Elihu H. Estey, MD
October 31, 2013

Slide 1 – Welcome and Introductions

Operator
Greetings, and good afternoon and welcome to AML: Update on Diagnosis and Treatment, a free telephone Web education program. It is my pleasure to introduce your moderator, Ms. Lauren Berger.

Ms. Lauren Berger
Thank you and hello everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you and special thanks to Dr. Eli Estey for sharing his time and expertise with us today.

We would like to acknowledge and thank Sunesis Pharmaceuticals for their support of this program.

Slide 2 – Elihu H. Estey, MD

Ms. Lauren Berger
I am so pleased to introduce Dr. Eli Estey, Professor, Division of Hematology at the University of Washington School of Medicine and Member and Director of AML Clinical Research, non-transplant, in the Clinical Research Division at the Fred Hutchinson Cancer Center in Seattle, Washington. Dr. Estey has treated patients for AML for over 35 years, including many years at M.D. Anderson Cancer Center.

On behalf of The Leukemia & Lymphoma Society, thank you for volunteering your time and expertise, Dr. Estey. I am now privileged to turn the program over to you.

Dr. Eli Estey
Thank you very much, Ms. Berger, and welcome, everybody. I'm going to start with some slides. But, I certainly don't want to go on with them too much because the main point is answering your questions.

Slide 3 – Topics

Dr. Eli Estey
But, the topics that we'll consider are, what is AML, and then we're going to consider the two major causes why patients are not cured. One is that the treatment proves fatal treatment-related mortality, versus the treatment doesn't work, which we call resistance.

Then we're going to talk about the fundamental--there's a choice that people have to make when they're diagnosed between standard therapy versus investigational therapy, for example in a clinical trial. We'll say a couple words about transplant and then a couple words about making people's lives more pleasant.

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Slide 4 - Typical Case

Dr. Eli Estey
So, I'll start with the typical case that is probably familiar to many of you. It's the patient who has common symptoms of fatigue or shortness of breath. And eventually the patient goes to their doctor and the blood is drawn. And it shows anemia, which of course is responsible for the symptoms that the patient had.

And usually the platelet count and the neutrophil count are also low. And platelets have to do with bleeding, and so a deficit in platelets possibly leads to bruising. And neutrophils are important for preventing infection, so people can also have infections. But, the most common symptom is the fatigue resulting from the anemia.

And then bone marrow is obtained because the bone marrow is the site of blood cell production.

Slide 5 – What is AML?

Dr. Eli Estey
Red cells, PMNs (or neutrophils), and platelets have a very limited lifespan. So, there has to be a mechanism to replace them, and that mechanism resides in the bone marrow.

The way it works is that immature cells, which are called blasts, mature in the bone marrow to mature red cells, neutrophils, and platelets. The rate at which they are produced and released balances the rate at which they are removed.

So, everybody has blasts. But, in AML, some normal blasts become abnormal. And, because they're abnormal, they don't mature. Because they don't mature, they stay immature and they accumulate.

And in ways that are not totally clear, lead to bone marrow failure. The presence of these immature blasts that accumulate prevents the normal blasts from maturing. And then, as I said, leads to the low counts that lead the patient eventually to seek medical attention.

And occasionally, the abnormal immature blasts in the marrow escape into the blood, which would never happen normally.

So really, what this illness is, fundamentally, is bone marrow failure. And that, as I said, leads to the presenting symptoms. And then, often over time, it leads to infection, which is probably, over time, the major cause of mortality.

Dr. Eli Estey
The diagnosis is relatively easy, because basically, the abnormal blasts don't mature, they accumulate. And so, when a bone marrow is done, you see an excess of blasts, because the abnormal blasts are not maturing. And this excess of blasts leads to the diagnosis.

Slide 6 – Principles of Treatment

Dr. Eli Estey
There are several principles of treatment. Principal one is a reduction in the number of abnormal blasts allows the normal blasts to mature. And, that leads to remission.

Remission is defined based on blood counts. The platelet count has to be over 100,000. The neutrophil count has to be over 1,000. The marrow has to have less than five percent blasts.

And, it's generally been thought for many years that CR is necessary for cure. I always compare it to scoring a run in baseball. Nobody scores a run without touching first base. First base is the equivalent of remission, and scoring a run is the equivalent of cure.

But, just as many people who get to first base don't score a run; they're thrown out at second, or something like that. What can intervene between cure and remission is, of course, relapse.

A question that's often asked is, "Well, how long do I have to be in remission before I can consider myself to be cured," because many people are familiar with the five year figure. But, in this disease, it's been shown that if the remission continues for three years, the likelihood of relapse then becomes very, very small, and is probably maybe around five percent.

The major problem in treatment is distinguishing abnormal from normal cells. It would be easy to get rid of all the blasts in the marrow, but, of course, you would get rid of the normal cells as well. And of course, distinguishing the abnormal from normal cells is what so-called targeted therapy is all about.

Slide 7 – Reasons for Treatment Failure

Dr. Eli Estey
So, we'll turn for a minute to the two major causes of treatment failure. The first is the treatment proves too toxic for the patient and the patient dies as a result of the treatment. And, in principle, that could happen over a shorter period of time than it would happen without treatment.

Dr. Eli Estey
But, as we're going to hear, the principal reason for treatment failure is resistance to treatment. Resistance can take one of two forms. It can take the form of the patient does not die as a result of the treatment, but they do not obtain a remission. Or, more commonly, they obtain a remission and they relapse.
One of the things that's very, very important for people to realize is that, as we're going to talk about in a minute, the major problem in the disease is not the toxicity, not the treatment-related mortality, but the resistance.

Slide - 8 "Less Intense" Rx

Dr. Eli Estey
So that, of course, leads to the topic of less intense treatment. And those things, I think, would include things like azacitidine, which is commercially known as Vidaza®, or decitabine, which is commercially known as Dacogen®.

And the putative advantages of these medicines are that they're less toxic, which is often emphasized to patients. But, another putative advantage is, hopefully, they're more effective.

But, the fundamental point that I'm going to make in the next few slides showing some data is that the lack of efficacy is a major problem in AML therapy. So, even though, understandably enough and naturally enough, patients are generally concerned with the toxicity of the therapy, their real issue is not the toxicity but is the efficacy of the therapy.

Slide 9 - TRM vs. Resistance as Cause of Failure With 3+7

Dr. Eli Estey
This slide may illustrate it. This is a slide from the Southwest Oncology Group, and they're looking at people, lots and lots of people, of various ages. For example, you can see there are 246 people that were between the ages of 56 and 65, and 80 that were over 75.

CR stands for complete remission. TRD indicates patients who died as a result of treatment within the first 30 days. Resistance means people who did not obtain a remission. They did not die, but they were resistant.

And, what you can see is, even in the people over 75, that there the CR rate is 33 percent, which means that 67 percent did not obtain a remission. But, the majority of people who did not obtain a remission were resistant to the treatment but did not die as a result of the treatment. So, even in people over 75, the big issue is the resistance to the treatment.

Slide 10 - Relapse vs. Death in CR

Dr. Eli Estey
And then we also looked at that in people in remission. So, this is the work that we did at M.D. Anderson. And, the basic point is, for example, if you look at that last row. So, again, we're looking at people who are 70 years of age or above.

And PS is performance status. So, performance status when they went into remission of two to four means that they were not robust even when they went into remission. There were 71 of these patients. What we did, is, we looked at the rate of the two reasons that they were not cured. They either relapsed or they died in remission as a result, perhaps, of further treatment.

What you can see is that, even in people that are over 70 who are not in the best of shape, the ratio of relapse to dying in remission is threefold. And, I think this kind of data really indicates that the real problem in this disease is efficacy, not toxicity.

Slide 11 - Effect of Time (1991-2009) on TRM

Dr. Eli Estey
Furthermore, the rates of treatment-related mortality are falling with time. So, this is work that we looked at from the SWOG, many patients, and M.D. Anderson, many patients, and they received many different types of chemotherapy. What we said is, well, let's look at the rate of treatment-related mortality, which means the patients died within the first four weeks of treatment, as a function of time.

Slide 12 – TRM Summary

Dr. Eli Estey
And if you look at the next slide, basically, we're looking at the SWOG cohort and the M.D. Anderson cohort. And you can see, that over time, for example in SWOG, the rate of treatment-related mortality was 18 percent 20 years ago. It's now three percent. And the data is the same at M.D. Anderson, even though they tend to use higher dose regimens than are done at the SWOG.

And so, again, this really emphasizes something that I see every day. When people come, their first question is about the toxicity of the chemotherapy. And, that's certainly something that's important and needs to be addressed.

Slide 13 - Decline in TRM with Time

Dr. Eli Estey
But, I'm always saying to myself, "Wow, the thing they really should be concerned with is not as much the toxicity, as important as that is, but the fact that the treatment won't work," because as you saw in the previous slides, that is what ultimately leads to most patients not being cured.

That's just reinforced in the last one, that the major issue is efficacy and not toxicity. So, I really want to emphasize that.

Slide 14 - **Management Options for AML**

Dr. Eli Estey
So, that's going take us to the next point, what are the management options for someone with AML? Well, there are basically three. One is supportive care only, which basically means just transfusions.

The second is standard therapy, which is what the great majority of people receive. And, that generally is what people call three plus seven, which means three days of a drug like daunorubicin or idarubicin, and seven days of a drug called Ara-C or cytarabine. Ara-C and cytarabine are the same thing. I'm in the habit of referring to it as Ara-C.

And the third option is a clinical trial. So, when I meet with a patient, my whole purpose is to say, okay, how should we proceed? Which of these three options should we choose, should you choose? So, let's look at what would happen with supportive care only.

Slide 15 - Supportive Care Only

Dr. Eli Estey
So, when the papers first describing this disease were published in the early 1960s, the life expectancy was very short. Life expectancy is certainly better today than it was when originally described. But, that has to be viewed relative to the 20 or 25 years life expectancy for helping patients age 60 to 70.

So, even though survival without treatment is certainly better than it was many years ago, because the antibiotics are better and transfusion practices are better, if you look at Social Security tables, you'll see, even if you're 65, which is a typical age for someone with this disease, if they're otherwise healthy, they would likely live to be 85. And, certainly that won't happen with this disease if they're not treated. If they're treated, then it becomes a possibility, but not if they're not treated.

Dr. Eli Estey
And, the next thing I say is, "Well, gee, you know, you'll live longer than you might have been told," because when people hear the word AML, leukemia is the word that first comes to attention, but then acute comes to attention.

When people hear the word acute, they think, "Oh, I'll be dead in a month, or two months, or three months," which is often what they're told without treatment. And in fact, you can live considerably longer without treatment for that, but you won't live to your normal life expectancy.

And, of course, the other problem is, during the time that you're alive, there are always morbidities. You have to go and get transfused. You have to go to the doctor and wait for the doctor. You have to wait for the transfusion. And, all the time you're fatigued and there's not much hope. So, that's not necessarily an option that is necessarily too appealing to people, which is, of course, why they come to large centers such as Fred Hutch or M.D. Anderson to get that.

So, they say, "Well, gee, we really want to be treated." So, basically, there are two choices. There's standard treatment and there's a clinical trial, or investigational therapy, or experimental treatment, or whatever word you choose to use.

Slide 16 - Standard Therapy vs. Clinical Trial

Dr. Eli Estey
And, by definition, standard treatment has been given to so many patients that the results are not in doubt. And, examples, as I mentioned, are the three days of daunorubicin or idarubicin plus seven days of cytarabine. I think decitabine or azacitidine could be considered standard treatment these days.

Now, in contrast, in a trial, the results are largely unknown, and that follows from several things. First of all, it's very difficult today to know from the preclinical rationale whether the trial is going to work. And so, you have to treat patients. There's no other way to really know.

And, at any time in any trial, a relatively small number of patients have been treated and the patients differ. So, for example, it would be sort of idle to compare somebody who's 65 with what people would call prognostically unfavorable cytogenetics, which we'll get to in a second, with somebody who's 40 with what somebody would consider to be favorable cytogenetics.

So, the patients differ and they just can't be lumped. "Well, we treated 20 patients." But, they may fall into three or four separate groups.

Dr. Eli Estey
And then, of course, the follow up is short because the trial usually hasn't been going on that long. And, in principle, you would rather be in a trial where the remission rate was 80 percent but all the people were cured than in a trial where the remission rate was 100 percent and everybody lasts with it a year.

So, for those reasons it's very difficult to know the results of the trial. And this is really the fundamental point. Deciding between standard treatment and a trial depends on how the patient views the results of the standard therapy.

And that, I feel, is my primary job when I meet with patients. "Okay, assuming you want to be treated, here are the two options. We can do standard or we can do a trial. I really don't know how the trial will work out. Many don't work. Some do, but I don't know." And so, the decision has to be made on how you view the results of standard therapy.

And so, for example, somebody might say, "Wow, the standard therapy is not perfect, but I'm afraid if I go on the trial it could be worse because you don't know what the results of the trial are. So, although it's not perfectly satisfactory at all, I'll do the standard." And other people, given the results of the standard therapy, will say, "No, no, I can't do that. How much worse can the trial be?"

And so, I basically view myself as somebody who provides information to patients about what the results of standard treatment might be. And, don't forget, there have been so many people that have been treated that we generally know the results of the standard treatment.

Slide 17 - Prognostic Factors With Standard Therapy: TRM

Dr. Eli Estey
So, that takes us to the prognostic factors of standard therapy. This actually is something that I find all the time. Patients come to see me and they really haven't been told what the results of the standard therapy are. I can see it. To me, it reminds me of where people would say, "Don't ask, don't tell."

I think lots of times patients really don't want to know and so they don't ask. They're afraid to ask. And, a lot of times doctors don't want to tell them because they feel the patients don't want to know.

But, what this leads to is many patients, in my opinion, getting therapy that you almost know is not going to work before it's given. And that, of course, asks the question, why do we do this, aside from that it's comfortable, but I'm not sure it's in anyone's best interest.

Dr. Eli Estey
But, anyway, turning to the topic of prognostic factors with standard therapy, the first is what would predict that the therapy would be too toxic to the patient and might cause them to die as a result of the treatment. The most important is performance status, which basically is a word describing how well the patient is feeling when the treatment begins.

So, it's sort of common sense that somebody who only has minimal symptoms, a bit of fatigue, is less likely to have toxicity from the treatment than somebody who is very sick when the treatment begins.

Another factor is comorbidities. So, for example, if somebody has heart disease, or high blood pressure, or diabetes, or they're obese, they're much more likely to have treatment-related mortality and toxicity than if they're not.

Age is important, but age is not the most important factor, and that's very, very fundamental. Age has got to be looked at in terms of everything else.
So, for example, if you had an otherwise healthy 50 year old, their treatment-related mortality might be less than three percent. On the other hand, if you had a 75 year old who is debilitated with abnormal kidney function, their treatment-related mortality might be more than 50 percent.

But, it's easy to show that you would rather be a 65 year old who's healthy than a 55 year old who's got a lot of comorbidities. So, it's very, very, very important to think beyond age.

Slide 18 - Prognostic Factors with Standard Therapy: Resistance

Dr. Eli Estey
We talked about the things that might predict toxicity or treatment-related morality. But, we said earlier that the major problem is resistance to the therapy. The patient lives long enough, they don't die as a result of the therapy, but they don't get a remission or their disease comes back.

So, what are the prognostic factors of standard therapy to predict resistance? By far, the most important are the chromosomes in the AML blasts. And basically they can fall into three or four different groups.

The first are the best. So, these are people who have inversion 16 or an 8;21 translocation. This sort of average group is people who've got normal cytogenetics, which is often abbreviated NK for normal karyotype. And then there are below average, where people have abnormalities that are not the best, and then the worst is something that's called a monosomal karyotype, or MK.

Dr. Eli Estey
Now, remember this all applies with standard therapy, because we don't know whether the same things will apply with the trial. But, the decision is going to be based on standard therapy, what the results are of standard therapy.

So, the next prognostic factor, particularly in patients who have a normal karyotype, are various mutations. These include FLT3 and NPM and CBPA. It's generally felt that, just as everybody with AML should have their cytogenetics determined, in 2013 they all should have these mutations studied.

And, another important factor is whether the patient has what's called secondary AML. Secondary AML takes one of two forms. The first is they were treated--they received chemotherapy for breast cancer or lymphoma or something several years ago, and now they have AML, presumably a result of receiving that chemotherapy, which did in fact cure the other disease.

The second type of secondary AML occurs after a patient has had myelodysplasia, MDS, or other hematologic disorders. And again, last on the list is age.

So again, just to focus on age is really doing yourself a disservice. Generally, yes, it's true that patients who are older tend to have more comorbidities. They tend to have worse cytogenetics. They tend to have secondary AML. But, if they don't have those things, then the situation can be very different than if they do.

Slide 19 - Effect of Monosomal Karyotype on Survival

Dr. Eli Estey
So, this is just data basically showing the effect of different cytogenetic abnormalities on survival. And, the way these curves are, basically at the start, you can see that everyone's alive. And then, on the X-axis, where it says 12, 24, 36, 48, are months.

It's very difficult talking about survival to patients. But, I think it's fundamental, because I have always felt that if you don't mention it, people are wondering about it. They may not want to ask about it and you may not want to tell it. But, I've always felt that's my job, because I have to help them to decide what kind of treatment that they want, and this information is critical.

So, for example, if you look at the top blue line, these are people with the best abnormalities, CBF, inversion 16 or 8;21. And you can see, if you look--follow that blue line--you can see that, at four years, 48 months, the likelihood is that three quarters of these patients will still be alive.

Dr. Eli Estey
In contrast, if you look at the line that says MK positive, which is the red line, you can see that, at 12 months, the likelihood is that only about 20 percent of those patients will be alive. And, if you look at where it says point 50, that's the average or median survival. That's only around six months.

So, certainly this information, you can see how it would be very useful. For example, if somebody were in that best group, they'd say, "Wow, the standard therapy isn't perfect, but, you know, there's a very high chance of success, relatively speaking. And, how do I know that if I get your clinical trial, Dr. Estey, it won't be worse? I'll take the standard therapy."

In contrast, if you're on that red line, well, then you would think that very few people would want to get the standard therapy. Nobody wants to be on that red line, so they would say, "Gee, you know, I realize the trial may not work, but how much worse can it be than being on that red line?" And this is something, to me, that's fundamental, that people need to know this information, because only then can they truly make an informed decision.

And then, if you look at the lines in the middle, the yellow line and the black line, there you could see how some people might decide, "Gee, you know, the results are good enough. I'll do the standard therapy because I'm afraid to do the trial."

On the other hand, some people faced with that same information, might say, "I want to do the trial because those results of the standard therapy in those cytogenetic groups are not good enough for me. I want to be in the trial."

Slide 20 - Outcome According to FLT3/ITD Expression Level

Dr. Eli Estey
So, the next slide is more of the same. It just shows the influence of FLT3 internal tandem duplications. And, you can see that in a group that has a high level of FLT3 internal tandem duplications, that's the line in green at the top, 80 percent of those people relapse with standard therapy. So again, people in that group might want to consider being on a clinical trial.

Slide 21 - AML14 Intensive: Overall Survival by AML11 Risk Group

Dr. Eli Estey
This is looking at it again in older patients. This is data from the United Kingdom, their big group. And, basically they look at many different factors, and they break these older people up into one of three groups.

Dr. Eli Estey
You can see that in the good risk group, 29 percent of the people are alive in three years, when in the worst group only 9 percent of the people are alive in three years. Certainly many of these people, I think, if they knew this data before they began treatment, would say, "Gee, I don't want to get the standard therapy."

Slide 22 - Overall Survival (Kaplan-Meier Method) in a Protocol-specified 2009 Clinical Cut-off Analysis of Decitabine and Treatment Choice (TC) in the Intent-to-treat Population

Dr. Eli Estey
What this is showing is there's been a lot of analysis of a drug called decitabine or Dacogen. And that's very, very frequently offered to patients. Well, what are the data?

Well, basically this is a study that was done, an international study in patients aged 65 or above. What we're looking at here is patients were randomized. There was a flip of the coin, and if it came up heads, they received decitabine. If it came up tails, they received a choice between standard approaches in this age group: transfusions and antibiotics alone or low doses of ara-C. On this slide, TC is treatment choice that is between transfusions/antibiotics only or low doses of ara-C.

And, you can see that perhaps the decitabine is a little bit better, but not really that much better. And the same is true with randomized studies that have been done with a drug called Vidaza or azacitidine.

Slide 23 - Medical Significance Azacitidine Trial

Dr. Eli Estey
So, azacitidine, or Vidaza, improved survival, and we'll look at the actual data in this slide which was also done in older patients

So, remember, and if you look at Social Security tables, that if you're healthy, a 70 year old might expect to live 15 years, or 180 months. With standard treatment, low-dose cytarabine, for example in older patients, the results in the azacitidine study in which patients were randomized much as they had been in the decitabine study to azacitidine or low dose Ara-C, they lived 16 months.

Thus, they retained only 9 percent of their life expectancy. With azacitidine, it was better. They lived 24 months. But, in fact, that translates to only retaining 13 percent of their life expectancy.

So really, a drug like azacitidine or decitabine, yes, they may be better in a statistical sense. But, what the patient has to decide is, are they really better in a medical sense.

Dr. Eli Estey
And that's something that is very easy to get confused by. Doctors get confused by that.

You can just look at ads in journals to realize that people put up statistical P- values. But, there's a big difference between having a statistically significant result because you've treated hundreds and hundreds of patients, and a medically significant result.

Slide 24 - Trial vs. Standard

Dr. Eli Estey
Fundamentally, this is the key point to really make. This is the fundamental decision that a patient has to make. Do I go on a trial or I get the standard therapy? The reason to go on a trial is dissatisfaction with the results of the standard therapy. And therefore, the only way you know is to hear the results of the standard therapy, as unpleasant as it may be, which is what I just tried to do.

The same information can lead to different decisions in different patients. Some people would be more satisfied with the result than others, and some people would be more conservative than others, etc. And fundamentally, the results of the standard are often not discussed with the patient. I mentioned that before.

Slide 25 - Which Trial?

Dr. Eli Estey
So, let's say that patient says, "Gee, I want to go on a clinical trial. Well, which trial should I go on?" Well, if you go to the NCI website, which is called Clinicaltrials.gov, and if you put in AML patients over 65, which is a very common age group, you'll find there are 33 trials for patients.

Why are there so many trials? Well, I think the only implication is that no one is certain which trial is best. Otherwise, there wouldn't be 33 trials. And again, we can go, “Why is there this uncertainty?”

We touched on this before. There is imperfect understanding of the difference between the AML blast and its normal counterpart. An insufficient number of patients have been treated. The patients differ among themselves. And there is a short follow-up.

Slide 26 - Which Trial?

Dr. Eli Estey
So, which trial should you go on? Well, if it can't be decided scientifically, and the other point that figures in is the trial that you're offered depends on where you go. So, if you

Dr. Eli Estey
go to M.D. Anderson, you might be offered trials A and B. If you come to Seattle, you might be offered trials C and D.

And this, again, is a very, very fundamental point, because you see patients, and they're on the Internet and they've read this on the Internet. And they had this question and they had that question.

But, I can tell you, based on lots of experience, that it is very difficult to intellectualize the best trial for the reasons that I referred to. And therefore, even though it's so tempting to go on the Internet and try to intellectualize it, it cannot really be done, in my opinion.

And so, therefore, what I recommend is that you go on a trial in an academic center where you are most comfortable. And that, for example, might be the center that's closest to home, for obvious reasons.

One thing to make sure of is that the trial has stopping rules. A stopping rule basically says, well, before we treat a hundred people, we're going to look and we're going to make sure that the results in those first people that we've treated, as uncertain as it may be, are not worse than what could be obtained with the standard. That's fundamental. So, I would certainly ask the doctor who you're speaking to about the trial, "Can you tell me a bit about the stopping rules you have in place in the study?" And, if they can't really answer the question, then that's obviously not good.

And fundamentally, I always tell people you have to be realistic and optimistic. And realism is obvious. Many trials are not successful because we lack the knowledge.

But, you always have to be prepared for success, PFS, and because it's very, very important to remember that many currently curable diseases once had the same prognosis as some of these patients with AML did until trials were done. And the most obvious example is AIDS, which now is very, very different than when it was first described 30 or 40 years ago. Chronic myeloid leukemia and acute promyelocytic leukemia are types of leukemias that today are routinely curable because trials were done.

Slide 27 - “Targeted Therapy”

Dr. Eli Estey
So, let me say a word about targeted therapy, because it's a word that's bandied about, personalized medicine, etc. And obviously, what's supposed to happen is it selectively affects the AML blasts. So, that's why it’s targeted. It targets the AML blast and not the normal blast that gave rise to the AML blast.

Dr. Eli Estey
But, it's almost certain that there is not one target that's wrong in the AML cell, unlike CML where Gleevec® or imatinib is super effective, cures patients, because in that disease there is only one target. There's only one thing wrong.

But, in AML, several targets may need to be affected simultaneously, which makes things more complicated. And a striking observation is that today in AML, most targeted therapies have wound up being combined with chemotherapy.

And a question I always ask myself is, "Well, if this is always the case, why don't we just start combining the targeted drug with chemotherapy rather than waiting three or four years to do that," which is normally what happens.

Another very promising area of targeted therapy is to boost patients' immunologic response to their own disease.

Slide 28 - Allogeneic Hematopoietic Cell Transplant (HCT) in CR1

Dr. Eli Estey
So, let me say a word about transplant, because this is a commonly asked question, "Should I receive a transplant or should I not? I'm in first remission," generally when transplants are done.

And this is a large series that was reported from many centers in America. And basically, all you really need to look at is the HR, which is the hazard rate. And a hazard rate of one means that survival with the transplant, which is the donor column, is better than if you did not get the transplant. One means it's the same, transplant, which is the donor column; no transplant, which is the no donor column. And, an HR less than one means that it was better with the transplant.
So, what you can see is, if you're in that best cytogenetic group, generally people feel that there's no reason to do a transplant because there's no survival advantage. The hazard ratio is greater than one.

Generally in people who are in the intermediate cytogenetic group, who are in that worse cytogenetic group, that red line, for example, the general feeling is that those people should receive a transplant because there is some benefit to survival with the transplant.

Slide 29 - Relapse-free Survival in CR1 According to Availability of HLA-Matched Sibling

Dr. Eli Estey
In the next one, we're looking at a very similar thing. Here we're looking at molecular information. And you can see that if you happen to have a normal karyotype and (a) a mutation in the NPM gene but no mutation in the FLT3 gene or (b) a mutation in the CEBPA gene, there's no advantage to the transplant. That's the slide on the left, donor, which is transplant, and no donor, no transplant, come out to be the same.

But, for other patients with a normal karyotype , there probably is an advantage to getting the transplant. And again, that speaks to the importance of having these mutational tests done when you're diagnosed.

Slide 30 - Extensions of HCT Beyond Ablative Sib in CR1

Dr. Eli Estey
A question that comes up today is, “Well, gee, you know, I'm too old for a transplant,” or, “I don't have a sibling,” or “I don't have a matched sibling.” But, one of the things that’s certainly ongoing today is that nowadays there are reduced intensity transplants that can be done at least up to age 75. And they rely on the so-called graft-versus-leukemia effect.

This is the effect that the donor cells have at getting rid of the leukemia. It's an immunologically mediated effect, hence our focus on the immunology that we talked about before.

And as I mentioned, these days matched unrelated donors, which is somebody not related to you but happens to be a match, could be done with reduced intensity transplant up to age 75.

If you don't have a donor that way, people can use umbilical cords. And in many instances, there are haploidentical transplants. So, for example, from a parent to a child or from a brother that's not a full match to a patient.
And then, just as we showed the results with chemotherapy were treatment-related mortality was less as time went on, there is no question that survival with transplant is better today than it was 20 years ago.

But, it shouldn't eliminate the fact that results with transplant are still not optimal. And so, there is need for clinical research and clinical trials in transplant just as much as there is in chemotherapy.

Slide 31 - Future

Dr. Eli Estey
And I think the future is going to see merging of transplant and chemotherapy. And that's going to take place in several different ways. So, it's known that patients may be in remission, but if they have very minimal residual disease before the transplant, that makes them more likely to relapse.

There are programs to see if various chemotherapies can be used to eliminate minimal residual disease before transplant. And then, because relapse is the major problem after transplant, just as it is after chemotherapy, they're going to be using various therapies such as various targeted therapies, or Vidaza or azacitidine, and various immunologic therapies, T-cell therapies, that are going to be used to prevent relapse after transplant.

Slide 32 - Making Patients' Lives Easier

Dr. Eli Estey
Something I'd like to just focus on is, I think there are many ways of making patients' lives easier in the year 2013. For one, we've shown and published that it's very practical to be discharged once induction chemotherapy is completed; that there is no need to stay in the hospital for 30 days. In fact, if anything, you're more likely to get a serious infection in the hospital than outside the hospital. And, if your doctor or your provider is prepared to do that, and if there is an outpatient follow-up that can be arranged, and if you live close enough and are willing to come back several times a week, it's very plausible to get chemotherapy in the hospital and then be discharged. We've also shown that once your fever is gone, it's possible to discharge a patient regardless of their neutrophil count. Nothing bad will happen.

And this is another very interesting example. People are often told about a neutropenic diet; that they can't eat fresh fruits and vegetables; they have to cook everything. Well, in Houston several years ago, we did a study and we randomized patients between a neutropenic diet and a regular diet. We just said, "Well, if you want to eat fresh fruits and vegetables, just wash them."

And the way it turned out--this was published, was that there was no difference in results and infection rate or any outcome in patients who ate the neutropenic diet and patients who did not eat the neutropenic diet.

I think this is something that really needs to be kept in mind by patients, not only with respect to this, but with respect to so many medical practices that are done. You have to wonder, all these things that make patients' lives less comfortable, "Oh, you can't go

Dr. Eli Estey
to the mall. You have to wear a mask." What is the empirical basis for that? Because I always tell people that many years ago when I was in medical school, we were taught that if somebody had a heart attack, they had to stay in bed for a week. And as time has gone on, that's been proven to be certainly wrong.

And I wonder if a lot of what we do just makes peoples' lives harder, and the intention is obviously good. Everybody's well intentioned, but you wonder how much of what we do is really necessary. And, certainly, the example of staying 30 days in the hospital or eating a neutropenic diet, there's a lot of data that suggests that's probably really not necessary.

So, thanks for your attention. I hope I haven't gone too fast. And I'm looking forward to the questions.

Slide 32 - Question & Answer Session

Ms. Lauren Berger
Thank you so much, Dr. Estey, for your very clear and informative presentation.

It is now time for the question and answer portion of our program. We'll take the first question from the Web audience. And this question is from Alan. "I was diagnosed with AML in January 2013. I was treated and I got to remission. My blood counts seemed to recover."

"Then I had consolidation therapy and my counts did not recover. My blood counts are low and I have not been able to receive additional chemotherapy. What can be done for me?"

Dr. Eli Estey
So, that's a very good question, and it's a very common situation. The patient has low counts. And there are two possible reasons.

One, the chemotherapy has been too toxic to the normal cells. And obviously, if that were the case, well, you wouldn't want to give more therapy. The second is that, in fact, the counts are low because there's still disease in the marrow that you can't detect. Well, in that case, you want to give therapy.

One possible way to address it, depending on the patient's age, etc., is to do a transplant. And that addresses both problems, because if you get the transplant, you get normal cells from the donor which will replace the cells that might have been damaged by the chemotherapy. And second, of course, the transplant has anti-leukemia effects too.

Dr. Eli Estey
So, probably, you know, in the best of all situations, assuming it could be done, the answer to the question would be the best thing to do would be to consider a transplant. It's a very common situation.

Ms. Lauren Berger
Thank you for your question, Alan. We'll take the next question from the telephone audience, please.

Operator
Our first question from the phone comes from Mary from Iowa.

Ms. Lauren Berger
Hello, Mary.

Mary
I'd like to know about graft, in a transplant when you have signs of rejection. I have lower leg edema that is, like, hard, and they're saying that that's a sign of rejection and that people have that, like, all over their body.

I was just wondering about that, if that is a sign of rejection, or what can I expect from that? I have had some little signs of kidney failure. My creatinine's been 1.5. And I'm wondering if that's a result of that, this swelling and hardness in my lower legs. They're very painful, too.

Dr. Eli Estey
Well, you know, rejection is really very, very uncommon. And it's generally easy to diagnose because your blood counts don't recover. So, that basically means the cells didn't take and the counts are low.

So, the diagnosis of rejection is usually not really difficult. Probably what you want to do is to ask, are your counts low? If your counts have come back, it's probably not rejection.

And what it could be is graft-versus-host disease. And that might explain the rash, but I'm not really sure it's rejection, you know? But, the best way to find that out is just seeing what your blood counts are.

Ms. Lauren Berger
Thank you for your question, Mary. We'll take the next question from the Web audience. And this one is from Morgan. And Morgan asks, "Is the treatment for pediatric AML the same as for adults?"

Dr. Eli Estey
Yes and no. You know, the same prognostic factors apply, cytogenetics, de novo versus secondary AML, mutational status, etc.

The major difference is twofold. One, children tend to have better prognosis disease than adults, and so are more likely to do well with standard therapy than adults. And also, they can tolerate therapy more, so they can take more intensive therapy. Intensive therapy is usually beneficial in people who do well with standard therapy.

So, the answer to the question is, in principle yes, but keeping in mind that children are more likely to do well with standard therapy and they're more likely to benefit from intensification of that standard therapy because they generally have better prognosis disease. But, again, age is not everything.

And so, for example, if you had a child that had a very poor prognosis because of cytogenetics with standard therapy, they too would be candidates for a clinical trial, just as an adult would be. It's just less likely for that to happen than in an adult.

Ms. Lauren Berger
Thank you for your question, Morgan. We'll take the next question from the telephone audience, please.

Operator
Our next question is from Cindy from New York.

Cindy
My mother is 77 years old. She's currently on azacitidine. And I know you said statistically it's better, but is it better in the medical sense? What does that mean exactly and for someone her age?

Dr. Eli Estey
Okay. So, let's say you're 77 and assuming she's healthy. And if you were to look at the Social Security table, you would say, "Okay, she'll live to be 85," eight years.

Now, let's say if she weren't treated, she would live to be 78, okay, with just standard treatment, or with the azacitidine, she might live to be 79. She's 77 now, and that's the average result.

And unfortunately, we're not smart enough to know which patient will benefit more than any others from azacitidine. The cytogenetics can be helpful. But, the fundamental decision that your mother would have to make is, is that result good enough? It's statistically different, but would that difference of a year make a difference whether she would not want to go on a standard treatment.

Dr. Eli Estey
So, for example, I could certainly see somebody say, "Well, you know, it's not what I had in mind. I'd like to live more than a year and a half or two more years," which is the likely outcome with the azacitidine. "But, I'm afraid that if I do a trial it won't work, and I won't even live as long as if I had the azacitidine."

On the other hand, you could see somebody else saying, "Wow, you know, that azacitidine result is not good enough, doesn't give me enough hope. I'm willing to take the trial." And again, it just depends on the type of person your mother is. How would she use that information? Does that make sense?

Cindy
Thank you.

Ms. Lauren Berger
Thanks for your question, Cindy, on behalf of your mom. The next question we'll take is from the Web. And this question is from Chris. And Chris asks, "Are there options for patients who relapse after an allogeneic stem cell transplant?

Dr. Eli Estey
So, a major factor in that, as with all relapsed patients, is how long the remission lasted.

So, generally, if somebody relapses, say, within a year of transplant, in the past they have not done well. They are very unlikely to be cured. So, these are prime candidates for a clinical trial.

If, in contrast, the remission lasted, say, a year and a half or two years, or something like that, then the prognosis is better. And they could get donor lymphocyte infusions, and things like that.

So, the answer to your question largely depends on when the relapse occurred after the transplant. The shorter the remission, the more likelihood that standard therapy will not prove successful.

Ms. Lauren Berger
Thank you for your question, Chris. We'll take the next question from the telephone audience, please.

Operator
Our next question is from Adrian from Texas.

Adrian
I'm Adrian. I'm 17 years in remission. I'm just asking, does GVH ever stop?

Dr. Eli Estey
It may be chronic graft-versus-host disease. I mean, it does, but if it's a problem, then it's just like anything else. I mean, if it doesn't respond to standard treatment and if it's very bothersome, then what I would recommend is that here are trials for chronic graft-versus-host disease and acute graft-versus-host disease in the same way that there are trials for relapsed or AML.

Ms. Lauren Berger
Thank you for your question, Adrian. We'll take the next question from the Web. And this one's from Juneau. And Juneau asks, "Could you speak to fertility concerns with young patients who will undergo transplant?"

Dr. Eli Estey
So, I think one of the things that is very, very important to do is to see if you can save eggs or bank sperm. I mean, I think that's something that we try to do routinely when people are first diagnosed. That's certainly something that should be done.

You know, I think it's hard to know. There are certainly people who have been transplanted who have conceived children. There's no question about that.

I'm sure there is more risk of fetal malformation, etc., or other problems than there would be if they hadn't had the transplant. The odds would still greatly be in your favor, I think. But, you know, it just depends how much of a risk you're willing to take, etc.

The best answer to the question is the preventative answer, which is, everybody should have sperm, if possible, or eggs stored before they begin treatment.

This actually leads to another interesting question, because people are often told that, "Wow, I have AML and the doctor says you have to begin treatment tomorrow or yesterday," you know? But, in fact, that's not true. The only cases where you really need to begin treatment right away are people with very high white counts. And that's generally a great minority of people.

In most cases, there is time to wait and in particular to get the results of the cytogenetics. There's time to use that information to make a decision--standard versus clinical trial. And there's certainly time to store sperm and eggs.

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

Operator
Our next question comes from Ernie from California.

Ernie
I had a transplant. I gave my own bone marrow and they cleaned it up and reinfused it. As I said, that's been 21 years. How is that--I didn't hear you mention that type of transplant. I wonder what's the status of that transplant.

Dr. Eli Estey
So, that type transplant is called an autologous transplant. It's much more popular in Europe than in the United States. People have done these randomized trials, and they've compared autologous transplant and chemotherapy.

And the general feeling is that there is not much difference between the two as currently done. There are obviously people who are cured with either one. But, on average, the general feeling is that there is not much difference, at least in survival.

Now, one thing that needs to be said is that they are both fertile areas for further investigation. So, for example, there perhaps are different ways of cleaning up the bone marrow. There are ways of inducing graft-versus-leukemia in people who get an autologous transplant, etc.

But, if the answer to your question is how do they compare in general, I think most people would say there is not that much difference between them.

Ms. Lauren Berger
Thank you for your question, Ernie. We'll take the next question from the Web audience. And this is from Mannen. "Is there a difference in outcome for patients who need two inductions rather than one to achieve remission?"

Dr. Eli Estey
That's a very, very good question. It's still somewhat debatable. It's a bit complicated.

But, I think many people, including myself, feel that, yes, if it takes two, that the remission, everything else being equal, would be shorter. And that might be more of a grounds for saying, "Okay, I'll do a transplant," if I'm not sure whether I should do one. Other people disagree, and they say, “Well, if it takes, it doesn't make any difference if you take two.”

And this is technical, but one of the problems in answering the question is what proportion of people who are not in remission after a first actually get a second, because if they all don't get a second, there can be all this bias in interpreting the results.

Dr. Eli Estey
But, it's a very good question, and the answer is not totally clear. My personal opinion is that generally the outcome would be worse if it takes two rather than one--the likelihood of relapse.

Ms. Lauren Berger
Thank you for your question, Mannen. We'll take the next question from the telephone audience, please.

Operator
Our next question comes from Jeannie from Pennsylvania.

Jeannie
Hi. My daughter was two years old when she was diagnosed. She's three now.

And I was just wondering, she's 24 weeks into remission. But, if she relapses, they were talking about a bone marrow transplant and they took the umbilical cord blood off of her little sister I just had in April. How would they know--what further testing do we have to do to see if it's an exact match for Jazz?

Dr. Eli Estey
I'm not an expert at this. But, generally speaking, there are less problems with graft-versus-host disease with cord blood. And the reason is that the cord blood, the immune cells are not that mature.

So, generally speaking, you can accept a broader degree of HLA, which is the matching disparity, than you would with an adult, just because the cord cells are younger.

Ms. Lauren Berger
Thank you for your question, Jeannie. And if you'd like more information on things related to stem cell transplant, I'll provide the Information and Resource Center telephone number at the end. And they can also help you with additional resources.

We'll take the next question from the Web audience, please. And that's from Sharon. And she asks, "What is APL and what is the current standard of care?"

Dr. Eli Estey
APL is acute promyelocytic leukemia. Unlike other types of AML, its hallmark is hemorrhage. That's the dominant feature.

So, many years ago, it was fatal from hemorrhage, very, very rapidly. But now, it should be essentially curable in all patients, or in the great majority of patients. And the most modern therapy is something that we've actually worked on in Houston and recently

Dr. Eli Estey
was shown to be effective compared to standard therapy in a large randomized trial done in Italy.

If your white count is low when diagnosed, meaning under 10,000, then the standard treatment, I think, as shown in this trial, should be all-trans-retinoic acid (ATRA) and arsenic trioxide, and there's no need for chemotherapy in people with low white counts. In people with higher white counts, the general idea is to combine arsenic and ATRA with chemotherapy. But, in people with low white counts, which is probably three quarters of people with newly diagnosed AML, there should be no need for chemotherapy as such, and the disease should be curable in the great majority of people with just arsenic and ATRA.

And it's interesting because it brings up an important thing that I should elaborate on. So, this result applies in academic centers. People have said, "Well, gee, this high cure rate, is that really the same if you look in the community?" So, people go to big databases of people that are treated in the community, and it turns out that the results are not nearly as good in the community as they are in academic centers.
And of course there are two explanations. One is that only the best patients are taken by the academic centers. The second is that the academic centers are simply more practiced in treating it, because APL is something where attention to transfusion support is really, really important. But, you know, it's certainly very likely to be cured today if treated, I think, in an appropriate place.

Ms. Lauren Berger
Thank you for your question, Sharon. We'll take the next question from the telephone audience, please.

Operator
Our next question is from Todd from Illinois.

Todd
I was diagnosed in January of 2013 with AML. I had a very high white blood cell count. I was curious what that means, like why that needed to be treated so quickly. And I've been very healthy. I've gone through everything very smoothly, had my transplant.

And I was curious, you'd mentioned prognosis as well. I had an M5. Do high white blood cell counts at the start make a difference to the prognosis in the end as well? Thank you.

Dr. Eli Estey
So, there are two aspects to the question. Immediately, the reason that you have to treat people with high white counts is because the leukemia cells can invade organs

Dr. Eli Estey
and the lung and the brain. And, of course, that can be potentially fatal. So, one difference is it requires more immediate treatment.

The second thing about the prognosis of the high white count, the white count itself is not prognostic. But, oftentimes people who have high white counts, particularly if they have normal cytogenetics, have this FLT3 mutation, and that tends to make their prognosis with standard therapy poorer, which is one of the reasons that people are interested in doing transplant.

So, I'm not sure the height of the white count is important. It needs immediate treatment to prevent the disease from getting in the brain or the lung. But, if it's not associated with a FLT3 internal tandem duplication, there's nothing bad about having a high white count.

And oftentimes, you can have a high white count and have an inversion 16, which is the chromosome abnormality that's curable without transplant. So, the white count is not as important as things like cytogenetics or molecular abnormalities, except that you do need to treat it quickly.

Ms. Lauren Berger
Thank you for your question, Tom. We'll take the next question from the Web audience. And the question is, "Why don't we do more autologous transplants to help and perhaps eliminate graft-versus-host?"

Dr. Eli Estey
It's just something that's not done. I think, frankly, one reason is obvious. It's that many trials of new therapies are sponsored by pharmaceutical companies. And this has not been a particular area of interest for pharmaceutical companies. I think that's probably one reason.

There are probably more trials of autologous transplant in Europe than there are in the United States. But, if you were to say, “Why aren't there more in the United States?”, I would say it's just not the way the companies are aligned with what they do. And one thing that I think I've learned over time is that it's very, very difficult to know which new therapy is going to be better than another.

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

Operator
Our next question is from Elise from Florida.

Elihu H. Estey, MD
October 31, 2013

Elise
Thank you very much, Doctor, very informative presentation. My husband was diagnosed four years ago with AML, with a FLT3 mutation, and he had his transplant over three and a half years ago. We went for his three year biopsy back in May, and we were told that he is 100 percent donor infused, in remission, and as close to zero percent of this returning as you could get. He was off all his immunosuppressive drugs at the time and got his last baby shot of MMR.

Shortly after returning back home and getting that MMR shot, he had a flare-up. I don't know if it was related to the MMR shot or not. But, he had a flare-up of the graft-versus-host of his mouth and his eyes, and he had to go back on the Prograf® and the Rapamune®, and prednisone was introduced into the process.

He wound up in the hospital with a strep infection, and then he was discharged after 10 days to IV antibiotics at home. And 10 days later, he was called to go for IV hydration, and we found out that the Prograf and Rapamune were at toxic levels, and he was in kidney/renal failure and had to be readmitted to the hospital, and he wound up with a blood clot as well. He was unable to get blood thinners at that time because his platelets were too low. They were 40,000, so he wound up with an IVC filter.

The IVC filter has since been removed, and the clot is dissolving, and he is on Lovenox® injections. And of course he is as bruised as anybody can imagine.

It's very hard to wrap your head around getting such a wonderful report on your three year biopsy and coming home to all these problems this far out from transplant. How common is all of this to a transplant patient, to get all these problems this far out from transplant?

Because in your head you understand it's not the leukemia, but in your heart, watching your husband, and he, as the patient, watching himself deteriorate since May, where he is now on a rolling walker, unable to walk very well and in terrible pain, and he was doing fine back in May, how common an occurrence is something like this to happen?

Dr. Eli Estey
Well, frankly, it's rare, but of course that doesn't help you. But, you know, luckily enough it's really rare.

The one good thing, of course, is that since he's been in remission from his leukemia for three years, the likelihood is that he's cured of the leukemia. But, of course that doesn't help with the other problems, which fortunately enough, on average, are very rare.

Ms. Lauren Berger
Thank you for your question, Elise. We wish your husband the best. And thank you all for your questions. We hope this information will assist you and your family in your next steps.

Slide 34 - LLS Contact Information

Ms. Lauren Berger
If we were not able to get to your question, please call The Leukemia & Lymphoma Society's information specialists at 800-955-4572 or reach us by e-mail at infocenter@lls.org. We can provide you with information about AML research, clinical trials, other questions you may have about treatment, and questions about financial assistance for treatment.

I'm pleased to also announce that The Leukemia & Lymphoma Society's new online chat for caregivers will begin on Tuesday evenings in mid-November. The chat provides a forum for family members and friends to address the stresses and triumphs shared by caring for someone with a blood cancer, and the chat is moderated by an oncology social worker. So, for information on how to participate, please go to lls.org/chat, or you can contact an information specialist at LLS.

Please help me thank Dr. Estey for volunteering his time and expertise with us today. On behalf of The Leukemia & Lymphoma Society, thank you all for sharing your time. Goodbye, and we wish you well.