Young Adults with Blood Cancers:
Managing Treatment and Beyond

Michael E. Rytting, MD

Slide 1
Young Adults With Blood Cancers

Carson Jacobi:
Good afternoon, everyone.

My name is Carson Jacobi, and I'm the vice president of National Education Programs at The Leukemia & Lymphoma Society. It is my pleasure to welcome you to this continuing education symposium entitled *Young Adults with Blood Cancers: Managing Treatment and Beyond.*

I would like to thank our speakers, Dr. Michael Rytting, Ms. Nicole Rosipal, Mr. Eric Cohen and Ms. Sage Bolte for being with us today. I would also like to recognize The Leukemia & Lymphoma Society and thank the Centers for Disease Control and Prevention for providing funding to make this program possible this afternoon.

So the program goal, we're talking about young adults today, and those are the ages between 18 and 39. Young adults are often underserved in our healthcare system at a time in their life when they are experiencing physical, emotional and financial changes. And you add the burden of cancer, and the challenges can be overwhelming.

The incidence of cancer in young adults increased steadily over the past quarter century, and survival improvement trends indicate a worse prognosis for young adults diagnosed with cancer today than 25 years ago, in contrast with all other ages.

This symposium this afternoon will identify treatment challenges for young adults with blood cancer, including the unique physical and psychosocial factors, desire for independence, sexuality, fertility issues and lack of an underutilization of insurance, which is a big issue these days. Our discussion will focus on the gaps in services for this age group, adherence to treatment and follow-up care, long-term late effects of treatment and survivorship issues, to help nurses more effectively communicate with and treat young adult survivors.

The Leukemia & Lymphoma Society is committed to providing the most up-to-date information about blood cancers. Our vision is one day that the great majority of people who have been diagnosed with a blood cancer will be cured or they will be able to manage their illness with a good quality of life.

The Leukemia & Lymphoma Society is the world's largest voluntary health organization dedicated to funding blood cancer research, education and patient services. Since its founding in 1949, the Society has invested over $600 million for research, specifically targeting blood cancer. We will continue to invest in research for cures and programs and services to improve

the quality of life of patients and their families, and we're thrilled to be able to be here with you today and share this information with you.

Our speakers this afternoon—we have four speakers—and I will introduce each of them briefly, and then they all will continue on with their presentations.

Dr. Rytting is the associate professor of pediatrics and holds a joint appointment in adult leukemia at the University of Texas M.D. Anderson Cancer Center, Children's Cancer Hospital. Dr. Rytting will address the treatment challenges and long-term late effects in young adults with blood cancer.

Ms. Rosipal will discuss treatment adherence and the need to keep young adults integrated in the healthcare system for follow-up care. She is a certified pediatric nurse practitioner for pediatric stem cell transplant and cellular therapy at the University of Texas M.D. Anderson Cancer Center, Children's Cancer Hospital.

Then we have Eric Cohen. Eric is currently a program manager for patient and family education at *Life with Cancer*®, a nonprofit, community-based support organization dedicated to education support for those affected by cancer. He will address the gaps in services available for young adults with blood cancer.

And Ms. Sage Bolte. Ms. Bolte is an oncology counselor for *Life with Cancer*, and she will identify and discuss survivorship issues facing young adults with blood cancer.

I now have the pleasure of introducing Dr. Rytting to the podium. I'll turn it over to you.

Slide 2
Treatment Challenges & Long-Term Effects

Dr. Michael Rytting:

Thank you.

Good afternoon, and I'd like to thank The Leukemia & Lymphoma Society for inviting me to come and speak.

I am an associate professor down in Houston, and I have an appointment in pediatrics and also an appointment in leukemia. And my major focus of work is with young adults, ages 12 to 40, in treating ALL [acute lymphoblastic leukemia]. And I'll talk a little bit about that later in the talk.

Slide 3
National Cancer Mortality Rate

So this slide comes from Dr. Archie Bleyer, who was former head of the Children's Oncology Group and sent me a set of slides with some data from the SEER registry. This illustrates one of the problems that people are grappling with for young adults that have cancer, and what these

bars show is the improvement that we've seen per age group in survivor rates. But as you notice, the group between 15 and 24 has the lowest amount of improvement. And I was actually very heartened to see that the older folks, where I'm approaching, are actually seeing a lot of improvement as well, probably thanks to you all, taking care of adults with cancer.

The other group that hasn't had such a great improvement is the 25- to 34-year-old group of patients. So they've had the least amount of improvement, and we don't know exactly why.

Slide 4
Why the Slow Improvement?

Now one of the thoughts about why improvement has been slow is that enrollment for this group of patients is low on national trials. So looking at countries that have really good registries of who gets cancer, if you look at the United Kingdom—I thought this was really striking—between 2006 and 2007, they didn't have a single teenager enrolled on any brain tumor protocol. Maybe they didn't have many protocols open, maybe a lot of their protocols closed, but that's pretty astounding. And then looking at their enrollment for patients between 20 and 24, they averaged less than 10% of enrollment on a trial. So a lot of these patients are not being put on trials, and that may explain why there hasn't been much improvement.

The other thing is, care is fragmented for this group of patients, especially patients between 15 and 25. They may go and see a pediatrician and they may go to an adult office, so there's not a unified treatment approach always for these patients.

And then the next issue, which is really I think a major issue, is insurance—and this is especially true for patients that are completing college, because they come off of their parents' insurance and they don't have employment, so they don't have any insurance. So getting those patients enrolled at a large cancer center, which can be a very expensive place to go without insurance, is difficult.

And finally, there are some issues about compliance. However, in speaking with my adult colleagues and also from my own experience, yes, we run into compliance issues with young adults older than 18 but less than 30, but it hasn't been extreme, at least on the study that I'm doing. And of course, we run into that with pediatric patients as well. They do have their parents that are making them take medications, but at the same time teenage boys get to be as big as their parents and they can refuse to take pills.

I had a former football player patient who moved out of his house, and his mother said when she cleaned his room there were pills everywhere, under the bed and in the planters. And fortunately, it looks like he's cured, but nevertheless, there are compliance issues. There are compliance issues with all of these kids.

Slide 5
French ALL Trials: FRALLE vs LALA

Well, what started what I do, which is to look at ALL in young adults, is some comparisons that

were made, particularly in Europe, looking at teenagers or young adults treated for leukemia and comparing what happens in an adult office with what happens on pediatric trials. So the pediatric trial is the top one, FRALLE, and the adult trial is the bottom, LALA94. And these were very matched patients. You can see that at about six years of follow-up, where the curves become really flat, where there's not very much—there's hardly any more relapse in these groups of patients—there's a broad distinction between where patients get treated. So it looks like a pediatric type treatment might be superior here. And this has been followed up by treatments by the Nordic Oncology Group, also in Holland. And also in the United States, where looking at similar groups of patients, similar ages, but treated in different office settings, adult versus pediatrics, the pediatric curves appear to be a little bit—or significantly better.

Slide 6
Comparison of CCG vs CALGB

Okay, and so that was the French comparison. And this is a much more recent, so—that was about I think 2000 or even a little bit earlier—this is a much more recent paper from 2008, looking at the United States experience. This is looking at a large group of CALGB for adults, comparing that with the CCG outcomes for young adults.

Slide 7
Survival: CCG vs CALGB

These are patients between ages 16 and 21 treated for leukemia. And again, you can see that there's a very, very significant *P* value between those curves. Now this is not a prospective evaluation, this is retrospective, so there's always some chance of introducing bias. But nevertheless, if patients in that age group were treated on a children's protocol, they do extremely well or they do relatively well, not extreme, because it's still at about 60%. But the patients that are treated in that age group between 16 and 21 at an adult office, put on an adult treatment regimen, don't do nearly as well.

Slide 8
ALL Biological Risk Factors

Now why can that be happening? There's lots of reasons that that can be happening, and I don't think it's due to physicians. That leads to a lot of rancorous discussion between adults and pediatricians. But I don't think that the leukemia doctors are that different. I think that adult leukemia doctors are just as competent as pediatric leukemia doctors.

There are differences in the genetics of leukemia between adults that have leukemia and children that have leukemia. Adults with leukemia have much more Philadelphia chromosome abnormality, so that, of course, is a very high-risk group for ALL. There's also very much less hyperdiploidy and hyperdiploidy in a pediatric patient is quite good. And then there's hardly any cases of what are called triple trisomies in adult patients with ALL, and that's trisomies of chromosomes 4, 10 and 17. Those patients have well over—well, at least a 95% chance of being cured in pediatrics. You just don't see that in an adult patient with ALL. I've looked at the database at MD Anderson and I found one patient that had a triple trisomy in the whole group

that they have, and it's hundreds of patients.

The interesting field, I think, for explaining where there might be differences, why there seem to be different biological behavior between these groups, is epigenetics. So that's changes in genes that occur postformation of the human being. So methylation and deacetylation of genes might be very important in determining biological outcome of ALL. And older patients tend to have more epigenetic changes in their genome.

Slide 9
Response to Therapy

Now if you look at response to therapy, I'm not unique in trying to study these treatments in patients that are younger. If you look at responses to therapy, there's a large trial from Spain, and they showed that event-free survival and overall survival, if you took a pediatric-based regimen and applied it to adolescent and young adults, you could get good results with the adults.

Slide 10
Spain: Survival Curves in Young Adults

They do slightly worse than the adolescents, but still the cure rate for the adults is at 60%, which is significantly better than they had been doing with their adult patients. So they actually came to the conclusion at the end of this paper that applying pediatric-based treatment might be the way to go for all patients with ALL. Now that may not actually hold true as patients get to over 45 because there's a French study where the patients over 45 had a high early mortality rate with the treatment.

Slide 11
Augmented BFM Protocol in ALL

Now what I do is I took a trial that basically was completed by the Children's Cancer Group, called CCG1961 and I made a few adjustments to it. It's an augmented Berlin-Frankfurt-Munster trial, that just comes from the three cities in Germany where this treatment sort of was engendered, and we put patients on that are less than 40. And so far we're above 41 patients now, we're about to 50 patients, and we've had about 80% of the patients have a rapid response to treatment and go into remission by day 15 of therapy. So then that's comparable with pediatric data. So the average age of the patients on the study is over 20—I think it's 22.

There are some slow responders, but almost all of them achieve remission. And that's true in other adult trials as well treating leukemia. A good remission rate to look for with any trial is about 95%. That's sort of what you would expect in a young adult being treated for ALL.

We've only had a couple of patients require extended induction, and we've had one patient fail induction.

Slide 12
Augmented BFM: Overall Survival

And this is a comparison which is very early, of looking at the augmented BFM or the pediatric-based regimen versus the more typical adult regimen. And there is some separation, but it's not statistically significant. I didn't even analyze it really statistically because it's quite early. Nevertheless, the treatment looks like it might actually be pretty good for adults up to age 40.

Slide 13
Treatment-Related Toxicities

Now there are toxicities, and that's the main thing that people worry about when they start to apply these really pretty complex and toxic regimens to adults. I have had, unfortunately, one patient that did develop avascular necrosis of both hips. Had to have both hips replaced. She just got married—she's about 24. And that's a devastating complication. But that is seen in about—it varies from the single digits, less than a few percent in very small children treated for leukemia, to as high as upper teens, like 17% for teenagers that are treated for leukemia. I don't know what the overall rate of avascular necrosis will be on my study, but it doesn't seem like it's extremely high. But any cases are significant.

The main dysfunction, and I don't think I'll run through all of them, but the main dysfunction has been hepatic. There's been a lot of elevation of liver enzymes on this study. And by a lot I mean more than a third of patients have had elevated liver enzymes to grade 3 or grade 4, that it has so far all resolved with time. It may be related to a lot of the medicines we use with these patients besides their chemotherapy.

And finally, I would say that the infectious complications have been really well managed. We haven't had a single infectious death in induction, and I think that comes from the adult approach actually, not the pediatric approach, but the adult approach of giving prophylactic antibiotics to patients as they go through an induction. I think that might actually be an advance for both age groups in the future.

Slide 14
Following-Up: Fertility

Now switching gears, I was asked to talk a little bit about following up, and I think this is a fascinating area and could be the subject of a very long talk, which I did about a week ago, and it was a really long talk. But this one is going to be really short.

So following up with patients. A lot of questions for young adults that have ALL have to do with fertility, especially young women that are coming in. And the first thing—one of the things I counsel young women on is that we don't know when menopause is going to occur for these women. They can't wait—I don't think they should wait and wait and wait and say I'm going to have a baby when I'm 36. That may not be possible for patients that are treated for leukemia.

Slide 15
Preserving Fertility

The patients that are at risk for impaired fertility are the patients that get lots of alkylators. But also radiation to the testes is particularly bad for boys. And radiation, of course, of the ovaries is bad for women as well.

Now what are the options for preserving fertility? There are quite a few options for boys or men. Sperm banking is obviously the easiest thing for them. But then if there's a marked decrease in the sperm count, they can still take one—and they've got the technology now to do intracytoplasmic injection and inject those. So there are options for men. And there are some recent papers that have been really heartening where fertility has returned in men that have survived transplant and so on.

And are there risks for success? What if you really do successfully have a child? Well, there is not—there has not been an increased risk of cancer in those children, or children of survivors.

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Second Malignancies

Second malignancies. There are two main types of AML that we worry about: AML that occurs really rapidly after epipodophyllotoxins, which can occur in the first couple of years after treatment, and then AML that occurs after alkylators, which is later. The main thing that I would like to emphasize there is we only follow those patients significantly for about 10 years with CBCs, but after that you hardly ever see a secondary AML—and then the incidence of second cancers is about 9%.

This is follow-up from a 30-year review of patients that have survived childhood cancer. The interesting point about that was that when they followed these patients up at 20 years—so 10 years early—the incidence of secondary cancers was judged to be about 2.3%. So things are changing, depending on how long you follow these patients.

Slide 17
Skeletal Problems & Cardiac Effects

There can also be problems with, as I discussed, avascular necrosis and osteoporosis. The main thing I would like to say about the osteoporosis risk is that calcium and vitamin D are pretty benign, and I recommend that patients be started on that. The question about bisphosphonates and other medications, those questions haven't been answered. So whether or not the bisphosphonates are useful, we don't know for sure. We would like patients to be on trial to see if we can get a certain answer for those drugs.

Cardiac effects are significant, of course. There are a couple of papers, though, that have recently shown that children treated with anthracyclines have actually done quite well with no cardiac late effects, as long as they haven't gotten radiation.

Slide 18
Cognitive Impairment

And finally with cognitive impairment, about 50% of survivors right now have had problems with cognition. That's because we used to use a lot more radiation than we use now, and hopefully that's going to decrease with time. Again, the major culprits are intrathecal methotrexate and radiation. The problem with cognitive impairment is it takes testing to discover it. The testing is long, it's expensive and it's not free, and it's usually not covered. But if you can get testing for these patients, I think it's very useful.

I think I'm going to leave the social outcomes out, because the information is still limited and emerging, and I hope that we've got discussions of that to come.

So thank you very much.

I'd like to introduce Nicole, who's the next speaker. Nicole.