

Slide 1: Advances in Acute Myeloid Leukemia

Lizette Figueroa-Rivera:

Hello, everyone. On behalf of The Leukemia & Lymphoma Society, I would like to welcome all of you.

Special thanks to Dr. James Foran for volunteering his time and expertise with us today.

Before we begin, I'd like to introduce Dr. Louis DeGennaro, The Leukemia & Lymphoma Society's President and Chief Executive Officer, who will share a few words.

Dr. Louis DeGennaro:

I'm Dr. Louis DeGennaro, President and CEO of The Leukemia & Lymphoma Society. I'd like to welcome all of the patients, caregivers, and healthcare professionals attending the program today.

At The Leukemia & Lymphoma Society our vision is a world without blood cancers. Since we started in 1949, LLS has invested more than \$1.2 billion in breakthrough research to advance life-saving treatments and cures. We've played a pioneering role in funding many of today's most promising advances, including targeted therapies and immunotherapies that have led to increased survival rates and improved the quality of life for many blood cancer patients.

Though LLS is known for funding groundbreaking research, we do so much more. As this program demonstrates, we are the leading source of free blood cancer information, education, and support for patients, survivors, caregivers, families, and healthcare professionals. We also support blood cancer patients in their local communities through our chapters across the country and we advocate at the state and federal level for policies to ensure that patients have access to quality, affordable, and coordinated care. We're committed to working tirelessly toward our mission every single day.

Today you'll have the opportunity to learn from esteemed key opinion leaders. They each have volunteered their time and we appreciate their dedication to supporting our mission, their commitment to caring for patients living with blood cancers.

Thank you for joining us.

Lizette Figueroa-Rivera:

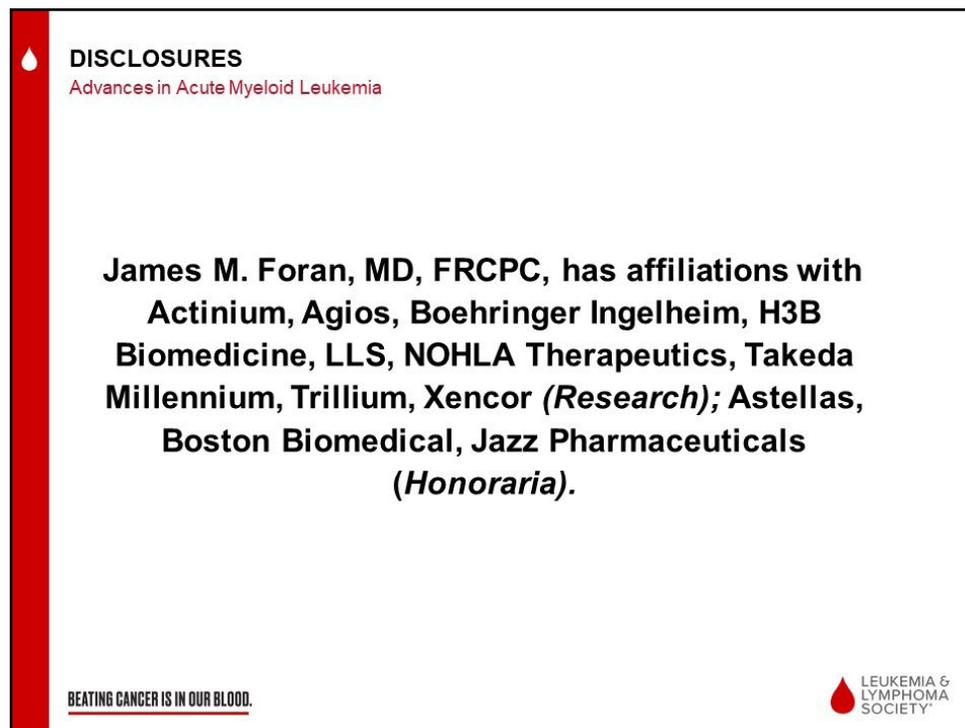
Thank you. And, we'd like to acknowledge and thank Agios, Celgene, and Novartis for support of this program.

I'm now pleased to introduce Dr. James M. Foran from the Mayo Clinic Cancer Center in Jacksonville, Florida. Dr. Foran, I'm privileged to turn the program over to you.

Dr. James Foran:

Thank you very much. It's actually a real pleasure to be invited to do this and have the opportunity to do this. I'm a big supporter of LLS and the work they do, so, very much appreciate the opportunity.

I'm just going to start scrolling through some slides and speaking for those of you who don't have access to them, speaking around the slides also to try to really tell a story about where we have come from, where we are now, and where the future opportunities are in acute myeloid leukemia (AML).



DISCLOSURES
Advances in Acute Myeloid Leukemia

James M. Foran, MD, FRCPC, has affiliations with Actinium, Agios, Boehringer Ingelheim, H3B Biomedicine, LLS, NOHLA Therapeutics, Takeda Millennium, Trillium, Xencor (*Research*); Astellas, Boston Biomedical, Jazz Pharmaceuticals (*Honoraria*).

BEATING CANCER IS IN OUR BLOOD.



Slide 2: Disclosure

Dr. James Foran:

I am going to start by just acknowledging that I do have some research disclosures. I get research support from several pharmaceutical companies for clinical trials we do and have received honoraria also from 3 others and that's in the slides, just so that you're aware of that.

Advances in AML in 2018

Learning Objectives

- i. Evaluate the optimal incorporation of newly-approved therapies in AML
- ii. Understand the role of mutations and deep sequencing in determining prognosis and selection for AML therapy
- iii. Consider the role of Allogeneic Transplantation as consolidation therapy after AML therapy
- iv. Optimize collaborative & supportive care



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Slide 3: Advances in AML in 2018: Learning Objectives

So, I have 4 objectives that I wanted to cover over the next half an hour or so. The first is, I want to evaluate the optimal incorporation of the now 5 newly approved therapies in acute myeloid leukemia in the past year and a half. The second is to try to understand the role of mutations and deep sequencing in determining both the prognosis and selection of therapy for patients with AML. The third is to at least briefly discuss the role of allogeneic transplantation or blood or marrow transplantation as a consolidation therapy after AML treatment. And, the final one is just to make some comments on optimizing collaboration and supportive care because I think it's an area that we need to continue to work on in AML.

What is Leukemia?

- Greek: “White Blood”
- Cancer of bone marrow (blood-producing) cells
 - Immature/primitive BM cells, proliferative - **acute**
- Abnormal Complete Blood Count
- Short-term survival without therapy
- Prognosis varies greatly
 - Requires detailed pathology review & diagnosis

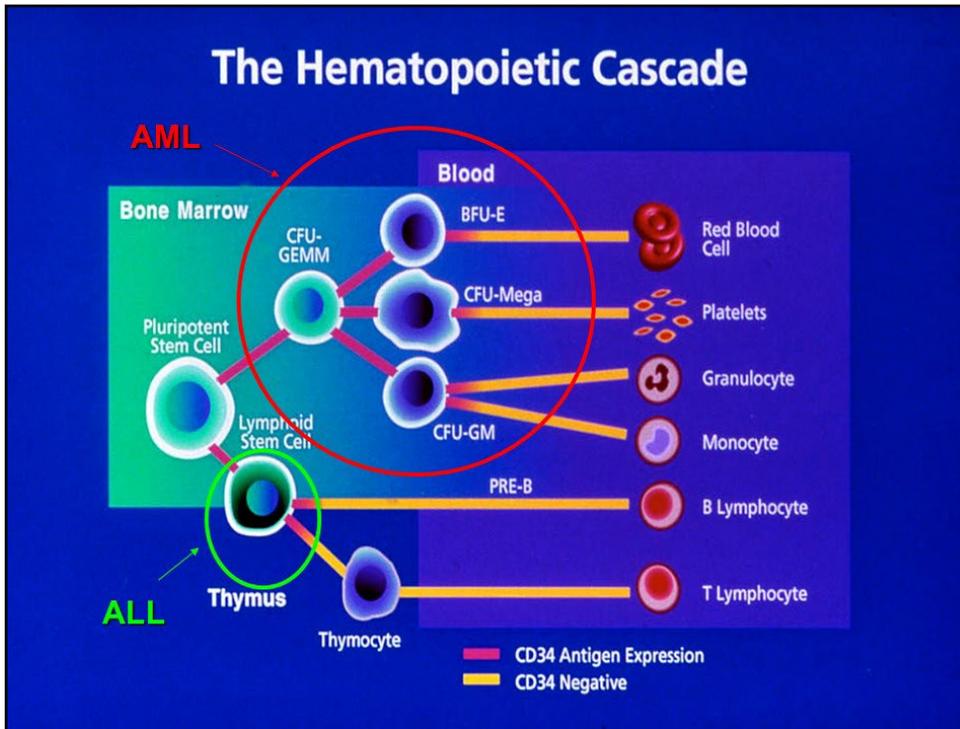


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Slide 4: What is Leukemia?

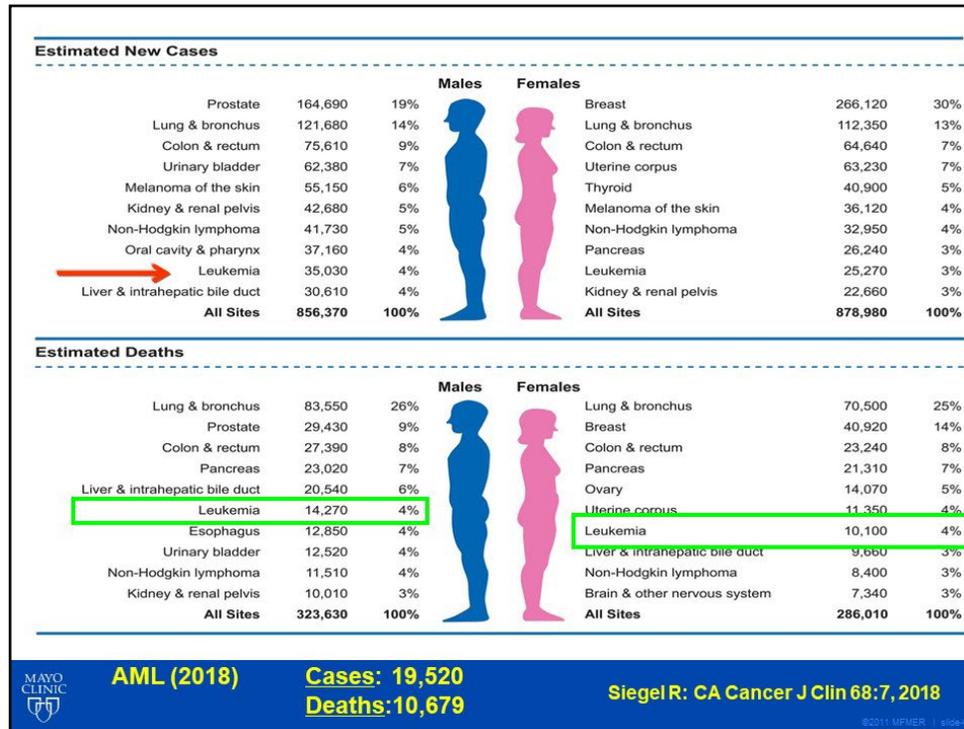
So, I'm going to start just with some comments that may seem obvious to many of you, but the first question is... What is leukemia? And, it really is a literal translation from Greek meaning white blood. It's a cancer of bone marrow or blood-producing cells. These are immature or primitive bone marrow cells that, instead of differentiating and growing into normal red cells, white cells, and platelets, are stuck because of damage or mutations at that early immature stage in the bone marrow and begin to proliferate in a cancerous fashion. And, that's why it's called an acute leukemia because of the growth of the cells.

Basically, everybody or virtually everybody with this disease will have an abnormal complete blood count or what we call a CBC. Often, you'll see a high white cell count in younger patients or even a low white cell count in older patients if the leukemia's predominantly growing in the marrow, and very commonly you'll see low blood counts with anemia, low hemoglobin or hematocrit, and frequently also low platelet count. We know that without treatment, the survival of leukemia, of acute myeloid leukemia, is short. And, so that it does need to be treated after diagnosis, usually pretty quickly after diagnosis. And, we also know that prognosis varies greatly. It requires a detailed review of a bone marrow biopsy to get to the right diagnosis and to help generate a prognosis that's specific for that person.



Slide 5: The Hematopoietic Cascade

So, I'm showing just a figure of what's called the hematopoietic cascade. That's really the growth from early bone marrow stem cells to mature blood cells. And, in the case of AML, acute myeloid leukemia arises from the cells that make red cells, white cells, and platelets, granulocytes, monocytes, or other white cells in particular, and platelets. So, it's the early stem cells in that line that turn into acute myeloid leukemia and it's whatever damages those stem cells or whatever damages those what we call precursor cells at that stage, will sometimes help determine whether your leukemia has some characteristics of a monocyte or a platelet or a red cell, even if it's an acute leukemia.




AML (2018) Cases: 19,520 Deaths: 10,679 Siegel R: CA Cancer J Clin 68:7, 2018

Slide 6: Estimated New Cases/Estimated Deaths

Now, this is information from the American Cancer Society, looking at the incidence of new cases of cancer and also deaths by cancer. And, as you will see on the slide, leukemia disproportionately contributes to cancer deaths. It's a serious disease. It's the ninth most common cause of cancer overall, but actually is either the sixth or seventh most common cause of death by cancer, mostly because of the acute leukemias. So, that is why there's been so much work, much of it, or some of it at least, funded by LLS to try to advance our treatments and outcomes in this disease. The estimates this year in the United States are just under 20,000 people will be diagnosed with the disease, but we also know that more than 10,000 will die of acute myeloid leukemia, which is why we're needing to work so hard to try to improve outcomes for patients.

Epidemiology of Leukemia Relevance in the Clinic

- The causes of cancer are largely unknown in individual patients
- Deeply relevant to patients and their families
 - “Why did this happen to me?”¹
 - Impact of the cause on the disease course
 - Risk of recurrence
 - Interventions, appropriate lifestyle changes, etc.
- Recognition of Familial Risk
- *Impact of specific leukemia risk factors on genetics, prognosis and outcome after diagnosis largely unstudied*



¹Dizon DS: ASCO Connection, 09 April 2015

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Slide 7: Epidemiology of Leukemia: Relevance in the Clinic

We don't talk about the epidemiology of leukemia in the clinic often enough, to be honest with you. Once somebody comes in with acute myeloid leukemia, the discussion focuses on what you do about it, how you treat the person in front of you, and we often don't spend a lot of time talking about how they got it or why they got it. But, it's an area that we're actively studying because we think it's very relevant for people and it's just a very common question. I think it'd be fair to say that the causes of cancer and the causes of leukemia are largely unknown in an individual. It's very hard to look back and say you got this because of some reason. And yet, it's deeply relevant to patients, it's deeply relevant to their families, and honestly why did this happen to me is one of the most common questions that you're asked. We know that the causes of leukemia can sometimes impact on the course of the disease, might even contribute to the risk of recurrence of leukemia, and in some cases could in theory, with an intervention, like a lifestyle change, if there was something that was a risk factor. And, as rare as it is, we're also starting to recognize the risk of leukemia that runs in the family, the familial risk. That's a rare thing, but a real thing that we sometimes find when we ask about family history.

AML Epidemiology

Exposures Identified in Case-Control Studies

	Relative Risk of developing AML	
Obesity	2-fold	<p>Some risk factors that have been associated with AML development identified in Population-Based Case-Control Studies</p> <ul style="list-style-type: none"> • Not proof of causality, but suggests increased risk • Further studies ongoing
Acetaminophen	1-2	
Aspirin	Lower risk ?	
Smoking	2	
Farm/Rural habitat	2	
Benzene	2-10	
Ulcerative Colitis	4	
Chemo/Radiation for other cancer	2-10	

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Ross, Cancer Epidemiol Biomark & Prev. 13:1810, 2004. Sandler, JNCI 85:1994, 1993
Sinner, Cancer Epidemiol Biomark & Prev. 14:2446, 2005. Natelson, Am J Hematol 82:826, 2007
Ross, Cancer Epidemiol Biomark & Prev. 20:1741, 2011. Johnson, Ca Caus. & Contr. 23:1083, 2012

Slide 8: AML Epidemiology: Exposures Identified in Case-Control Studies

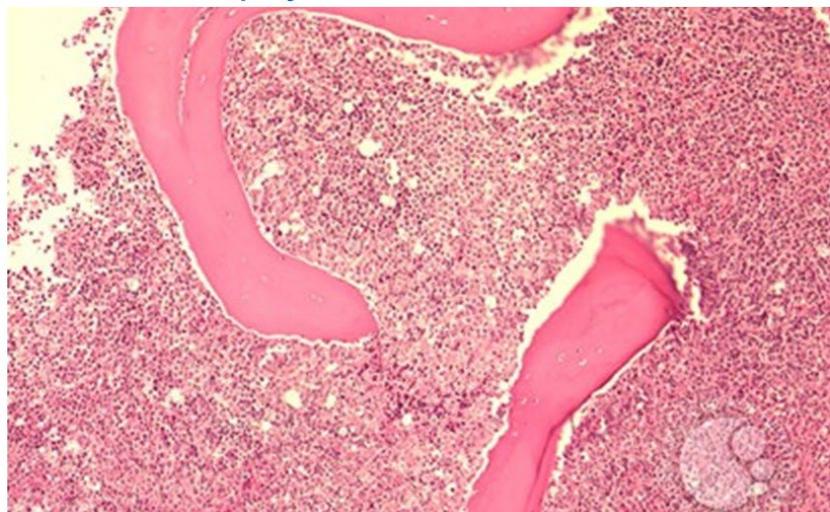
Now, it's been difficult to determine the impact of a specific risk factor for getting leukemia on the actual genetics of that leukemia or the mutations, and in many cases even the prognosis or the outcome, but one of the reasons for that is it really hasn't been studied very much and it's an area that we're trying to study going forward in some of the large clinical trials, to see if the causes of leukemia are apparent and also to see if they impact the outcome.

And, I'm showing a slide now that looks at some of the potential risk factors for leukemia that have been identified in epidemiologic studies, where they studied people who got leukemia and people who didn't and looked for differences. We think one of the biggest risk factors for leukemia actually is obesity. It about doubles the risk of acute myeloid leukemia. Some studies say that if you take Tylenol regularly it may raise your risk. If you take aspirin regularly it may lower your risk. I think that's more questionable. Smoking increases the risk of acute myeloid leukemia. And, some earlier studies, particularly done in the Midwest, suggest that if you grow up on a farm or live in a rural habitat that that also is associated with leukemia risk.

It's been well known for a long time that certain solvents like benzene, specifically benzene, can increase the risk of bone marrow damage and of leukemia. That's a controlled substance now. It's not commonly exposed in the West, but, was once upon a time. And, some recent studies also show that ulcerative colitis, inflammatory bowel disease, and indeed other autoimmune diseases might be associated with an increased risk of leukemia.

One of the most important ones is getting chemotherapy or radiation therapy for another cancer, like breast cancer for instance or lung cancer or Hodgkin's disease or one of the other lymphomas. We know that any previous chemotherapy or radiation increases the risk, and that range is 2 to 10-fold. It's quite variable. Now, these have been found in case-controlled studies, it doesn't prove it causes it, it just suggests a risk, and we're actually trying to study this going into the future prospectively to see can we actually link some of these what we call exposures or some of these risk factors with a certain strain of leukemia or a certain mutation in patients. And, we want to try to understand if this is really relevant for people.

AML BM biopsy



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Slide 9: AML BM biopsy

I'm showing a slide now of what a bone marrow biopsy looks like in somebody who's got acute myeloid leukemia. The blood counts are often low. Sometimes with a high white cell count, but often the other blood counts are low. And, instead of seeing normal functioning bone marrow, you see this bone marrow biopsy that just shows the sea of little black dots in the background of leukemia cells that have overrun the marrow and suppressing normal blood production. The large pink areas, they are just part of the bone projections in the marrow itself, but that image is really showing you a bone marrow that's replaced by acute myeloid leukemia. And, that's a very common picture, to see a hyperactive or hypercellular marrow with replacement by leukemia and what we call sheets of blasts. So, that is a typical scenario and those are the cells that we're trying to go after when we're treating patients.

Acute Leukemia

- Complications of Leukemia:
 - Infection Rapid onset, esp. if neutropenia
 - Bleeding Low platelets, low fibrinogen **DIC**
 - Clotting Hypercoagulable, even if low platelets
 - Fatigue Anemia, transfusions
 - Leukostasis “Sludging” - confusion, stroke, bleed, cardiopulmonary symptoms
- Importance of coordinated clinic evaluation & hospital care
 - **Acute Leukemia** Must see in 24-48 hours whenever possible
 - Frequently direct hospital transfer , or being admitted for urgent evaluation and initiation of treatment
 - ~4 week intensive “*remission induction*” therapy

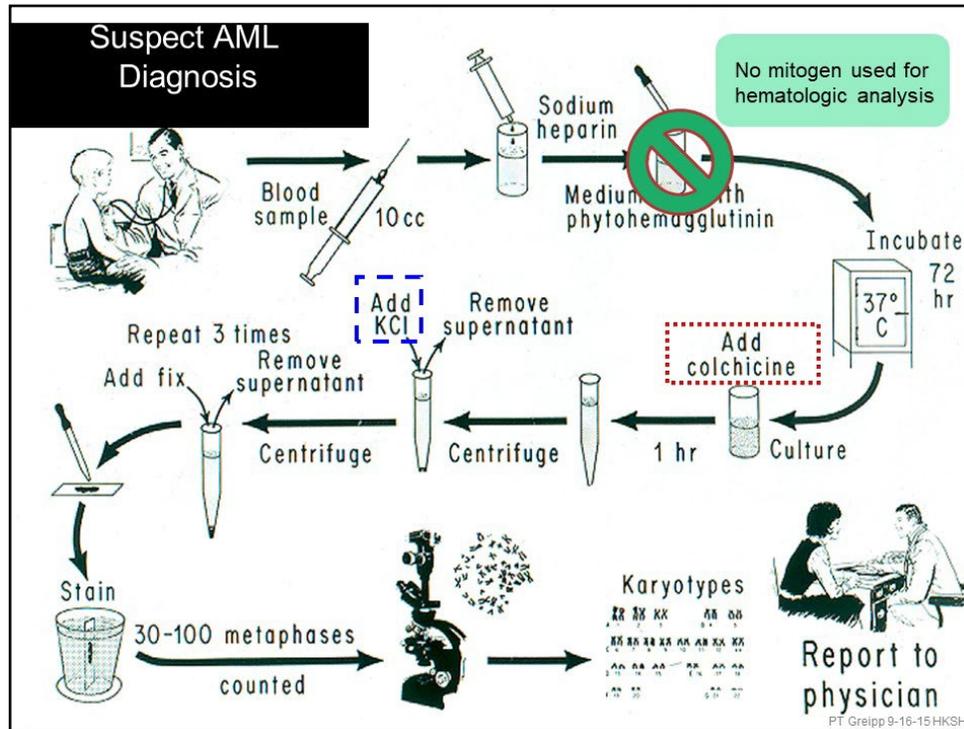


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Slide 10: Acute Leukemia

Now, I wanted to make a couple of comments early on about the complications of leukemia. These are for those of you who have this or have had this or have a family member with this, you'll be aware of some of these, but we know that infection can be a dangerous problem in acute leukemia. It can come on rapidly, particularly if the normal white cells, the neutrophils are low, we call that neutropenia. We know that bleeding is a common problem from low platelets, or sometimes the clotting system is activated, where the fibrinogen goes low, we call that DIC. We know that even when the platelets are low, paradoxically you can be at high risk for a blood clot, just because having leukemia is hypercoagulable or has an increased tendency to blood clots. Fatigue is a common symptom, often related to anemia, although that's something we can address, largely with transfusion. And, a complication of leukemia when the white cell count goes very high is called leukostasis. It's where the blood starts to sludge because the leukemia cells are sticky, and they actually start to stick in the small blood vessels, in the lungs, in the brain, where you can get confusion or stroke, bleeding, shortness of breath, even chest pain. Those are reasons to move very quickly to try to lower the white cell count with a treatment called leukapheresis or with some pills called hydroxyurea.

But, the point I'm really trying to make is it matters that patients seek attention and that we begin to address these problems very quickly in the first 24 to 48 hours when the diagnosis is suspected. It's done in a coordinated fashion with a care team. It's really best done at a center that does this regularly, has experience in leukemia, or is a specialty center. In my experience, it's frequently a patient who is at an outside hospital and is transferred directly to us or we get an urgent phone call that this is somebody with suspected leukemia and we expedite seeing them as quickly as possible to try to initiate treatment. And typically, if they're younger and fitter, we are admitting them to hospital to try to get them into remission or what we call remission induction therapy, which is often about 4 weeks in duration. So, if there's a suspected acute leukemia, we're trying to address these problems and move very quickly.



Slide 11: Suspect AML Diagnosis

One of the important tests that we do early on is evaluating the cytogenetics of a patient. Now, cytogenetics or karyotype is an evaluation of the chromosomes in the blood cells. And, chromosomes are the structures that your DNA lives in. They're numbered from the biggest, which is chromosome 1, to the smallest, which is chromosome 22, and then there's either an X or Y chromosome. And so, it's complicated to do this, we take a blood or bone marrow sample, incubate the sample for up to 3 days, it goes through a series of washings, it then gets treated with a medicine called colchicine or something like colchicine to stop those cells right as they're growing and dividing, so that we can pull out the chromosomes and stain them and analyze them and determine if there is damage in the chromosomes and where that damage is. Because, we have learned that the pattern of damage, if it's present on the chromosomes or in the cytogenetic sample, will often predict how sensitive is that leukemia going to be to particular treatments, and will often guide our treatment strategy going forward.

Cytogenetic Testing

Chromosome analysis

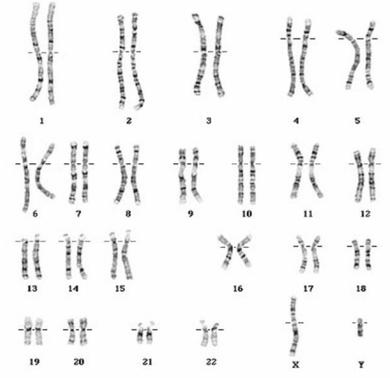
- requires dividing cells
- whole genome coverage
- low resolution (~5 Mb)

FISH analysis

- does not require dividing cells
- site-specific
- higher resolution (~100 Kb)

Microarray analysis

- does not require dividing cells
- whole genome coverage
- 2.6M copy number markers
- 750k SNPs
- high resolution (~25-50 Kb)



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Cytogenetic Testing

Chromosome analysis

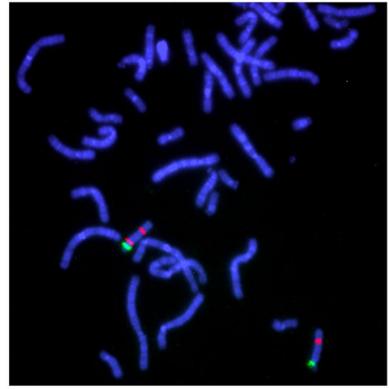
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- high resolution (~25-50 Kb)



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Cytogenetic Testing

Chromosome analysis

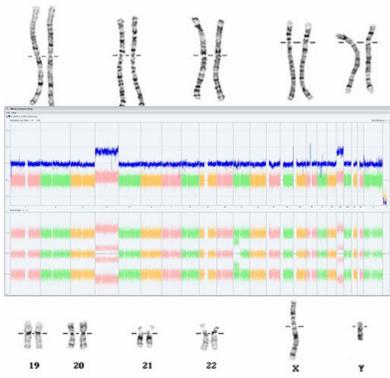
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FISH analysis

- does not require dividing cells
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Microarray analysis

- does not require dividing cells
- whole genome coverage
- 2.6M copy number markers
- 750k SNPs
- high resolution (~25-50 Kb)



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PT Greipp 9-10-15 HKSH

Slide 12: Cytogenetic Testing

I'm showing a slide now and these were both sent to me from the cytogenetics of Mayo Clinic from one of my colleagues, Patty Greipp, showing just an example of some chromosomes. To do chromosome testing you have to have dividing cells. It gives you a picture of the overall chromosome, but you would miss a very small abnormality. You would see a large abnormality, but you'd miss something small. Sometimes we do some fluorescent stains or fluorescent molecular probes called FISH, to look for very small abnormalities that have been seen before in AML. And, we can do that without having dividing cells. And, we get higher resolution. And, there's even a more sensitive test called microarray analysis that we sometimes do to look at different sites across all the DNA in the bone marrow cells. But, what's being done more and more now is called next generation sequencing or DNA sequencing, to evaluate for mutations. And, I'll come back to that in just a second about what mutations are and how we address them.

Mutations

- *A change that occurs in our DNA sequence, either due to mistakes when the DNA is copied, or as the result of environmental factors (e.g. UV light, or cigarette smoke)*
 - Typically 'acquired' in certain cells
 - Can be inherited ('germline')
- May disrupt normal gene activity and cause diseases, like cancer
- Can contribute to prognosis with standard therapies
- * Some gene mutations that involve a unique cell process can be targeted

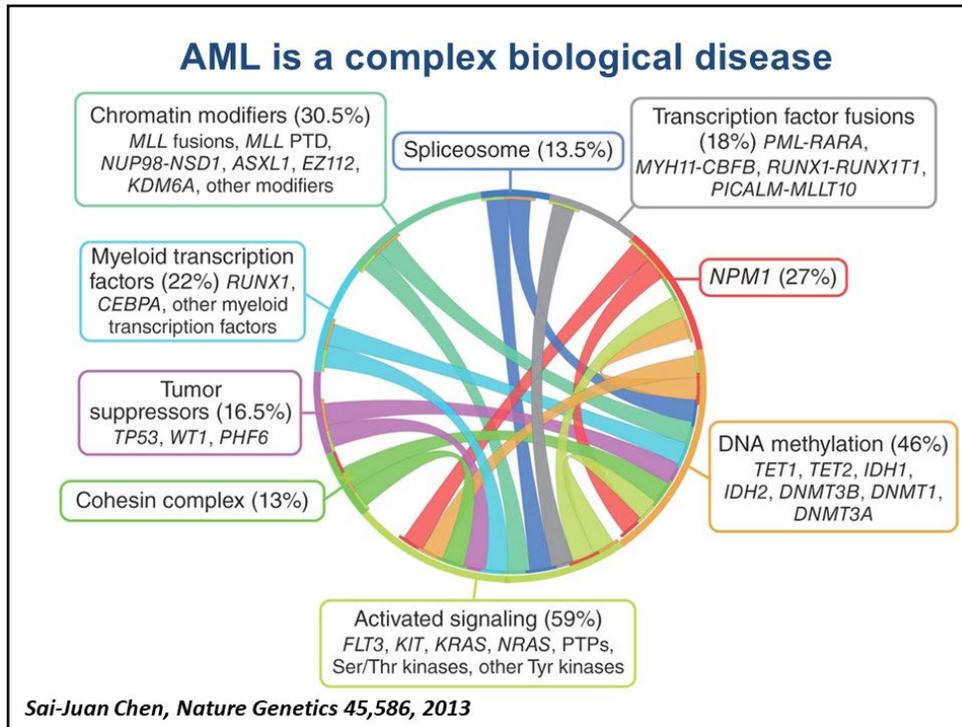


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Slide 13: Mutations

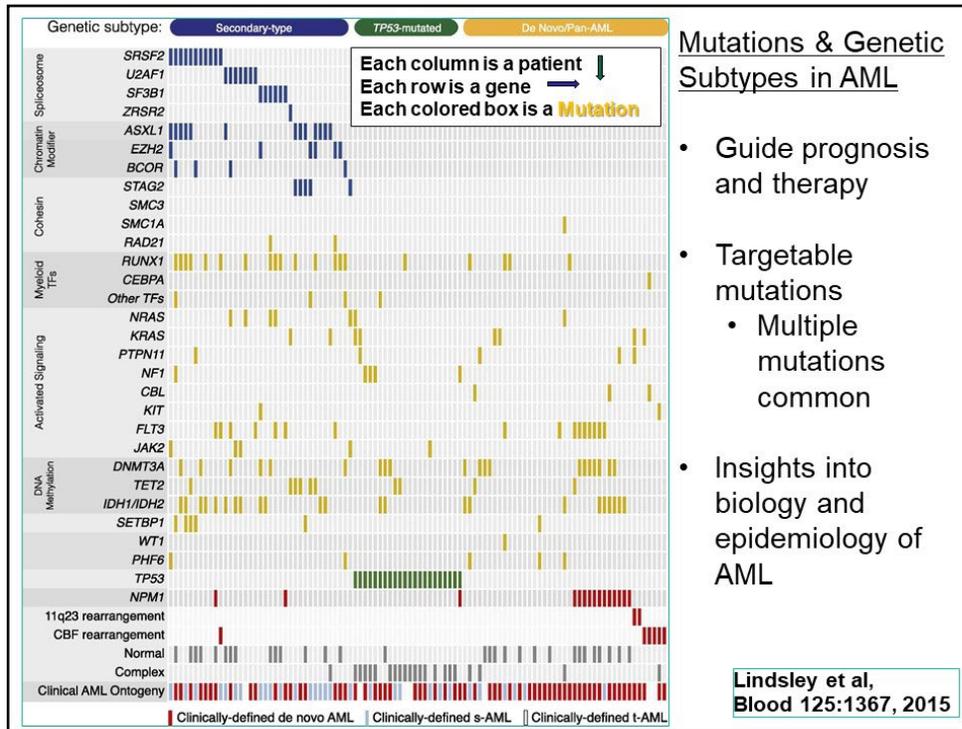
Now, mutation is a widely used word, but in this case, and scientifically, really refers to a change in the DNA sequence, either by a mistake, when the DNA is copying, when cells are dividing, or as the result of environmental factors, such as UV light exposure or cigarette smoke or previous treatment with radiation treatment where you can see some DNA sequence changes and mutations developed. And, it's typically acquired where you have a normal cell that becomes damaged and has a mutation in it. You can have an inherited mutation, it's called a germline mutation, that's rare in AML. But, most cases and the large majority are acquired. It's not something you're born with, it's just something that happens over time. And, the problem with that mutation is it disrupts the normal activity of that gene, whether it's making a protein or doing some function in the cell. And, by disrupting that activity, just by having a change in DNA sequence at that one spot, it can contribute to diseases like cancer, like leukemia, or sustain them or cause them to grow.

We know it contributes to prognosis. Some mutations are more aggressive than others or easier or harder to treat than others with standard therapies. But, there are some mutations that we can actually target now with some of the new treatments that have been approved by the FDA and studied, and other ones that are being studied, as long as that mutation involves a unique cell process that we can go after. So, having a mutation tells you that yes, it's part of the cancer and explains some of how the cancer might have developed, but sometimes gives us something we can target or at least gives us an idea of the prognosis for that person. It's very common now to do mutation testing.



Slide 14: AML is a complex biological disease

One of the problems in AML with doing mutation testing is that AML is very complex. We don't usually just see one mutation. You often see multiple mutations. And, as you can see in this figure, the mutations often travel together and they involve different processes in the cell, whether it's signaling for the cell, whether it's how DNA is read, sometimes mutations involve genes that suppress cancer and if you have a mutation in that gene, like a TP53, the leukemia can grow more easily, sometimes they're just involved with how DNA is spliced or how DNA is read, such as with a transcription factor or a spliceosome mutation. And so, that these will often travel together, and you can see examples of that where under spliceosome you see the blue line go over to activated signaling, to show you that they'll often occur together at the same time. So, going after one mutation is sometimes a little more difficult, or at least you want to know which is the driver mutation, before you really make a decision about how you're going to treat that patient.



Slide 15: Mutations & Genetic Subtypes in AML

And, this is a more common example about how we think of it. This is a list of genes, this is in 1 study, but it's a very common list of genes for us to look for mutations in. And, we break the different genes. Each row is a gene. Each column in this case is a patient. And, every time you see a colored box it tells you there's a mutation in that gene in that patient. And, if you go down from the top, you see many patients will have multiple mutations in different genes. They guide prognosis, they help guide therapy. Sometimes, like with an IDH mutation, that I'll talk about later, they can be targetable. But, it's also common to have multiple mutations because AML is a little more complicated. And, importantly for us, it gives us insight into the biology of the disease, the epidemiology or potential causes of it, and many of these are targets that we're studying to come up with better treatments for when we see this mutation in the future.

A complicated part of this is it means that not everybody's leukemia is the same. Every person's leukemia, just like every person's path is their own, will often have different mutations and sometimes that makes it harder to generalize about a treatment strategy or a prognosis in patients with AML.

AML biology predicts response to cytarabine + anthracycline chemotherapy

Risk status	Cytogenetics	Molecular abnormalities
Better risk	inv(16) or t(16;16) or t(8;21) without <i>c-KIT</i> mutation, t(15;17)	Normal karyotype with <i>NPM-1</i> mutation in the absence of <i>FLT-3</i> ITD or Isolated biallelic <i>CEBPα</i>
Intermediate risk	Normal karyotype Trisomy 8 alone t(9;11) Other not defined	t(8;21), inv(16), t(16;16) with <i>c-KIT</i> mutation
Poor risk	Complex (≥ 3 clonal abnl) Monosomal karyotype -5, 5q-, -7, 7q- 11q23 (not t(9;11)) Inv(3), t(3;3) t(6;9), t(9;22)	Normal karyotype with <i>FLT-3</i> ITD mutation



Adapted from NCCN Guidelines. Acute Myeloid Leukemia

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Stage 16: AML biology predicts response to cytarabine + anthracycline chemotherapy

So, at the beginning we do a bone marrow biopsy, we send off a sample to look at the chromosomes or the cytogenetics. We'll always try to get a sample when possible for DNA testing, for the DNA sequencing or next generation sequencing. And, then we break patients into groups as to whether their leukemia is better risk, or intermediate risk, or poor risk. So, some of the better risk abnormalities, called core binding factor leukemias, will have chromosome 16 abnormality or 8;21 abnormality. And, we know that's when chemotherapy is more effective. In the intermediate risk group, that's people who have normal karyotype or normal cytogenetics, or sometimes just an isolated abnormality like chromosome 8, an extra copy of that called trisomy 8. That's an intermediate risk group where we have a reasonable chance of getting a remission and a cure with chemotherapy alone, but sometimes we'll break it into better or worse intermediate to decide whether we should do something further. And then, the poor risk group are for patients where we see complex damage in the chromosomes or a mutation, as you can see on the right, and a gene called FLT-3, a mutation called an ITD, where we know that regular chemotherapy is not as effective and we're often looking for new therapies or even bone marrow transplants to increase the chance of cure. So that, the chromosomes and the mutations together help us plan treatment with the person, with the patient, based upon the risk profile, to come up with the best chance of controlling it and, if we can, curing it.

Principles of AML Treatment

- Improve symptoms and suffering from AML
- Cure whenever possible
- Treatment is better than no treatment for almost all patients
- Allogeneic transplant

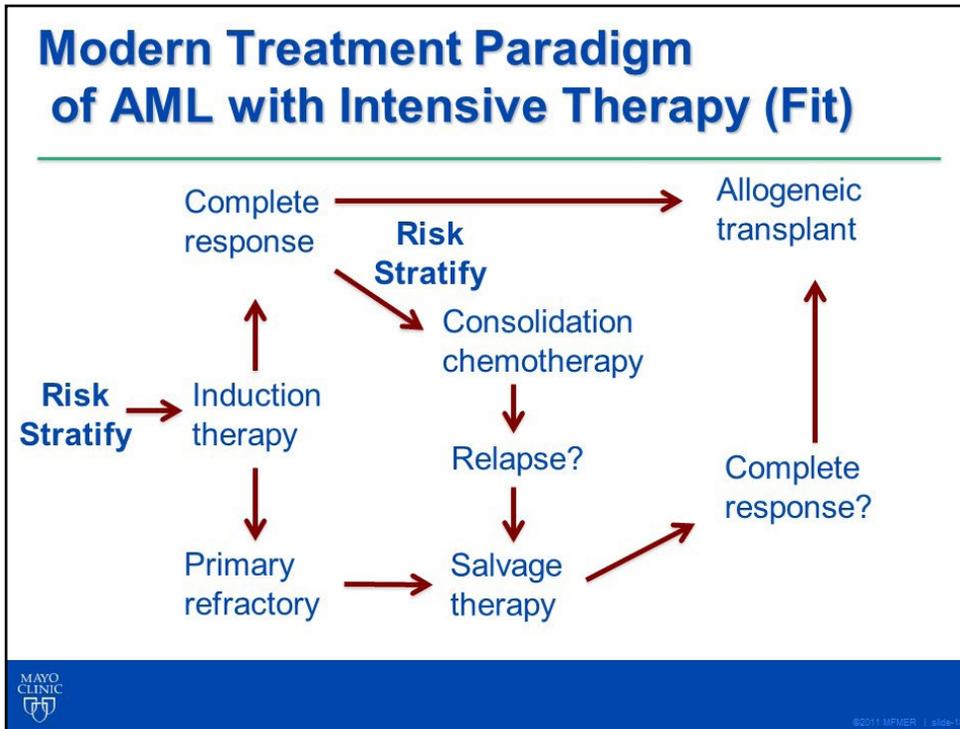


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Stage 17: Principles of AML Treatment

Now, just a couple of very simple statements on what are the principles of treatment of AML. They're obvious honestly. The first is you want to improve symptoms, you want to improve suffering, you want to get somebody better. That means treating an infection, transfusing them if they need that or they're willing to take antibiotics of course, and, whatever other things we can do to help them with their symptoms. If they're dehydrated, we give fluids, etc. Whenever we think we have a chance of cure, we're always thinking of that first. The only time we'd ever put somebody through a really hard treatment, like some of the chemotherapy we use, is because we need to get control, because they're facing an immediate danger, and because we're trying to cure them.

We know as a generalization that treatment is better than no treatment for almost all patients. I'm going to come back to this later, but even if someone is much older, 85 years old, or not very fit because they have heart failure, some low-dose treatment is better than no treatment at all because we know it helps alleviate suffering and helps people live longer in almost all cases. And, we know that allogeneic transplant or a blood or marrow transplant from a donor, either matched or related or unrelated or even partially matched, gives us the best chance of preventing a relapse, but you have to get the leukemia into remission first.



Slide 18: Modern Treatment Paradigm of AML with Intensive Therapy (Fit)

And, the next slide goes through just a brief animation about what is the modern treatment paradigm, what is the modern strategy for AML. Well, the first thing you do, you risk stratify. By that I mean, you decide based on the cytogenetics, the fitness of the patient, are they someone you can cure with regular therapy or do you have to use a low-dose treatment. So, you give them some kind of remission induction, based on their risk, to try to get the patient into remission. That's the very first important step. If they have a complete response where the marrow looks clear, the blood counts normalize, then we go on to either consolidation chemotherapy, if they've got a leukemia that we think, based upon the genetic testing, is likely to benefit from that. Or, if it's a very high-risk leukemia and we don't think that the chemotherapy gives a good enough chance of cure, we'll talk about a bone marrow transplant or blood or marrow transplant, called allogeneic transplant. Alternatively, if they get induction therapy, but it does not go into remission, what we call refractory leukemia, then we'll give them a backup treatment, called a salvage therapy. Now, they're heavy and they're harder, but they're designed to try to get a resistant leukemia into remission. If they go into remission or if they were in remission before and they relapsed, that person will go into salvage therapy and as long as they go back into a complete response, we will try and cure them at that point with a bone marrow transplant, which is really the best strategy. So, that remains the modern paradigm or the modern strategy for how we treat AML, but there's a lot of detail in there about what treatments we use, what drugs we use, and how do we individualize that treatment for patients.

Treatment of Acute Myelocytic Leukemia: A Study by Cancer and Leukemia Group B

By Kanti R. Rai, James F. Holland, Oliver J. Glidewell, Vivian Weinberg, Kurt Brunner, J. P. Obrecht, Harvey D. Preisler, Ismat W. Nawabi, David Prager, Robert W. Carey, M. Robert Cooper, Farid Haurani, J. L. Hutchison, Richard T. Silver, Geoffrey Falkson, Peter Wiernik, H. Clark Hoagland, Clara D. Bloomfield, G. Watson James, Arlan Gottlieb, S. V. Ramanan, Johannes Blom, Nis I. Nissen, Arthur Bank, Rose Ruth Ellison, Faith Kung, Patrick Henry, O. Ross McIntyre, and Sze K. Kaan

In a randomized study of acute myelocytic leukemia (AML), 352 patients of all ages were treated for remission induction by one of the four regimens: 7 days of cytosine arabinoside (ara-C) by continuous intravenous (i.v.) infusion or bolus injection every 12 hr, together with daunorubicin (DNR) by rapid i.v. injection on days 1, 2, 3; or 5 days of ara-C by infusion or bolus injection and DNR for 2 days only. The regimen of 7 and 3 infusion was significantly superior to the other 3 regimens, resulting in 56% complete remission (CR). For remission maintenance, ara-C was given for 5 days every month and each month one of the following four drugs added on a cyclic rotational basis: thioguanine, cyclophosphamide, CCNU, or DNR. Although ara-C dosage each month was the same, the route of ara-C

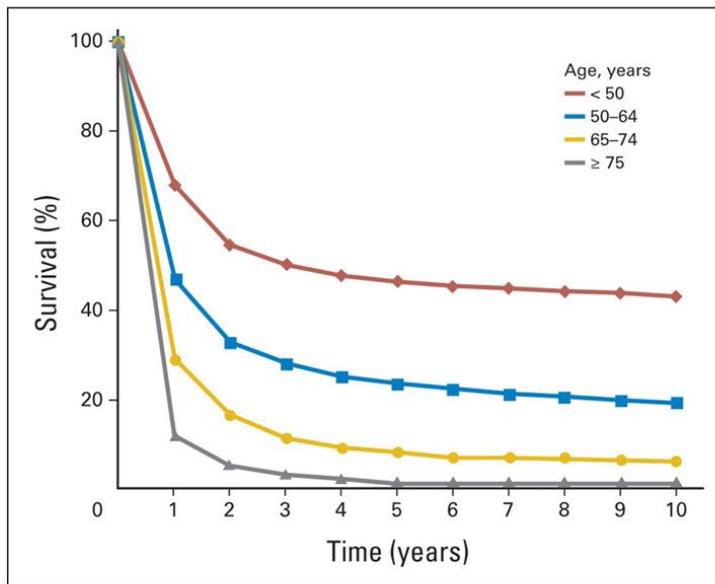
administration by random allocation was either rapid i.v. bolus or subcutaneous (s.c.) injection. The median duration of CR was significantly longer for s.c. ara-C group: 14 mo for patients less than 60 yr old (versus 8 mo for i.v.) and 31 mo for 60 or older age group (versus 9 mo for i.v.). Patients who received a combination of the best of the four induction regimens (7 and 3 infusion) and the better of the two maintenance schedules (s.c. ara-C) had a median remission duration of 22 mo and a median survival of 35 mo (the longest reported in a prospective randomized trial of therapy for AML). These results establish the validity of an intensive chemotherapy to produce rapid marrow aplasia followed by a sequential maintenance therapy for achieving prolonged disease-free survival in AML.

- First large randomized study
- Established '7&3' (Daunorubicin & Cytarabine) as the standard remission induction therapy in younger adults

Rai et al, Blood 58:1203, 1981

Slide 19: Treatment of Acute Myelocytic Leukemia: A Study by Cancer and Leukemia Group B

Now, we have been using the same type of chemotherapy, what we call 7 and 3, 7 days of cytarabine and 3 days of daunorubicin, since 1981. This is a figure or at least a picture from the first publication of a randomized study showing the potential benefits in patients with AML of daunorubicin and cytarabine induction, and that remains our standard therapy for younger patients or fit patients. But, we know it doesn't work for everybody.



Relative survival by time and age for Acute Myeloid Leukemia based on SEER data.

Klepin H et al; *Journal of Clinical Oncology* 32:2541, 2014

Slide 20: Graph: Survival Curve

And, I'm going to show you one survival curve. I don't love showing survival curves because they can often look quite scary if you don't have the right context. But, this is just to show you, this is more historical data, this is from 4 years ago, looking back in time from then at outcomes on the National Cancer Institute's SEER (Surveillance, Epidemiology, and End Results) database, about what is the relative survival for somebody diagnosed with acute myeloid leukemia based on their age. And, you can see in the top, on the top curve, that there's about a 50% chance back then of 10-year survival if you were under 50. There's somewhere around a 25% chance up to the age of 65. But, in older patients over 65 we know those numbers drop. Partly because, it's harder to treat older patients and they don't tolerate the treatment well and partly because, they get a more difficult leukemia that sometimes has more mutations or more complicated cytogenetics and therefore is not as sensitive to chemotherapy. But, that is the historical experience that we're trying to improve upon and there are several new medicines that are showing steps forward and that I think are really improving our chances on a person-by-person basis of getting a remission and getting a long-term cure whenever possible.

Advances in 1st line Intensive Treatment

- **Vyxeos™** - New chemotherapy formulation for 'secondary AML' (arising after prior chemo or radiation, or prior BM disease such as MDS)
- **Mylotarg™** – Antibody targeting a common leukemia cell surface marker called CD33, linked to a toxin -'immunotoxin'
- **Midostaurin (Rydapt™)**– oral inhibitor for FLT3 mutations

**Applies to younger (<75 yrs) and 'fitter' patients*



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Slide 21: Advances in 1st line Intensive Treatment

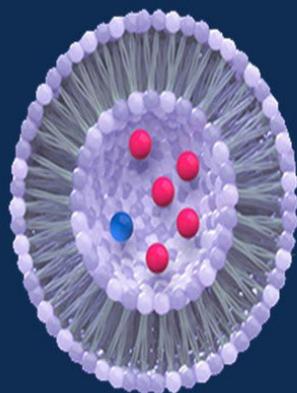
Now, there are 3 new strategies, 3 new advances, in the first-line intensive treatment of AML. The first is a new chemotherapy called Vyxeos™ or CPX-351. And honestly, it's not really a new chemotherapy. It's daunorubicin and cytarabine, but it's put together in a little lipid formulation, that actually makes it more effective when it's formulated this way. They did a randomized study in patients with secondary acute myeloid leukemia, that's leukemia arising after previous chemotherapy or radiation treatment or a previous bone marrow disease, such as myelodysplastic syndrome, and showed a significant advantage that I'll just go over with you in a moment after this slide in that setting. So, if somebody has secondary leukemia arising from some previous treatment or some previous blood disorder, then Vyxeos looks like it's the best option at the moment and gives better odds.

There's an older antibody against AML called Mylotarg™ or gemtuzumab. It's an antibody targeting a common marker on the cell surface of AML called CD33, and this antibody is linked to a toxin called calicheamicin. So, when you give it intravenously it actually binds to the leukemia cell and introduces that toxin directly into the leukemia cell. Now, we had this available from 2000 to 2010 in relapsed patients, but it had a lot of side effects. It was taken off the market voluntarily just because it was hard to show at the time it was really helping a lot of people. But, some follow-up studies showed that if you gave it with chemotherapy in the first-line setting and at a lower dose, it was much better tolerated, it was much safer to give, and it improved the survival for patients. So, it is back, approved again as of last year in certain situations.

And, the third new advance is a drug called midostaurin. It goes by the trade name Rydapt™. This is a pill. It's an oral kinase inhibitor for patients who have FLT-3 mutations and I'll tell you about FLT-3 mutations in just a moment. That's one of the common mutations you see.

I do have one little star in the bottom of this slide just to remind you that first-line intensive treatment really refers to younger patients, under 75, who are fit, in good shape, just because you have to be strong enough to get through the treatment to get the benefits.

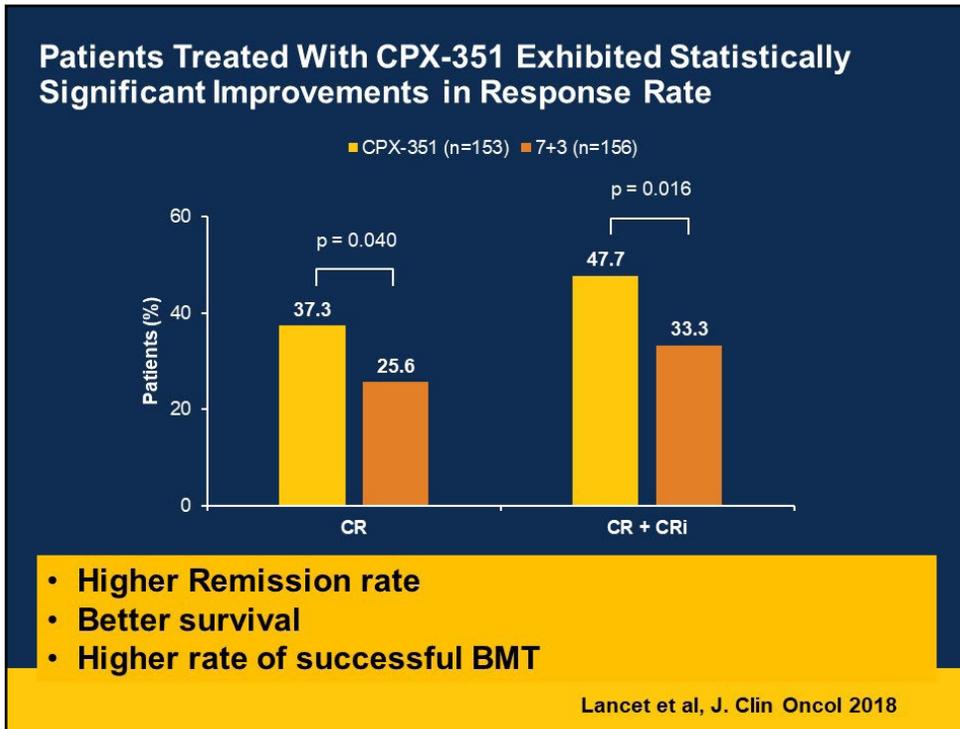
CPX-351 Uses a Nano-Scale Delivery Complex



- 100 nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin
- 1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin

Slide 22: CPX-351 Uses a Nano-Scale Delivery Complex

Now, this is a figure just showing you how this Vyxeos drug or CPX-351 works. They actually take daunorubicin and cytarabine and mix them together in a fixed concentration, put it inside a little lipid membrane and give it intravenously, so that when the chemotherapy is delivered to the leukemia cell it's delivered in the right ratio of the 2 drugs together because they work best in that ratio.

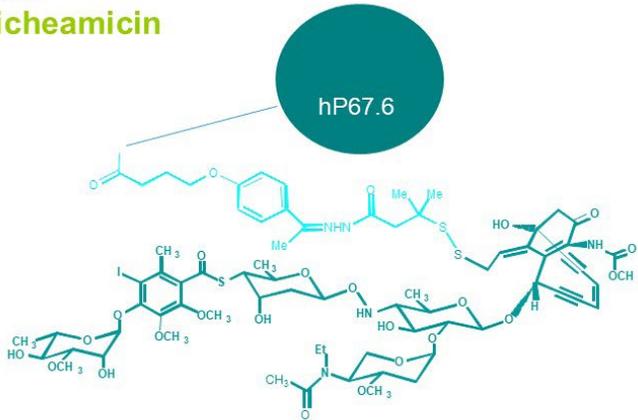


Slide 23: Patients Treated With CPX-351 Exhibited Statistically Significant Improvements in Response Rate

And, in the randomized study that was just published a few months ago, the patients who got this had a higher overall complete remission rate by about 14% if you include complete remissions and complete remissions with residual low platelets. They had better overall survival. They had a higher rate of going on to a successful bone marrow transplant afterwards. So, in the patients who have secondary leukemia who went on this study, there was a significant advantage and the FDA approved the drug for that use, it's now being commonly used at our centers and many nationally in that setting.

Gemtuzumab-ozogamicin (Mylotarg™)

- hP67.6 - humanized anti-CD33 antibody
- Linker
- Calicheamicin



Slide 24: Gemtuzumab-ozogamicin (Mylotarg™)

The second new treatment I mentioned already is this antibody called an immunotoxin, Mylotarg or gemtuzumab ozogamicin. It's a humanized antibody against a marker on leukemia cells called CD33, has a linker to a toxin called calicheamicin and it's given intravenously.

Gemtuzumab Ozogamicin (Mylotarg™)

- Benefit in significantly lowering the relapse rates by approximately 10-15%
 - Day 1,3,5 added to 7&3 intensive chemotherapy
- Most benefit in patients with 'Better' or 'Intermediate' risk cytogenetics
 - Probably not helpful in 'Adverse' cytogenetics
- Must watch for Liver toxicity, especially in patients who may ultimately go to allogeneic transplant
 - 'VOD' – veno-occlusive disease, a post-BMT complication



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Slide 25: Gemtuzumab Ozogamicin (Mylotarg™)

And, in the randomized studies, there was one done in France and there were two of them done in the United Kingdom, it showed a benefit overall in lowering the relapse rate by 10 or 15%. When they lowered the dose of the chemotherapy and gave it on days 1 and 3 and 5, with the 7-day induction therapy, it was much better tolerated, there was no significantly higher rate of bad side effects in patients, and significantly improved outcome. Most of the benefit was in patients in the better cytogenetic group or the intermediate group. Didn't seem to help in the adverse cytogenetic group very much. So that, if somebody had adverse cytogenetics this is probably not something that would be worth the extra cost or even potential side effect because it doesn't seem to help very much there. And, even though it's much less of a problem at the low dose now, you still have to watch for any liver toxicity side effects on the blood test, and that's particularly true if someone's going to go to a bone marrow transplant afterwards, because there's a post-transplant complication called VOD, veno-occlusive disease. This can contribute to that, and so you want to have at least a 2, 3-month period after treatment before transplant to make sure those effects wear off. And, that's become a standard thing to consider.

What is FLT3?

- FLT3 is an important growth factor receptor
- Necessary for normal signaling and growth of bone marrow stem cells

- **Flt3 mutations:** approximately 30% of AML patients
 - Causes abnormal leukemia signaling & proliferation
- Independent adverse prognostic factor, contributes to relapse

Gilliland, Blood 100:1532, 2002

Nazha, Haematologica 97:1242, 2012

Slide 26: What is FLT3?

The third new treatment I mentioned for initial therapy of AML is midostaurin, which targets FLT-3. So, this is a picture of FLT-3. FLT-3 has got these 5 little loops on the outside of the cell, a little area that goes across the cell membrane, and the 2 blue boxes on here are the signaling part of FLT-3. And, you can get mutations right where it comes across the membrane, it's called an internal tandem duplication or an ITD, in almost a quarter of patients. Another 5 to 8% can have a mutation called a D835 mutation, right where the signaling part of the protein is. Now, we all have FLT-3, it's an important growth factor receptor in our bone marrow cells and it turns on and off when it's supposed to. But, when you have a mutation, the FLT-3 gets stuck in the on position, gives a constant downstream signal for those cells to grow. So, it actually causes leukemia signaling, leukemia growth, leukemia proliferation. And, when you have a FLT-3 mutation, especially an ITD mutation, it's an adverse prognostic factor. It contributes to relapse, and we know that's a more difficult leukemia. But, that's an area where there's a new drug and that drug is midostaurin.

FLT3 Inhibitors

- Bind to mutated FLT3 receptor to 'shut down' signaling
- **Midostaurin** - ~10% advantage in survival in large randomized study if FLT3 mutation
 - *FDA-approved* in 1st line with 7&3 chemotherapy
- **Sorafenib** - possibly helpful with low intensity chemo
 - Not FDA-approved in AML
- In development for **relapsed** AML with FLT3 mutation
 - **Quizartinib** - superior survival to chemotherapy alone, targets the most common FLT3 mutations
 - **Gilteritinib** – complete remissions, targets both FLT3 mutations



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Slide 27: FLT3 Inhibitors

Now, there are several FLT-3 inhibitors that will soon be available. Midostaurin is now available and FDA approved. It binds to the mutant version, the mutated version of FLT-3. Offers about a 10% survival advantage in a large randomized study, as long as patients had a FLT-3 mutation, and has to be given with chemotherapy, where you start it for 2 weeks, the day after your chemotherapy ends. And, it's now been standard for patients to start this if they have a FLT-3 mutation.

There's also an older medicine called sorafenib that wasn't designed as a FLT-3 inhibitor but has some FLT-3 activity. And, there've been some studies, predominantly from Houston at MD Anderson Cancer Center, that show that it might be helpful with low-intensity chemotherapy. Although, it's not approved by the FDA in AML, it is in other diseases.

There are 2 new treatments. I'm not going to talk a lot about them because they're not FDA approved yet, but 2 new pills that we think might become available in the next 6 or 12 months for patients with relapsed leukemia with a FLT-3 mutation. One's called quizartinib, which actually looks like it might be better than chemotherapy for relapsed leukemia with a FLT-3 mutation. And, the other is called gilteritinib. It can induce complete remissions in relapsed leukemia. It targets both of the FLT-3 mutations, not just the ITD, and we're going to wait and see if this becomes available, but I think that will be a step forward for that almost one-third group of patients who have a FLT-3 mutation.

Principles of Incorporating New Agents

- Patients should be receiving new drugs, but it should be *on label*, and we must be thoughtful and selective
- New agents should not be routinely combined until there is data showing safety and superior outcomes
 - allowing for exceptional case-by case scenarios
- There is still a group for whom standard 7&3 is appropriate
- If possible, await FLT3 status and cytogenetics whenever possible **before** starting therapy
 - Not always possible to expedite these tests, therefore sometimes must start therapy with 'best guess'



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Slide 28: Principles of Incorporating New Agents

Now, it's kind of a complicated question about how do you incorporate these 3 new agents? You've got 3 new medicines that you can give for first-line induction therapy. They're all expensive. And, you want to make sure you're giving the right medicine to the right patient to get the best benefit for them, and you really want to be cost-conscious, too, that you want to be thoughtful and selective when you're using these. I think patients should be getting these new drugs. I think they're a step forward. But, it should be done in the way they were studied, and it should be done thoughtfully and selectively.

So far, we don't have a lot of information about combining the new agents, so we're not doing that routinely except in very exceptional circumstances. Frankly, there's still a group of patients for whom none of these drugs is going to help very much and the standard 7 plus 3 is still the right thing to do. But, the punchline here is that you really want to send off your tests very early on and try to wait anywhere from 2 to 5 days if you can, or even up to 7, if the person's fit enough and well enough, to find out do they have a FLT-3 mutation, do they have the kind of cytogenetics that would help them benefit from one treatment or another because you really want to pick the right thing for that person.

Problem is that leukemia doesn't always behave, and it doesn't always cooperate, and so you cannot always wait and sometimes you have to make your best guess at the beginning. However, the recommendation from NCCN (National Comprehensive Cancer Network®) Leukemia Panel, I'm a member of that panel, we debated this extensively, is that whenever possible we should try to hold off on initiation of treatment in a stable person with stable leukemia to get the information, because once you've started treatment you're kind of stuck with that and you're in it and it's hard to go back and revisit that.

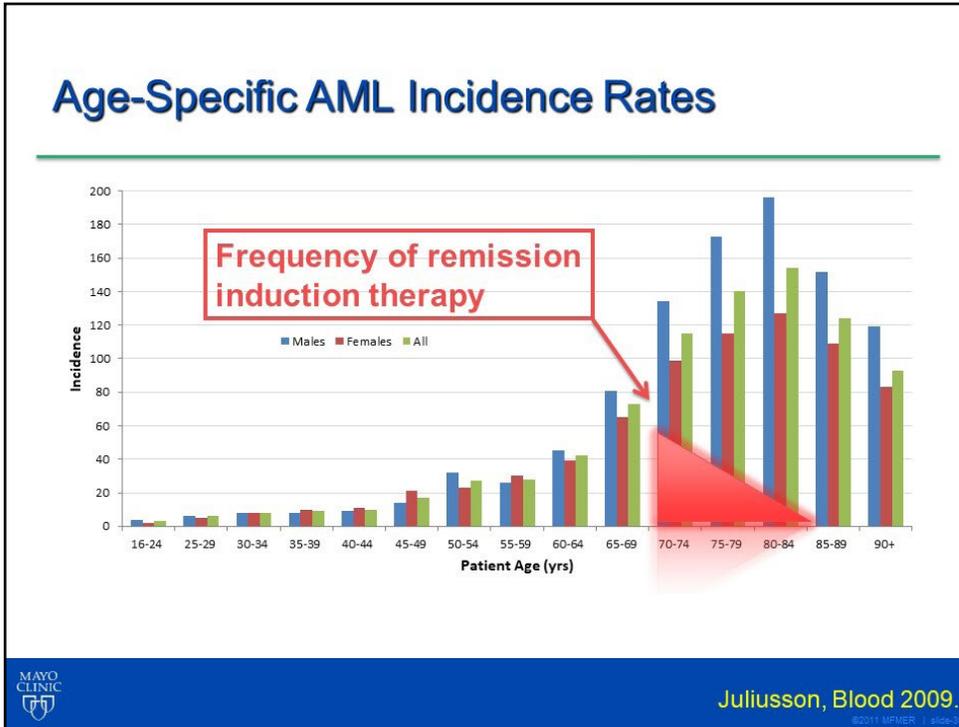
Proposed Mayo Clinic Treatment Guidelines incorporating new agents

	Age	Population	Cytogenetics	Dosing	BMT Candidate
Midostaurin	Any	FLT3 mutation	Any	D8-21	Yes
Vyxeos™	Any (60-75 years)	Therapy-related or secondary AML, prior MDS	MDS-related cytogenetics	D1,3,5	Yes
Gemtuzumab	Any	CD33+ve	Any (not 'adverse')	D1,4,7	Yes
Standard 7&3	Any	CD33-neg	Adverse; or if CD33-negative		Yes



Slide 29: Proposed Mayo Clinic Treatment Guidelines incorporating new agents

And so, this is a slide you can look at afterwards or download afterwards, just showing how at Mayo Clinic across the 3 Mayo sites in Minnesota, Florida, and Arizona, we've decided to incorporate these new medicines based upon what mutation they have and what cytogenetics and whether they're a transplant candidate. And, you can look at this table yourself, this is very common to guidelines that are being drafted at other institutions as well.



Slide 30: Age-Specific AML Incidence Rates

Now, a really important thing to say is that not every patient can tolerate intensive chemotherapy. When you look at the incidence of AML, when you look at the age that people get it, we know that this is much more common in older patients. The median age is somewhere between 67 and 72. And, we focus a lot on younger adults, but really there's also a large population of older patients or senior patients with acute myeloid leukemia. And, we also know, I'm going to animate this slide just to show you, this is an estimate that over the age of 70 it's less and less likely someone's going to be strong enough or fit enough to get full intensity heavy chemotherapy. That means there's a large group of people above that triangle who won't tolerate the heavy treatment but need something done. And, that's where low-intensity treatments come in.

Low Intensity Therapy for AML

- Older patients (>75), or those who are not fit for intensive therapy due to comorbid disease
- Represents the largest proportion of patients with AML
 - Survival often short without therapy, ~4 months
- Low-dose cytarabine (LDAC) - advantage over BSC
 - Azacitidine or Decitabine - possibly better
 - Newer oral versions in development
 - Possible role in maintenance
- Improve survival, but not curative
 - Convert AML into a more *chronic* or subacute course
 - Occasional remissions but stable AML is meaningful



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Slide 31: Low Intensity Therapy for AML

We know that there are many older patients who can't take heavy therapy. We know they represent actually one of the largest proportions of patients with leukemia. And, if they don't get therapy often, they get into trouble very quickly with a median or average time of survival of about 4 months.

An important study, just over 10 years ago, showed that low-dose cytarabine or low-dose chemotherapy was better than nothing. Had an advantage over best supportive care, that's what the BSC means on this slide. There're some slightly more modern versions of low-dose chemotherapy, azacitidine or decitabine, that are at least as good and possibly or probably better. And, there are even some oral versions of those that are in development. And, we're also looking at those medicines in maintenance therapy. But, we know it's going to help, we know it's going to improve the average survival, we know that after the first 2 months, when things get a little worse, that the average person actually feels better for it, so it improves quality of life, once you get through that first 1 or 2 months. But, we also know it's not curative for patients.

In this setting, if someone's not a candidate for intensive therapy, we're trying to convert their leukemia into a more chronic course or at least a subacute course to stabilize things. And, occasionally we see a full remission, 15 or 20% of the time, but even that group of patients where it's stable, that's still meaningful if people actually feel better on the medicine and improves how long they live.

Low Intensity Combination Therapies

- How to improve outcome?
- Many clinical trials ongoing, HMA combination
- Novel targets:
 - HDAC inhibitors
 - NEDD8 inhibitors
 - Monoclonal antibodies (e.g. CD33-based)
 - Mutations (e.g. *IDH1*, *IDH2*, *FLT3*)
 - Apoptosis (*BCL2*)
 - Immune [BiTE's, Checkpoint inhibitors]
 - **Many others....!**



clinicaltrials.gov

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Slide 32: Low Intensity Combination Therapies

So, how do you improve outcome for the older patients where you have to give them low-intensity or low-dose treatment? The answer is, we don't know yet, but there are many clinical trials where we're giving what's called a hypomethylating agent, that's azacitidine or decitabine, in combination with a new medicine, whether it's an HDAC inhibitor or NEDD8 inhibitor or monoclonal antibody, targeting a mutation in combination. Many different trials are going on to see which is the best combination or is there one that's right for that person that'll get the best results for them and try to improve how long somebody lives with tolerable side effects and better quality of life.

And, I could refer you to clinicaltrials.gov, although it's a very long list if you wanted to look there.

Venetoclax

- Oral BCL2 inhibitor
 - FDA-approved in CLL, chronic leukemia that is BCL2-dependent
- Targeting BCL2 (and possibly MCL1) expression is important in some patients with AML
 - Remission in ~20% with relapsed AML
- **Addition** to low intensity therapy (azacitidine) appears to increase complete remission rate and improve survival in 1st line setting



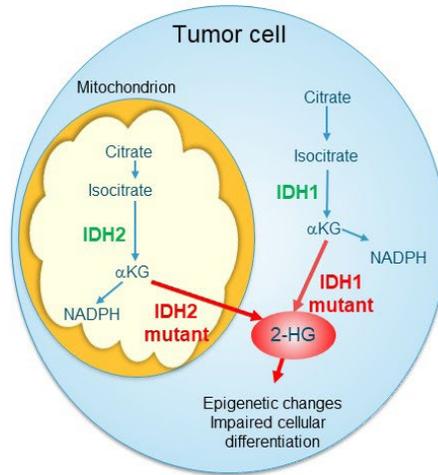
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Slide 33: Venetoclax

Now, a couple of medicines I want to specifically mention in this setting that seem like they might be a step forward. One is a medicine called venetoclax. It's FDA approved in CLL, a different chronic leukemia. Venetoclax inhibits BCL2, which is a protein that stops cells from dying. And, on its own, showed that you can get some remissions in relapsed leukemia and a paper was recently published, adding oral venetoclax to azacitidine or decitabine, low-intensity therapy, in the first-line setting, and showed a remarkable increase compared to what had been expected in the complete remission rate, a better survival than we're used to seeing in that setting, and there's a randomized study that's been done that we're waiting to see results on, to see is it truly better, but I know that at our institution and many others, if we can't get another therapy we're trying to get venetoclax, if they're not on a clinical trial, to add to low-dose chemotherapy to get a better result.

IDH Mutations as a Target in AML

- **Isocitrate dehydrogenase (IDH)**
 - critical enzyme of citric acid cycle
- IDH2 mutations: 9–13% of AML
- IDH1 mutations: 6–10% of AML
- **IDH mutations:**
 - Aberrant methylation
 - i.e. DNA not 'read' properly
 - Impaired cellular differentiation
 - i.e. cells 'stuck' as blasts
 - Drives leukemia



¹Based on literature analysis. Estimates will continue to evolve with future data.
²Dang et al. *Nature* 2009;462:739-44.

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Slide 34: IDH Mutations as a Target in AML

Another group of medicines that have recently been approved by the FDA for relapsed leukemia, and they're called IDH inhibitors. We know that IDH mutations, that's isocitrate dehydrogenase mutations, happen in anywhere from 10 to 25% of patients. And, IDH is an enzyme involved with glucose metabolism, sugar metabolism. We don't know why this mutation happens in leukemia. In fact, it actually was first found in leukemia, it's now been seen in gliomas and in cholangiocarcinomas and other cancers, but this mutation actually changes sugar metabolism to make an abnormal sugar metabolite that changes how DNA is read, stops cells from differentiating or growing properly, they get stuck as blasts, and actually part of the leukemia, it drives the leukemia.

Targeting IDH mutations in Relapsed AML

Enasidenib (IDH2) and Ivosidenib (IDH1)

- Oral agents that bind to mutated IDH
- Induce remission in about 30% of patients with relapse AML
 - Improve blood counts, decrease transfusions
- Impact in 1st line being studied, in combination
- Can cause 'Differentiation syndrome' side effect
 - Large number of leukemia cells that were *stuck* as immature 'blasts' begin to differentiate and mature, and to flood blood/system, causing high WBC, and pulmonary and organ dysfunction

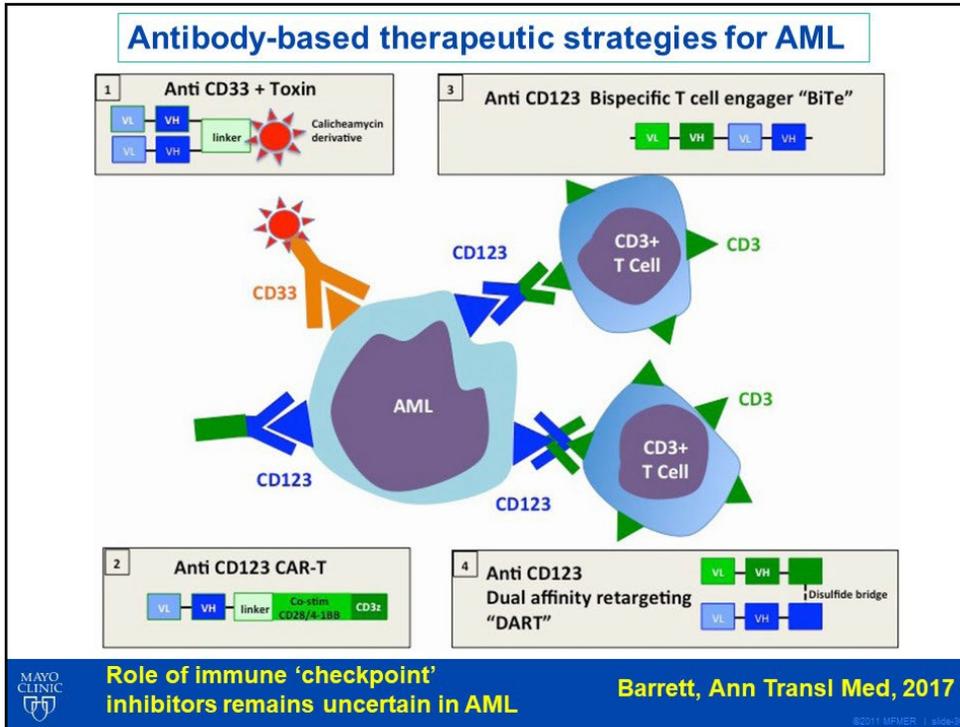


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Slide 35: Targeting IDH mutations in Relapsed AML

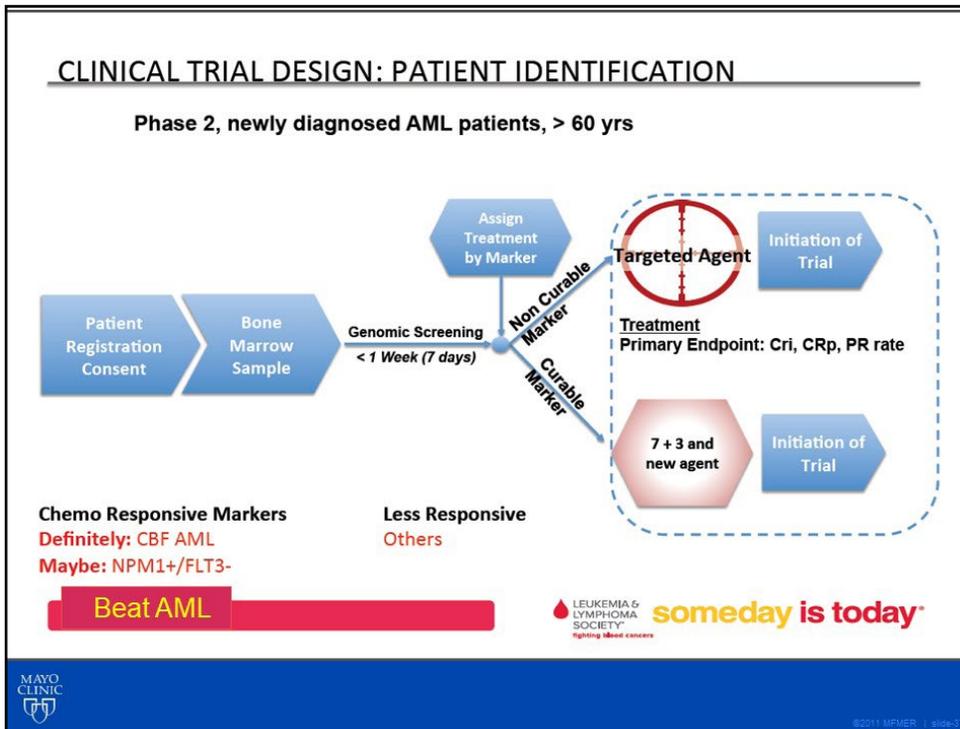
And, there are 2 new pills that target this mutation. One's called enasidenib for IDH2 and the other one's called ivosidenib for IDH1. They're oral, they bind to the mutated version of IDH and they can induce a remission in somewhere between 25 and 40% of patients. Let's say a third because that's about right in the studies. Even in the patients who did not go into remission with relapsed leukemia it often improved the blood counts or decreased the transfusions. We know that the remissions were not permanent. They lasted between 8 and 10 months, but there were some very long-term remissions in patients. And, it's now being studied in the up-front first-line setting.

There's a very unusual side effect, called differentiation syndrome. And, I won't go through all the side effects of that. It's on the slide and you can read about that. But, if you're on one of these medicines or you have an IDH mutation that they discover and they're going to give you one of these medicines, your physician and you will need to be watching for differentiation syndrome. As the leukemia cells differentiate into normal cells, they flood the blood system and can cause some side effects. And, there are strategies to take care of that. So, just something I wanted to say out loud.



Slide 36: Antibody-based therapeutic strategies for AML

Now, I have only a few more slides that I'll go through pretty quickly for you, but there are some new antibody-based strategies. There are some antibodies trying to bind immune cells called BITEs or DARTs. And, there are even some cell-based therapies called CAR-T that are used in a different type of leukemia, ALL, that are being developed or studied in AML. We don't have much in the way of results yet. But, getting immune treatments either with this or with a checkpoint inhibitor is being studied, it's just that it's early days for those and we don't have a lot of data.



Slide 37: Clinical Trial Design: Patient Identification

The Leukemia & Lymphoma Society, I'm going to give them credit, a lot of credit, for driving a study called the Beat AML study. And, this is just a picture about how the study works, but I'll simplify it by saying that patients over the age of 60 with a new acute myeloid leukemia will have rapid mutation testing done, sponsored by LLS, so that within a week we try to get a mutation result. And then, based on that mutation we decide what is the dominant mutation, what strain of AML or what basket to put them in. And then, to do a study of a new agent in that particular basket. So, that we're actually trying to individualize the diagnosis and individualize the treatment.

How is Therapy Assigned

1. Molecular and Cytogenetic Data Arrives with Top to bottom approach
2. Dominant clone at VAF > .3 chosen based upon classification
3. If no dominant clone at VAF > .3, go to .2 with top to bottom for assignment



```
graph TD; A1[Group a1: CBF] --> A2[Group a2: NPM1 mut/FLT3 WT]; A2 --> G3a[Group 3a MLL rearrangement]; G3a --> G3b[Group 3b MLL-PTD]; G3b --> G4[Group 4: IDH2 mut]; G4 --> G5[Group 5: IDH1 mut]; G5 --> G6b[Group 6b: TP53 mut]; G6b --> G6b2[Group 6b: Complex and WT TP53]; G6b2 --> G7[Group 7: FLT3 ITD/TKD mut]; G7 --> G8[Group 8: TET2/WT1 mut]; G8 --> G9[Group 9: Marker Neg];
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Beat AML



someday is today
fighting blood cancers



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Slide 38: How is Therapy Assigned

We assign the therapy based upon the molecular results from the mutations and then we have all these different subgroups of different mutations with an MLL rearrangement or an IDH mutation or a FLT-3 mutation or P53 or others, and each one of those groups there's a unique study of a new agent that looks promising in it, that we're trying to see can we get more remissions, can we make sure it's safe for patients. And, this is being done in collaboration with the FDA so that if we're seeing good responses and if it meets safety parameters, the FDA will even consider some of these treatments in that particular mutation group for rapid approval for new drugs. So, I think that's a big step forward or at least could be a big step forward. We are actively participating in that study and strongly supporting it and it's helping us as clinicians make sense of acute myeloid leukemia mutations.

Reasons to Evaluate for Allogeneic Transplantation

- Provides significant reduction in risk of relapse
 - Limitations of consolidation chemotherapy strategies
 - Currently must be in remission or 'leukemia-free'"
- Improved outcomes in *Modern Era*
 - High resolution/molecular HLA typing for URD's
 - Reduced intensity conditioning in older adults
 - Improvements in Supportive Care
 - *Older adults represent increasing proportion BMT recipients
- Increased availability of donors [unrelated, and alternative]
 - Haplo-identical – partially matched donors



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Slide 39: Reasons to Evaluate for Allogeneic Transplantation

I have a couple of quick slides to finish off with. One is just to say that we're still believers in allogeneic transplant. We know that that's the best way to prevent a relapse, but we also know it's hard. We get better outcomes in the modern era. There are several reasons for that and you can look at the slide or pull it up afterwards, but we've got better typing in our donors. We actually have preparative regimens that are better tolerated. And, we have more donors available, including partially matched donors, where we can safely transplant now.

Selection at BMT Center

- Patient-centered evaluation, discussion & decision taken together with BMT physicians
- Balance disease risks with risks/benefits of Allogeneic BMT
 - Leukemia risk & remission status
 - Patient eligibility
 - HCTCI, psycho-social assessment, consent
 - Donor availability, caregiver strategy/support, insurance
- Strict national standards, recognized indications¹
 - FACT [Foundation for Accreditation of Cellular Therapy], reviewed and accredited every 3 years
 - Stem Cell Therapeutic Outcomes Database *



¹Majhail et al, *BBMT* 21:1863, 2015

* <http://bloodcell.transplant.hrsa.gov>

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Slide 40: Selection of BMT Center

There is an ongoing role for allogeneic transplantation and I will just say that if there's ever a question you should get an evaluation at a transplant center because that's a patient-centered evaluation. It's a discussion and a decision taken together with the transplant physician, you have to balance the risk of the leukemia relapse versus the risk of a transplant and go through a very detailed process to decide if that's the right thing for you. And, I will also say that the centers are held to very high national standards in terms of how they treat and how they monitor patients and their outcomes. So, I think we're getting better at transplant and the more patients we're getting into remission, particularly the relapsed leukemia or difficult leukemias, the more we're looking at that.

Patient Support & Palliative Care in Acute Leukemia

- Hospice and palliative care underutilized in leukemia
 - Patients often require more intensive support even near the end of life
 - Antibiotics
 - Transfusion support
 - Inpatient care needed more often as AML progresses
 - Pain uncommon
 - *Nevertheless – effort to liaise with Hospice
- Caregiver support - who cares for the caregiver?
 - Social work initiatives – care for children of patients
 - Incorporate routine caregiver follow-up after BMT, and Post-BMT/CAR-T support groups



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Slide 41: Patient Support & Palliative Care in Acute Leukemia

Now, I want to say this is not something that gets talked about a lot, but it's about patient support and palliative care. And, in acute leukemia we don't do palliative care as often as other cancers for several reasons. The patients need more intensive support and they need antibiotics and transfusions and they often need to be in the hospital. We don't have as much trouble suffering from pain that some other cancers have, and so in the past traditionally we haven't worked as closely with hospice, but there's a big move nationally for us to work more closely with palliative care programs and hospice to get the support patients need and that's something we want to do together with our patients and with their families.

The other comment I would make is just to say that there's an open question about who cares for the caregiver. We have initiatives at Mayo Clinic and some other centers do to actually look for ways to support the caregiver, look for ways to care for the children or help care for the children of patients, and to actually offer support or support groups after leukemia therapy and after bone marrow transplant or CAR-T therapy for caregivers. And, it's something where I think we all need to do a better job of caring for the caregivers.

Pearls of Wisdom

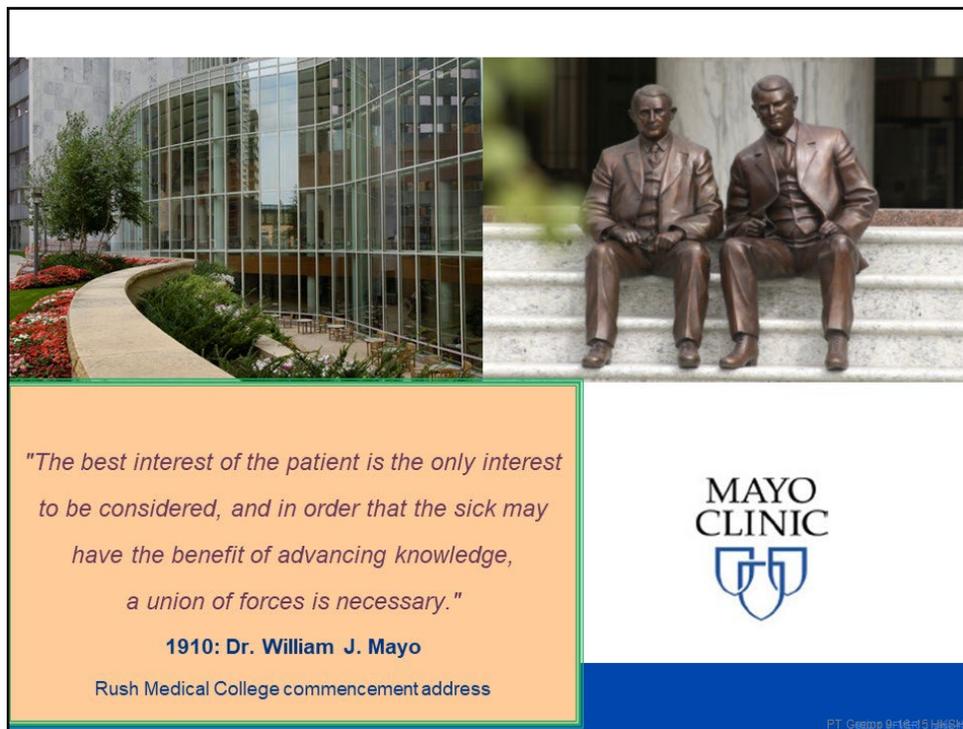
- Almost all patients benefit from therapy
 - Set individual patient goals
 - Treat with intensive therapy and for 'cure' whenever possible
- Current treatments still not adequate for many
 - We must work together to advance AML survival and outcomes
 - Clinical trials
 - Genomic tumor boards
 - Molecularly-targeted therapy



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Slide 42: Pearls of Wisdom

So, I'm going to end just by saying on some of my own pearls of wisdom is that almost all patients benefit from therapy. You have to set individual goals because each person's leukemia is a little different. But, I do think whenever we have a shot at an intensive therapy and a cure, we need to take that shot because this is a difficult disease. Our current treatments are not adequate for many patients. We're curing more than before and more than ever, but we need to cure more than we are. So, we have to work together to advance the survival, advance the outcomes. That involves clinical trials, involves societies like LLS, and working with genomic tumor boards and molecularly targeted therapies.



"The best interest of the patient is the only interest to be considered, and in order that the sick may have the benefit of advancing knowledge, a union of forces is necessary."

1910: Dr. William J. Mayo
Rush Medical College commencement address

MAYO
CLINIC

PT Group 9-16-R15 H162H

Slide 43: 1910 Quote from Dr. Mayo

And, I'm going to just read you a brief quote from one of the Mayo brothers who founded the Mayo Clinic, Will and Charlie. I shouldn't call them that. Dr. Mayo and Dr. Mayo, because I wasn't on a first name basis with them. But, the quote from 1910, over a hundred years ago, was "the best interest of the patient is the only interest to be considered, and in order that the sick may have the benefit of advancing knowledge, a union of forces is necessary." So, this is something that we have to do together as clinicians, as foundations, as patients, and as families, to try to move the field forward.

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

Acknowledgments

- Leukemia Clinical Team
 - Mayo Clinic Cancer Center



Jacksonville, FL	James Foran, MD
Rochester, MN	Mark Litzow, MD Aref Al-Kali, MD Michelle Elliott, MD Hassan Alkhateeb, MD Naseema Gangat, MD
Phoenix, AZ	Lisa Sproat, MD

Search '*leukemia*' at www.mayoclinic.org

MAYO CLINIC

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Slide 44: Acknowledgments

So, I'll end just by acknowledging my colleagues in the Mayo Clinic Cancer Center. We're the only 3-site comprehensive cancer center. Our headquarters in Rochester, Minnesota, we've got a cancer center in Florida, we have a cancer center in Phoenix. These are the list of my colleagues. The LLS has got outstanding patient information, but so does mayoclinic.org, if you search leukemia at that site.

And, I'll stop now, and I'll be delighted to answer any questions. I think I went a few minutes over time, but I wanted just to touch on several different issues. So, thank you very much.



Q&A SESSION
Advances in Acute Myeloid Leukemia

- **Ask a question by phone:**
 - Press star (*) then the number 1 on your keypad.
- **Ask a question by web:**
 - Click “Ask a question”
 - Type your question
 - Click “Submit”

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

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Slide 45: Q&A Session

Lizette Figueroa Rivera:

Thank you so much, Dr. Foran, for volunteering your time for us and informing us of all these important advances that are currently taking place in AML. And, it is now time for our question and answer portion of our program. For everyone’s benefit please keep your questions general in nature without many personal details, so Dr. Foran can provide answers that are general in nature.

And, we’ll take the first question from our web audience. Doctor, Iris is asking about minimal residual disease and how it relates to relapse.

Dr. Foran:

Yeah, that’s a really important question, Iris, thank you very much. Minimal residual disease means you got treated, you went into remission, your bone marrow looks normal or close to normal, we cannot detect any leukemia and your blood counts are good, but a molecular test or a sensitive test called flow cytometry picks up a tiny population of leukemia in the background. And, we’ve learned that patients with minimal residual disease, it means that we have not cleared their leukemia low enough to say they’re cured or on the path to cure with that particular therapy. Sometimes the, we call that MRD by the way, minimal residual disease, sometimes that will clear with a consolidation chemotherapy. Or, sometimes we’re considering alternate treatments like bone marrow transplants or even clinical trials. It’s still an evolving area for us on how best to measure it and there’s a national working group trying to figure that out. But, it’s an important question. And, if the MRD is there, then I think that’s a long discussion with your hematologist/oncologist about what’s the best strategy to clear it and to try to improve the chances of long-term remission.

Lizette Figueroa Rivera:

Thank you. And, we’ll take the next question from the phone audience, please.

Operator:

Yes, of course. The next question comes from Jasmine from Florida. Please state your question.

Jasmine:

Yes, I wanted to know, uh, what the process is for a donor, to donate some bone marrow. Because I’ve seen online that there was a couple of different methods and also, what would be the process for a person that would be able to donate from a long distance.

Dr. Foran:

That's a great question. Thank you very much. By the way, Jasmine, I hope you're safe. I'm in Florida also and I think we're way from the hurricane, I hope you are, too.

So, we're a transplant center and I'm on our transplant service as well. To donate stem cells or bone marrow cells you have to pass the same blood tests as a blood donor, so all the same viral testing, hepatitis testing and so on. You have to pass a physical to make sure that you don't have any diseases that would put you at risk if you donate or that you could transmit to a patient. And so, that if somebody had had cancer, for instance, they'd had melanoma or a leukemia themselves and were in long-term remission, you wouldn't be able to donate because of the potential fear that that could be transmitted, even if you yourself were cured. To go through donation at that point, most centers want the bone marrow cells from the bloodstream, we call them peripheral blood stem cells, so you would get three or four days of a growth factor shot. And, it stimulates the bone marrow cells. They actually mobilize into the bloodstream and we collect them from the bloodstream in the same way that a patient donates plasma or platelets. Those cells can then get collected and frozen and stored for use for the donor.

Now, if you're traveling from afar, you usually have to allow yourself ten to fourteen days, give or take, it's often less than that, but let's say ten to fourteen days of inconvenience because you have to go to wherever the donor center is, if it's for a relative, or to the local center if it's for unrelated donor, to be screened and evaluated and go through that process. But, it should not cost you or your insurance, it should be charged to the patient's insurance and not your own, even if you have to get support for putting yourself up or for travel.

So, it is a real thing to donate and we're very grateful for the people who do it. It's an amazing thing and a life-changing thing for the patients. But we know it's a real thing and there's inconvenience but I'm glad you're considering that or have that option and I hope if it's the right thing for you you're able to do it.

Lizette Figueroa Rivera:

Thank you so much. And, our next question comes from our web audience. Chris is asking about the efficacy of newer drugs like Tibsovo® and what trends on the horizon in the next year.

Dr. Foran:

Tibsovo is a small molecule inhibitor, is being studied, and like many drugs there's a suggestion of remission, a suggestion of benefit, but it has to be flushed out a little further before it can go to the next level and get approved, where we really can say here's the chance it's going to benefit, here's how it works and here are the side effects. And, those are key questions. We want to get access to new drugs for patients, but we also want to do it in an ethical and safe way where we're really doing good and not just, taking random chances. And so, it has to be done in a clinical trial.

I think the big trends coming up in AML are more of the targeted drugs that we've mentioned so far against different mutations, and some of the new immune-based treatments. We and other sites are doing studies for instance, with some of the new called BITEs or DARTs. And, these are antibodies that are designed to bind one half to your leukemia cell and the other half to an immune cell in your body called a T-cell, to try and activate it to fight leukemia. So, to see if we can actually get the immune system to fight leukemia, I think is one of the big trends. It works in other cancers in different ways and we're looking to see can we adapt that into AML, to use a different non-chemotherapy-based approach to try and use someone one's immune system to fight the cancer. We're not there yet, we've got hints and we've got suggestions and we've got promise, but I think there's more work to be done before that becomes an immediate reality.

Lizette Figueroa Rivera:

Thank you. And, we'll take the next question from the phone audience, please.

Operator:

Yes, thank you. Our next question comes from Steven from California.

Steven:

Hi. My question pertains to graft-versus-host disease. I'm a past AML patient and clear from cancer but dealing with multiple side effects from graft-versus-host. I was looking at ibrutinib but it's too cost-prohibitive. Can you address graft-versus-host for us?

Dr. Foran:

Yeah, so thank you very much. You're in a funny spot I suspect, where a very dangerous disease is resolved and you're in remission, but now you've got a side effect from the treatment, a chronic immune side effect which can be difficult in its own. So, this is a side effect of allogeneic stem cell or bone marrow transplant where the donor cells can cause chronic

graft-versus-host disease. It's really a form of chronic rejection. The donor cells are the new immune system. They're rejecting leukemia, preventing relapse, but they can also as a side effect reject some normal cells in your body. And, that can have many manifestations. And, Steven, I don't know all of yours, but sometimes it can be diarrhea or mouth sores or dry eyes or even lung problems.

Now, we know that most patients do ultimately get better from it and most patients do ultimately come off the immunosuppressive treatment you need to settle down that rejection. There is a new treatment that the FDA approved, oh, gosh, I think it was last year called ibrutinib that can sometimes work for some forms of graft-versus-host disease, and so that's worth pursuing if you can get it. And another one, without generalizing too much because I don't know the treatments you had is to use a cell-based treatment called photopheresis, because it actually helps settle the graft-versus-host disease and keeps people off of steroids, so you don't get the steroid side effects. But, it matters that you do the physical therapy they prescribe, it matters you stay active. You now have a long-term autoimmune disease that I hope will settle over time and usually does and you have to work your way through the process, and I'm sorry you're suffering from that and I hope that these treatments can help you.

Lizette Figueroa Rivera:

Thank you. And, the next question comes from Florence. Florence asks, has there ever been any investigation of the effect of tattoos upon the development of AML.

Dr. Foran:

Not that I know of. That's an interesting question. The short answer is no. I could make up a long answer as to why you have to be careful about where you get your tattoo done, but no, a tattoo itself should not have anything to do with AML or recovery. But, I will tell you that after bone marrow transplant, I tell my patients not to get a tattoo for at least a year. Many people want to, but I don't want them to do that because it can sometimes flare the immune reaction of graft-versus-host disease if you do it within 3 or 6 months of being on your medicines or if you had graft-versus-host disease. So, I'm going to give a roundabout answer and say no, except don't get a tattoo until you're well after your transplant if you want to get one.

Lizette Figueroa Rivera:

Thank you, Florence, for that question. I've never heard that question either.

Dr. Foran:

That's really interesting, yeah.

Lizette Figueroa Rivera:

Yeah. And, Brenda is asking if exposure to formaldehyde can cause AML.

Dr. Foran:

No. The short answer is that has not popped up as an event in studies. We've not seen that in patients in a large patient sample we just looked at and there's not a strong database for that. Formaldehyde can cause other problems but is not specifically linked to leukemia or if it is it's not strongly linked enough that it's popped up in the big studies.

Lizette Figueroa Rivera:

Thank you.

Dr. Foran:

But I'm not saying that you should play with formaldehyde.

Lizette Figueroa Rivera:

Sure. And, Mona is asking if chemo-fog gets better or gradually worse.

Dr. Foran:

So, usually it gets better. And, the problem with chemo-fog is it's a very vague thing that's a little different for everybody and sometimes it's an effect of chemotherapy and sometimes it's an effect of all the other things that change in your life and in your psyche as you're going through this. And so yes, it usually gets better, but it's not something you should suffer through on your own if you're really struggling. It's definitely something you should talk to your oncologist or hematologist about. We have a psychologist embedded in our practice who sees many of our patients and helps discern or helps dissect how much of that is from anxiety, how much is from depression, how much are life factors or family factors, and how much of that is the treatment, so at least we can neutralize the other components or address them as best as possible. I do hope it gets better because it usually does over time.

Lizette Figueroa Rivera:

Thank you. And our last question today, Archaver asks what does it mean when leukemia is cured. For example, after how many years of no signs of leukemia can we conclude the patient is cured?

Dr. Foran:

Most of the relapses, if they're going to happen, are in the first 18 months. That's the highest risk period, which is why we watch patients so closely in the first 18 months. In the next 18 months that risk lowers and after 3 years it's very low. After 5 years, it's very, very rare to see a relapse, so that's when we say we think you're cured. And, I'm going to give you a really crass, terrible answer to the question, which is to say, if somebody gets old and dies of something else, that's when we know they were cured of leukemia. But, usually after 5 years is when we say that it's not something that you should be distracted by. It's very distracting in the first year, it's somewhat distracting in the second year, and then it varies after that. Usually the distraction goes away so that you're able to not have to think about it every day and you can get on with your life. I hope that happens for her soon. And, that's usually the time frame that we address with our patients.

Well, thank you, Archaver, for your question, which was our final question today.

And, thank you so much, Dr. Foran, for your continued dedication to patients.

For those of you who participated in today's program, we hope the information presented today will assist you and your family in your next steps.

LLS EDUCATION & SUPPORT RESOURCES

- **Information Specialists**
Master's level oncology professionals, available to help cancer survivors navigate the best route from diagnosis through treatment, clinical trials and survivorship.
 - EMAIL: infocenter@LLS.org
 - TOLL-FREE PHONE: 1-800-955-4572
- **Free Education Booklets:**
 - www.LLS.org/booklets
- **Free Telephone/Web Programs:**
 - www.LLS.org/programs
- **Live, weekly Online Chats:**
 - www.LLS.org/chat



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Slide 46: LLS Education & Support Resources

If we weren't able to get to your question today or you want more information, you may speak to an LLS Information Specialist at 1-800-955-4572. We're here from 9 AM to 9 PM Eastern Time or you can reach us by email at infocenter@LLS.org.

LLS EDUCATION & SUPPORT RESOURCES

- **LLS Podcast, *The Bloodline with LLS***

Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: www.thebloodline.org
- Education Videos**

Free education videos about survivorship, treatment, disease updates and other topics: www.LLS.org/educationvideos
- Patti Robinson Kaufmann First Connection Program**

Peer-to-peer program that matches newly diagnosed patients and their families: www.LLS.org/firstconnection
- **Free Nutrition Consults**

Telephone and email consultations with a Registered Dietitian: www.LLS.org/nutrition
- What to Ask**

Questions to ask your treatment team: www.LLS.org/whattoask
- Other Support Resources**

LLS Community, discussion boards, blogs, support groups, financial assistance and more: www.LLS.org/support

Slide 47: LLS Education & Support Resources

Information Specialists are available to answer your questions about treatment, including clinical trials. Now, we can assist in narrowing down a list of clinical trials you get from clinicaltrials.gov that Dr. Foran mentioned through our Information Specialists and Clinical Trial Support Center, who take also into consideration your individual needs.

For more information about LLS's groundbreaking collaborative Beat AML Master Trial you can also visit www.LLS.org/beataml. And, as Dr. Foran mentioned, caregivers are very important. Our Who Cares for Our Caregiver tele-web will occur next month on November 28 for National Caregiving Month.

Again, we'd like to acknowledge and thank Agios, Celgene, and Novartis for support of this program.

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

Goodbye and we wish you well.

END