erythemic, across the entire trunk of a patient and sometimes the extremities. And they can develop a concurrent fever as a result of the side effect. And it's really important to be able to distinguish the fever as, is it a side effect with this drug versus an underlying infection. And you can use their counts, their neutropenia, to gauge what treatment you give these people.

Slide 48. Cyclophosphamide

Cyclophosphamide is another one of the myelosuppressive drugs. It has a great potential to be very emetogenic for patients. We frequently utilize concurrent administration of Emend® or aprepitant prior to dosing. It's given in a three day dose pack to help reduce the nausea associated with this administration. It's important to note that when you prescribe this drug to patients, you need to write the prescription for concurrent steroid administration. I found out the hard way that pharmacists don't always include this for you in a dose pack, so if you don't write for it and they don't get the steroids, it's not really as efficacious unless it's combined with that.

Another thing I want to point out with this drug is metabolites of the drug are excreted through the kidneys. And those metabolites can really irritate the lining of the bladder, so it's important to instruct your patients to drink frequently throughout the day, for 24 to 48 hours afterward, in addition to making sure they get up and go to the bathroom frequently. We give this agent following administration of a liter of IV fluids.

We had an interesting case of a 20 year old gentleman who had received Cytoxan® without incident for three doses and upon the fourth dose he developed this burning pain and frequent urination. He had gross hematuria in his urine. We gave him supplemental IV fluids. The patient

increased his fluid intake and we ended up giving him pyridium for symptom management. But the hematuria went on for four weeks, still detectable on his urinalysis. So we weren't really sure what was going on, why we were seeing such prolonged effects of the therapy. We did a cystoscopy which showed continued inflammation of the bladder epithelial four weeks post-drug administration and we ended up referring the patient to urology, who told us what we already knew, that we needed to be administering the Cytoxan with the bladder protectant mesna.

So upon subsequent administration, he did get this drug, mesna, with the Cytoxan and you can see that it needs to be given at a dose of 200 milligrams per meter squared 15 minutes before, 3, 6 and 9 hours post-infusion. So you may have to admit your patients if they have issues with this.

Slide 49. Daunorubicin/Doxorubicin

Anthracycline therapy. Dr. Kamen mentioned it's really becoming one of the up-front treatment drugs. Either daunorubicin or doxorubicin is the agent used. And it's important to note that this drug is a vesicant, it should not be administered peripherally. It can increase the potential for tissue damage should the drug extravasate into the tissues. Additionally, I want to point out that there's cardiac toxicity associated with the drug. It has a cumulative lifetime maximum dose dependency for that toxicity. And I've seen patients after just one dose of this medication have a 10 percent drop in their ejection fraction.

For acute myeloid leukemia patients, it's really routine practice, following its administration, to have a repeat echocardiogram or MUGA scan. However, because the dosing is slightly different in ALL it's not as common practice. But I think that's something to think about, as we're seeing really late effects of cardiac toxicity occurring in survivorship for these patients.

Slide 50. Methotrexate

Methotrexate is a medication given intravenously and by mouth. It's given by mouth in the maintenance phase of treatment and given IV, we use it in an escalating dose fashion. I think other regimens are using a similar treatment plan. The ECOG regimen I think has a similar course of therapy, but I'm not entirely sure about that.

The main side effects with this medication, Dr. Kamen went through a couple of them, it is myelosuppressive and has some GI toxicities. And they're what I like to refer to as the "itis-es." So you have your gingivitis, glossitis, mucositis and stomatitis, which are all inflammation and irritation of the oral and esophageal mucosa.

We had a particularly bad case of mucositis at our institution in a 23 year old gentleman that resulted in his admission to the hospital, so we could administer prophylactic IV antibiotics, IV fluids, because the patient's esophagus was so excoriated he was having difficultly swallowing food and fluids. Additionally, he required a morphine PCA pump. And this young man is a really good example of why you need to review patient medication lists. Because upon further assessment with him we discovered he'd missed a dose of his PCP prophylaxis, Bactrim, and took

it on the following day when he received treatment. And additionally, the evening of treatment had taken a dose of ibuprofen for back pain. And it's important to know that there's a drug interaction between sulfa medication, NSAIDs and salicylates like aspirins. They're medicines metabolized through the same pathway in the liver. So this can lead to a decreased clearance of the methotrexate causing heightened, more extreme side effects, as seen in the case of our young man.

Slide 51. Lumbar Puncture/CNS Treatment

ALL is a disease that likes the brain and spinal cord. Often on diagnosis patients present with CNS disease. This is classified below, which you can read on your own. But I just wanted to point out that patients classified as having CNS-3 or having blasts present and greater than 5 per unit liter of white blood cell count in their CSF, administration of intrathecal therapy is recommend via an Ommaya reservoir that's placed intraventricularly. This placement varies from institution to institution. I'm not sure what Dr. Kamen does at his institution, but it's not something that we routinely place for our CNS-3 patients because we've seen several cases of just horrific infected Ommayas. However, its placement can facilitate ease of administration of intrathecal therapy for the clinician. And I say for the clinician, because if you've ever given intrathecal therapy via an Ommaya, you know that patients experience this almost instantaneous reaction with nausea, vomiting and headache being the most common side effects. So if you're interested after this presentation, I can share a little premedication cocktail that we use that seems to reduce the side effects with IT Ommaya treatment.

Slide 52. Lumbar Puncture: Side Effects

Our preferred method of administering intrathecal therapy is by a lumbar puncture and we do this in one of two ways, either with a procedure team in clinic in our infusion suite, or for our larger patients and those that have developed fibrous tissue in their lumbar region from repeated LP's, we utilize a guided lumbar puncture done in radiology.

Lumbar punctures are really involved processes. Most patients dislike getting them done and they are done so frequently, the most common side effect that's reported is headache. And this is due to a leak in the CSF fluid that occurs over time at the site of insertion.

We have a young woman who is 21 years old that we're currently attempting to remedy her headaches. She experiences these really debilitating headaches for two to five days post all of her lumbar punctures, where she can't get out of bed. And what we did just this last time for her is first to ensure that patients all lay flat for the appropriate amount of time, everyone should be doing that. We told her to try an old nursing remedy of drinking warm cola post the lumbar puncture. We're also using a smaller LP needle called a sprotte needle, which you may or may not have at your institutions, but could call your radiology department or your procedure service just to find out, that this can help minimize the CSF leak. And if all of that fails, what we do is we consider treatment with a blood patch. And this is where we take a sample actually of the patient's blood and we'll readminister it at the site of the lumbar puncture to clot off the leak. But

you should know that this can only be done for patients who have platelet counts greater than 50,000, so you'll need to assess for that prior to ordering.

Slide 53. Cranial Irradiation

Cranial irradiation is also used for CNS prophylaxis. And used more frequently in pediatrics. We use it prophylactically only in our T-cell ALL patients because T-cell ALL seems to have a greater affinity for the CNS space. The main side effects seen with this radiation are fatigue, headache, nausea, vomiting and scalp irritation. It does have the potential for quite a lot of latent side effects and just to note that for male patients who present with concurrent testicular involvement, they're also receiving testicular radiation following their consolidation therapy.

Slide 54. Mercaptopurine/Thioguanine

Mercaptopurine or thioguanine, Dr. Kamen discussed these in a little bit more detail than I'm going to. We give them in pulses throughout consolidation therapy. And they're a main component of our prolonged maintenance phase, with patients taking this drug every day. They're relatively well tolerated. The main side effect we see is hepatotoxicity, with increased levels of AST and ALT as well as hyperbilirubinemia. And it's important to educate your patients that this drug cannot be taken with milk or milk products because it can decrease its absorption. Additionally, pharmacokinetic studies have demonstrated an enhanced effect if this is taken at bedtime on an empty stomach. And you'll know that even when you call these prescriptions into the pharmacy, they never list that on the prescription bottle, so make sure that you tell your patients both of those two things.

Slide 55. Vincristine

Vincristine, another drug that Dr. Kamen touched on, is one of the non-myelosuppressive medications for ALL. And this drug has a really interesting side effect profile. Dr. Kamen had that table with the side effects, rare with the question mark for the neurotoxicities. And it's been my experience that the majority of patients who receive this medication will develop some form of neurotoxicity, the most common being a peripheral neuropathy in the hands, feet or both. The literature for treating this is a little discrepant in terms of utilizing medications such as Lyrica® or Neurontin® for that neuropathy. It's been my experience that patients, when treated with these drugs, either notice an immediate effect or none at all.

And for patients who are receiving this medication and develop early onset diabetes from glucocorticoid therapy or have a predisposition to diabetes, the neuropathy that we're seeing can really be quite heightened because of the diabetes. So the endocrinologists at our institution are actually treating diabetic peripheral neuropathy with Cymbalta®, an antidepressant drug that also has anti-neuropathic effect, so that's something that you could think about trying if that front-line therapy when Lyrica or Neurontin is ineffective.
Dose reductions for vincristine should be done for patients who have such severe neuropathy that it interferes with their activities of daily living. And you can do the assessment with them, having

them sign their name, button a button, zipping a zipper or asking if they're able to open cans, jars. Those all indicate that the neuropathy needs to be treated and we need to dose-reduce the vincristine like Dr. Kamen said, as little as 10 percent dose reduction can greatly improve the neuropathy.

It should also be held for and dose-reduced for hyperbilirubinemia, which you can see is one of the side effects listed as well.

Slide 56. Glucocorticoids

Glucocorticoid therapy is a cornerstone in the treatment of ALL, with utilization of both prednisone and dexamethasone. Research studies have shown that decadron may be more efficacious than prednisone, due to a longer half-life of this drug. It has a greater penetrance of the CNS, an increased affinity for steroid receptor activity. However, it also has the potential for greater toxicities, the main one being an increased incidence of osteonecrosis. In fact, our induction regimen had pulses of decadron, which was changed to 28 days of prednisone out of safety for our patients, because we were seeing so many cases of osteonecrosis early on in these patients.

Interestingly, there's some research that suggests that a 14 day course of glucocorticoid therapy may be as cyto-reductive as 28 days. So that's something that needs to be further distinguished.

Slide 57. Glucocorticoids: Side Effects

The side effect profile of glucocorticoids is huge, as you can see, with all of them listed on this slide. The main ones I've bolded and italicized are what I see most frequently. We have seen a lot of osteoporosis, a decrease in bone mass on a DEXA scan as a result of this.

We had a 20 year old gentleman who has osteoporosis already because of this treatment and we've seen several cases of early onset type 2 diabetes requiring insulin administration for treatment.

There's a lot of bizarre side effects that can occur as well. So if your patients are taking a steroid and telling you some bizarre side effect, you should look into the side effect profile and see if it's something that could be occurring as a result of this.

Interestingly, when I first started working in this role, I had a young man who developed steroid psychosis on decadron and was actually brought into the ER by his family because he had cut his central line catheter with scissors and was experiencing homicidal ideation against his fiancée. So that's a very extreme example. With their situation, I can happily report that they were married last October. He's been out of maintenance therapy and in continued remission for about a year. So there can be reversible side effects.

Slide 58. Asparaginase: Mechanism

Asparaginase is a drug I want to spend some time on because of its mechanism of action. It's so fascinating, it's so much different than the other chemotherapy. Dr. Kamen touched on its activity a little bit and I'll just review.

The amino acid asparagine is needed for lymphoblasts for survival. And asparaginase is an enzyme which actually hydrolyzes asparagine to aspartic acid and ammonia. And this hydrolysis results in a depletion of circulating plasma asparagine levels, resulting in leukemic cell apoptosis, which allows for this selective treatment, since it doesn't really have an effect on normal cells.

Slide 59. Asparaginase Activity/Depletion

Dr. Douer at USC in Los Angeles has a pharmacokinetics lab that does a lot of work with this drug and measurement of asparagine levels in the serum. This graph from one of his research studies shows the concentration of asparaginase correlates to the extent of asparagine deamination, which you can see.

Slide 60. Asparaginase Depletion/Survival

This is important because in treatment of ALL, research has shown that patients with evidence of asparagine depletion showed greater survival. You can see the curve, the light gray curve, as those that had depleted asparagine levels with a greater overall survival at 31 months than their counterparts in the darker line that showed not depletion of asparagine levels.

Slide 61. Peg L-Asparaginase

IV is our preferred route of administration, though if you talk to Dr. Douer he'll tell you that he gives this drug exclusively intramuscularly. The unique mechanism of action is really coupled with really unique side effects. Dr. Kamen mentioned a couple of these. Patients are at risk for developing hyperglycemia. They're also at risk for coagulopathy, so it's really important to have a normal baseline PT/INR and fibrinogen level, that you can compare these levels to later on in treatment. Fibrinogen and clotting factors can be depleted in the blood for several weeks after administration and patients who experience this are at risk for both bleeding and for clot formation. If fibrinogen and factors are low, you could consider administering cryoprecipitate to replete this. We've also seen several extreme cases of pancreatitis and we're not exactly sure what that mechanism of action is. The pancreatitis was evident with the lab values, clinical presentation, as well as radiographic findings, which resulted in the discontinuation of this drug. As patients present with abdominal pain, you should draw the pancreatic enzymes amylase and lipase to assess for inflammation.

I know our pediatricians are very familiar with administering this drug more so than our adult hematologists. And we have a tendency to over-check these lab values and really want to treat the lab values, to which we're repeatedly told that it's unnecessary and should only be done if the

patient has clinical symptoms. So you can do that at your discretion with what you're comfortable with.

Another unique aspect of this drug is the risk for developing hypersensitivity reactions. Patients should be monitored for 30 minutes to four hours post its administration. And if giving it intramuscularly should know that there can be a delayed reaction response. Patients, when they're leaving clinic that day, should be educated on the signs and symptoms of a hypersensitivity reaction and should one occur at home, they should take Benadryl® and go to the nearest emergency room.

Our pediatricians and others I've spoken to in the Chicago area actually supply the patient and family with an EpiPen post-PEG administration and I've seen some patients develop some pretty horrific reactions, full body urticarial reactions to this drug, with large wheals, erythema, edema, fever and chills that can last for several days. We actually had a patient who developed a full body urticarial reaction, however we weren't 100 percent certain of the reaction of the drug because he also had a platelet transfusion that day and there was no transfusion work-up performed. So we decided to retest the drug with premedication ahead of and 30 minutes into the drug's administration. And it was my lucky assignment to be with the patient when the drug was administered so that appropriate medications could be given should he have a reaction. And of course he did, he had an anaphylactic reaction, became severely hypotensive and tachycardic. He had oxygen administered, epinephrine, hydrocortisone, Benadryl, Pepcid®, the histamine blockers, and thank God we didn't have to intubate him in our infusion suite, but we did learn the lesson the hard way, that you should not retest any allergic reaction.

Slide 62. Issues in Treating AYA's

You can see just from discussing all these medications that there's obvious potential for issues in these patients with the chemotherapy drugs alone. But there's also other issue in treating the AYA patient and this is mainly to do with compliance. I like to joke with my colleagues that noncompliance is merely a side effect of ALL because every patient seems to have some issue with the therapy, either missing visits, refusing therapy on the specified days or misdosing their oral treatment medications.

There should not be any delay in treatment, not even for vacation. That line listed on your slide is actually taken directly from our protocol. And I think we have a lot of work to do as practitioners, to optimize this therapy and take a more stern approach with our patients.

Slide 63: Teach, Teach, Teach

I also like to joke that my second career is that of a babysitter because what I feel like a lot of the time is that I'm babysitting these patients. So I can educate and educate until I'm blue in the face and somehow something doesn't go according to plan. I resort to follow-up phone calls and nagging these people as if they're my own kids. And then I educate some more. So what I've developed to help with adherence is a really thorough assessment as well as what I've done is

creating these packets for treatment for our patients. I also keep a copy. It contains their treatment plan, a calendar for their treatment, as well as a spreadsheet of the medications. And at each visit we review the upcoming therapy, we go through the schedule, we go through all of their medications and drugs. We can change this in clinic on a computer and make sure that the patient is given a new copy of the calendar and the medication list.

I ask that patients bring these packets and all their medications to clinic at every visit, but that's sometimes wishful thinking. A pediatric nurse I spoke to about adherence to drug regimens, she actually uses color-coded medication cards to help with the confusion. And something I've thought about, since this population seems to be so geared towards technology, everyone has their cell phone or a BlackBerry now, is really being able to put the calendar and the medication list into the phone so that they always have it and have that reminder right with them.

Slide 64. Teach, Teach, Teach (cont'd)

I mentioned what I do with my patients at each visit. I also think it's really important to be frank with patients and ask them directly about their adherence to the treatment regimen. Patients have stopped taking drugs without telling us because of side effects. I've heard that the medications taste bad and all kinds of other excuses. And what I tell patients is to at least notify me that there's a problem, so that we can at least discuss it and come up with a solution or counsel them against being noncompliant.

Additionally, I think it's extremely important for the oncology practitioner and the nurse to be aware that this is a population that doesn't seek medical care very frequently. And often we're the sole medical provider this patient is seeing, so it falls on us to do a lot of the primary care role in terms of teaching patients to maintain a healthy lifestyle, to abstain from alcohol, drugs and tobacco, and so frequently this assessment is missed and we're not asking patients about this aspect of their life and it is really important.

Slide 65. Assessing Quality of Life

Assessing quality of life is really important as well. When I first started working as a nurse I worked on our stem cell transplant unit here at the university and we saw some sick, sick patients. And I remember one gentleman who had leukemia and had failed numerous treatment modalities. He was back in-house again for a second transplant and was surprisingly upbeat and I inquired how he was coping so well with this and he said, "Kate, cancer is in the car with me, but it's not driving." And I love this phrase. I've shared it with so many patients because it is so true.

We need to really assist our patients in transitioning their life to this diagnosis, but not let it run their life. This age population, they just want to be normal. They want to go to college or spend time with their friends and the length of treatment, this frequent back and forth to the clinic, changes to their lifestyle, as well as body image changes with hair loss, catheter placement. These issues are something we really need to be incorporating into our assessment and asking about and not ignoring.

Additionally it's important to identify the support network for these patients. We've already talked about emancipated adolescents. Additionally they might have transportation issues. And financial issues can be huge. If these patients were in college and they have to drop out because they can't do school with the treatment, a lot of times they no longer qualify to be on their parents' insurance and we need to ensure that we're linking them to a social worker, assisting them in applying for public aid, so that they don't go into debt and do have some coverage for their medical bills.

There are so many resources out there for our patients. You just have to look for them. They're all over the internet and The Leukemia & Lymphoma Society Web site is really a good place to start and where I always go first. They have lots of patient advocacy groups, they have support groups that will link patients up to something in their area. You can even give them the information and they can be called by patient volunteers, so that your patient can talk with another patient who's either been through it or gone through something similar, in the same age range, so that they can identify with other people who have been through the therapy and they're now finished. They also have grants and financial assistance on the Web site as well. Social workers are a wonderful resource as are psycho-oncologists. We're lucky enough to have two psycho-oncologists on staff who only deal with our oncology patient population.

Slide 66. Potential Late Effects

I know we're running out of time here. I just want to briefly touch on survivorship and the potential late effects of therapy. As our patients complete therapy and are living longer, we need to be continually assessing the potential for latent effects of treatment. And there's a lot that we really don't know about these drugs and how they affect patients in the long run. As I mentioned previously, there's cardiac toxicity from anthracycline therapy and we should be ordering an echocardiogram for our patients every five years to assess for heart failure and complications.

Additionally, with intrathecal methotrexate and cranial radiation, there are long term side effects, mainly neurocognitive deficits and cerebrovascular complications, as well as increased risk for a second malignancy for those who get cranial radiation.

Slide 67. Potential Late Effects (cont.)

Risk for infertility and hypogonadism, I see all the time in patients who have gone through testicular radiation. They can also occur as a side effect of Cytoxan administration. Our female patients can have premature menopause with Cytoxan. And steroids, as we discussed, can mitigate early onset diabetes as well as osteoporosis and osteonecrosis.

Slide 68. Future Directions

So there's a lot that we just don't know in terms of latent effects. And one of our future directions for treatment should be to examine these in greater detail. Additionally, future directions of therapy should include the development of novel therapies for treatment in ALL. As Dr. Kamen

mentioned, these drugs have been around for 40 years and we're really just starting to develop and enhance our lab techniques for understanding the genetics and epigenetics of ALL. Dr. Kamen talked about pharmacogenetics and pharmacodynamics and really tailoring the drugs to patients, based on their genetic profile.

Quality of life is also an issue that we talked about. One thing that we're currently addressing in our current research protocol is administering quality of life questionnaires, so we can quantify this aspect of treatment. And additionally, a big question for me is, I wonder where's the cutoff age for this pediatric-based therapy? Do we give it to adults greater than 30 years of age to maximize outcomes for these patients who have a good performance status? I can speak for just our institution, but we've taken several 50 year olds through this treatment regimen and that brings about an entirely different issue of getting the patient through this lengthy therapy. So those are some things that we should be thinking about as we look forward to the future.

So that concludes my talk. Right before we go to questions I just wanted to thank two of our nurse practitioners who directly and indirectly helped me with this talk, and they help me every day. Carol White and Jean Ridgeway, thank you so much.

Slide 69. Question-and-Answer Session

Carson Jacobi:

Thank you very much to both Dr. Kamen and you, Ms. Breitenbach, for this information and your wonderful presentations.

Okay, I just received a question that came through the Web and the question comes from Laura. "Can myelosuppression due to chemotherapy cause red blood cell depression in ALL if all other evidence presents that the leukemic blasts are not in the bone marrow peripheral blood?"

Dr. Barton Kamen:

I suspect that's one I can answer very easily because the red cells we talked about, turn over 1percent every day, and methotrexate and mercaptopurine as anti-metabolites will actually cause a megaloblastic anemia, just as if you were folate deficient. So the simple answer to the question is yes, you can be anemic. We sometimes actually use the size of the red cell and whether they were macrocytic as an attempt to see if there was actually compliance because typically, I'll let Kate say if she sees this, we typically see the kids have MCVs, the mean corpuscular volume, up in the 100 to110 range rather than the 90 microns. And then we know they're actually taking mercaptopurine and methotrexate. So yes.

Katherine Breitenbach:

Just to add onto that, we see patients all the time whose hemoglobin and hematocrit levels don't really fully normalize for months after therapy. And patients are still getting this maintenance

therapy, as Dr. Kamen mentioned, with 6-mercaptopurine, methotrexate. And we do see that quite frequently, that their red blood cells are depressed.

Carson Jacobi:

Thank you, Laura, for the question. I have another question that came through from Nanette. And the question is "What is the mechanism of action for steroids reducing lymphocytes?"

Dr. Barton Kamen:

Well, there are glucocorticoid receptors and steroid active elements down in the nucleus, so I could probably give a whole lecture on how steroids really, really work and they're clearly multi-factorial. I think the important observation I made earlier, we know that steroids rapidly make you lymphopenic and actually raise the neutrophil count. And we've know that for 60 years. We can teach a whole course on mechanism of action, just like you could teach a whole course on the side effects. We don't have enough time to give a better answer than that right now.

Katherine Breitenbach:

Interestingly, we had a woman admitted to our inpatient stay and we started her on glucocorticoid therapy actually prior to doing her pretreatment bone marrow biopsy and she'd just gotten it for seven days, but with that initial bone marrow biopsy we saw such a reduction in lymphoblasts in our pathology department. So it really can have an impact on reducing those.

Dr. Barton Kamen:

Kate brings up a very important point to make a longer answer there. The German group, the Berlin-Frankfurt-Münster Group, and others around the world and sometimes here in the United States, we actually start with a seven day course of steroids because the responsiveness to steroids sometimes shows how well the rest of the medicines are going to work. And we've seen many, many people clear blasts just with a week of the steroids alone. I mentioned to you that steroids, weekly vincristine, four doses of vincristine and several doses of asparaginase, dependent on whether we give them the regular kind or the PEG, will cause a remission in 95 percent of the kids. So again, without delving into the mechanism, the potency is incredibly well known.

Carson Jacobi:

Thank you, Nanette, for the question. And Kate, we have a question that came through the Web from Sarah. And she asks, "What is the anti-emetic cocktail that you mentioned in your presentation?"

Katherine Breitenbach:

This is actually what we used for an older woman. She's actually 58 and we had a lot of challenges getting her through this treatment. And she had an Ommaya placed at an outside hospital and then came to us after induction therapy. And what we give her is 8 milligrams of IV Zofran®, 8 milligrams of IV dexamethasone and 1 milligram of IV lorazepam, 30 minutes prior to getting her Ommaya. And she does beautifully. I've never seen anyone do so well.

Dr. Barton Kamen:

A counterpoint to that for these young adults, again, speaking as a pediatrician, typical pediatric trials will have anywhere from 15 to 20 spinal taps over the two to three years. And with relaxation and sometimes a little benzodiazepine up front, we do most of these lumbar punctures in the clinic and we don't have to do much. And I could probably count the number of Ommayas we've put in because again as pediatricians, we say roll over and you get the tap and very importantly you lie flat. Kate talked about the spinal leak. When we do spinal taps, we have the kids lying recumbent or even Trendelenburg for up to 45 minutes and then I've had them go back to school. But I think don't underrate the power of keeping them flat or actually head down for 45 minutes after the tap. And I've had kids go back and they just do great.

Carson Jacobi:

We have another question that came through the Web from William. And he asks, "Is there any good evidence to support the use of imatinib or dasatinib indefinitely for Philadelphia-positive patients, especially with their overall poor risk?"

Katherine Breitenbach:

Oh, absolutely. That's actually something that we use front-line in their induction therapy and then throughout the treatment for that disease. Because those patients are a poor and unfavorable cytogenetic risk, we usually will take them on to transplantation and have an ongoing trial currently where patients will get either an allogeneic stem cell transplant, if they have a sibling donor. We do do autologous transplants occasionally for those patients, though that's not the preferred choice. But even after transplant, the continuing therapy that they get is Gleevec or imatinib and if they don't tolerate that we will switch to some of the newer agents, either dasatinib or nilotinib.

Dr. Barton Kamen:

From the pediatric aggressive view, Kate's absolutely right. Only 2 or 3 percent of the kids will be Philadelphia positive. If they have a good response to initial chemo, we know now that simply adding imatinib has made an incredible difference and it's part of the maintenance therapy. How long we do it and even if you have to transplant, if all the other risk characteristics were good, is still a point that needs to be evaluated in clinical trials.

Carson Jacobi:

Thank you both and thank you, William, for the question. We have another question that came through from Kayung. He asks, "Cytogenetics in ALL, especially MLL rearrangement versus translocation, in the perspective as prognostic facti."

Dr. Barton Kamen:

So MLL stands for mixed lymphoid leukemia or mixed lineage leukemia and it's a mistake on chromosome 11. In kids we usually see it in the under 1, it's part of the infant leukemia and it's associated with very poor prognosis. And it's often with 4;11, there are a number of 11 chromosome translocations, but most of them are pretty bad prognostically. The other place we see it is not in de novo ALL in the adults, but we see it in the chemotherapy-related. So we've had kids get anthracyclines and drugs like etoposide where they've come back with secondary leukemias. But the bottom line is when you see an 11q, when you see a chromosomal 11 abnormality, this MLL, it portends a very poor prognosis almost all the time. But again, it's mostly treatment-related or in the patients less than 1.

Carson Jacobi:

Very good. Another question comes through from Karen and she asks, "For patients with anaphylactic reactions to asparaginase, is there another form or preparation that may be available?"

Katherine Breitenbach:

Oh, I'm so glad you asked that question because I did leave that out of my talk. For people who have hypersensitivity reactions to the pegylated asparaginase, they are able to get asparaginase in a little bit different preparation, it's called Erwinia asparaginase. It's been my experience that this is a very difficult drug to get for patients. It's expensive, it's not usually supplied to institutions, so there is a large process to jump through, just to obtain the drug. And then other hoops to jump through in terms of the patient's insurance in getting the medication covered. It does cost several thousand dollars and I have yet to be able to give this to our patients. The dosing schedule with Erwinia is a little bit different as well. They get it over several consecutive days versus just one intravenous administration. So for all of our patients thus far that have had a hypersensitivity reaction, we've just omitted this medication, which is unfortunate, because it's such a great drug in treating ALL.

Dr. Barton Kamen:

I would have nothing to add. We are reminded that the asparaginase is made from bacteria and the two that are available, as we talked about, E. Coli and this Erwinia. There's actually some others out there. And if you're lucky you don't cross-react. But there's also data that Erwinia isn't as potent as the E. coli, which is why we use the pegylated asparaginase now because it lasts longer

and it may be less immunogenic.

Carson Jacobi:

There is another question that come through from Nanette and she asks, “Is it safe to give methotrexate and, this is abbreviated, L’asp on the same day in adults?”

Dr. Barton Kamen:

There’s a protocol that actually calls for it. There’s multiple ways that asparaginase and methotrexate have been used. For those of you long time in the field, it’s actually called the Capizzi regimen. In fact, Dr. Capizzi said you give asparaginase, you actually wait a week and then you can come back and give the methotrexate because the asparaginase makes the cells a little more sensitive. On the other hand, the asparaginase may also protect against some of the toxicity of methotrexate, so our protocols when we give the methotrexate, we usually give the asparaginase four to six hours later. And then we follow up a week later with another cycle. And that’s actually called the Capizzi regimen. It’s been standard for at least several decades.

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Carson Jacobi:

Our program has come to an end. If you can please help me thank our experts today, we’re so very grateful that they have donated their time to us and we thank them for all the work that they do every day in supporting families touched by cancer. We would also like to thank again Enzon Pharmaceuticals Inc. for their support.

So on behalf of The Leukemia & Lymphoma Society, thank you all for sharing this time with us. Our best to you all. Good-bye and we wish you well.