

# Update on Acute Myeloid Leukemia

September 29, 2016

**Speaker:** Joseph G. Jurcic, MD



**someday  
is today®**

---

## Slide 1. Welcome & Introductions

### **OPERATOR:**

Greetings, and welcome to *Update on Acute Myeloid Leukemia*, telephone and web education program. It is now my pleasure to introduce your moderator, Lizette Figueroa Rivera.

### **LIZETTE FIGUEROA RIVERA:**

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

We have over 500 people participating from across the United States and several countries around the world, including Canada, the United Kingdom, and Uganda.

Special thanks to Dr. Joseph Jurcic for sharing his time and expertise with us today.

Before we begin, I'd like to introduce Dr. Lee Greenberger, our Senior Vice President and Chief Scientific Officer of Research from The Leukemia & Lymphoma Society, who will share a few words. Dr. Greenberger, please go ahead.

### **DR. LEE GREENBERGER:**

Thank you, Lizette. I'd like to add my welcome to the patients, caregivers and healthcare professionals attending the program today.

The Leukemia & Lymphoma Society exists to find cures and ensure access to treatment for blood cancer patients. Our vision is a world without blood cancers.

For more than 60 years LLS has helped pioneer innovations such as targeted therapies and immunotherapies that have improved survival rates and quality of life for many blood cancer patients.

To date we have invested over \$1 billion in research to advance therapies and save lives. Until there is a cure, LLS will continue to fund promising research from bench to bedside.

In addition, as this program demonstrates, we are the leading source of free blood cancer information, education and support, and we touch patients and their communities through our 56 chapters across the United States.

LLS also acts as a voice for all blood cancer patients. We advocate for patients and survivors and their families, helping them navigate their cancer treatments, and ensure that they have access to quality, affordable and coordinated care.

We are very fortunate to have as our presenter today Dr. Joseph Jurcic, one of the nation's leading experts in leukemia. Dr. Jurcic is located at Columbia University College of Physicians and Surgeons in Manhattan, New York. He is Professor of Clinical Medicine and Director of the Hematologic Malignant Services of the Hematology-Oncology Division. He holds a medical degree from the University of Pennsylvania and has completed fellowship at Hematology-Oncology at Memorial Sloan-Kettering. He has been at Columbia University for a long duration and is one of the leading hematology-oncology doctors at that site. We appreciate his dedication to supporting our mission and his commitment to caring for patients living with blood cancers. I'd like to thank him for providing us today with important information on acute myeloid leukemia.

Thank you all and now I'll turn the program back to Lizette.

# Update on Acute Myeloid Leukemia

September 29, 2016

**Speaker:** Joseph G. Jurcic, MD



**someday  
is today®**

---

## **LIZETTE FIGUEROA RIVERA:**

Thank you, Dr. Greenberger.

And we would like to acknowledge and thank Celgene Corporation and Stemline Therapeutics for their support of this program.

## **Slide 2. Update on Acute Myeloid Leukemia**

I'm now pleased to introduce Dr. Joseph Jurcic.

Dr. Jurcic, I'm privileged to turn the program over to you.

## **DR. JOSEPH JURCIC:**

Thank you so much. It's a real pleasure to be here this afternoon.

So it's a pleasure to really talk today about an Update on Acute Myeloid Leukemia. What we're going to be doing today is talking about several things. First, some updates in diagnosing acute myeloid leukemia, various subtypes of leukemia, and then talking about some of the newer targeted therapies.

## **Slide 3. Disclosures**

My disclosures. I do receive research funding from several biotech companies as well as I have done consulting.

## **Slide 4. Outline**

## **Slide 5. Development of Acute Myeloid Leukemia**

In this slide we talk about the development of acute myeloid leukemia. So when we think about cancer in general we think about how normal cells develop and how these cells may be perturbed in their development to cause cancer. And so we know a lot about the production of normal blood cells. There's a hematopoietic stem cell labeled in the panel on the left, HSC. This cell is capable of self-renewal, but also of maturing into a multitude of different cells that comprise the blood.

And so there are two major bifurcations in this pathway. The first is towards a common myeloid progenitor, which eventually gives rise to the red blood cells, the platelets, as well as a number of normal myeloid cells, most importantly the neutrophil, which is sort of our most potent infection-fighting cells. Then we have the lymphoid progenitor cells, which give rise to T-cells and B-cells, also important components of the immune system.

Well, in leukemia, specifically in AML, what happens, really two major hallmarks. The first is that there's a genetic abnormality that can occur either in the stem cell or one of the progenitor cells just beyond the stem cell that blocks differentiation. So these cells can no longer mature into normal infection-fighting cells. They get stuck at an immature stage. And there's a number of genetic abnormalities that we know that can cause this.

The second hallmark is increased proliferation. So there's a second hit, a second genetic abnormality that occurs somewhere later on in the development of these cells that causes these abnormalities to grow out of control. And again, there are a number of abnormalities that I've listed there, that can result in this sort of increased proliferation.

---

## DR. JOSEPH JURCIC:

I think importantly, we're going to be talking about the FLT3 abnormality, which has become an important target for therapy.

### Slide 6. Key Diagnostic Questions in Leukemia

When we're confronted with someone who's coming in with a new diagnosis of leukemia, there are certain key questions that we must address.

The first is, what is the lineage? Okay. What I mean there is this a myeloid leukemia or is this a lymphoid leukemia? What's the maturational stage? Are these immature cells comprised of what we call blasts, or are they more mature cells, say like promyelocytes? Or are they monocytes? All of this can play a role in accurate diagnosis. And finally, and perhaps most importantly, what is the genotype? What are the chromosome abnormalities associated with this leukemia, what are the genetic abnormalities associated with this leukemia? This ultimately is the thing that defines prognosis and in many aspects, with various advancements, now is responsible for determining proper treatment. And of course we do these diagnostic tests, generally speaking, on either blood or bone marrow. And I've depicted in the panel on the right there a bone marrow aspiration where we insert a needle into the pelvic bone and draw up some of the leukemia cells from the bone marrow where they're being made, to perform all of these tests.

### Slide 7. FAB Classification of AML

It used to be that we would think about leukemia simply as how it looked under the microscope. And there was the so-called FAB classification that was put together by French, American and British pathologists. And this was really a classification system designed simply to describe how these cells looked under the microscope, the morphology of the cells. And honestly I've listed all of the names there and I have many patients who ask me what FAB type they are and I have to say it really doesn't matter so much anymore because things have really moved forward. We still look at this under the microscope, we still think that this is an important aspect of the diagnosis of leukemia, but really what we're moving towards is thinking about the disease on a chromosome and genetic level.

### Slide 8. Syndromes of Leukemia

And that's because there are syndromes of leukemia. We know that there are unique types of leukemia that have a specific appearance under the microscope, a unique immunophenotype, certain proteins that are expressed on the surface, many chromosome and molecular abnormalities, and that defines clinical behavior. And so this was well recognized.

### Slide 9. 2008 WHO Classification

In 2008 the World Health Organization, another group got together and reclassified leukemia. The key difference here is in addition to that backbone that was set forward by the French-American-British classification system that used morphology, a whole new category of leukemia, AML with recurrent genetic abnormalities. And I've listed all of the ones that were part of this classification system there. Again, the exact types are not so important. The key is the shift in thinking, from the way the cells look under the microscope to the genetic and molecular abnormalities that can occur in these cells, to really define the disease.

---

## **DR. JOSEPH JURCIC:**

They also included a category known as AML with MDS-related changes. We know that people who have had a history of an antecedent hematologic disorder, particularly myelodysplastic syndromes (MDS) in this case, tend to have a tougher disease to treat. And so to sort of build in these patients, this category was added. We also know that patients who have had treatment for a previous cancer, who then develop acute myeloid leukemia, have a tougher disease, and so therapy-related myeloid neoplasms became its own category.

### **Slide 10. Genetic Alterations Affecting Prognosis in AML**

What happened since that time is that we now know that in addition to these chromosome abnormalities, these missing parts of chromosomes or translocations of chromosomes where part of one chromosome changes place with another, we know that in patients who have normal chromosomes there still can be a number of genetic abnormalities, single gene mutations, that can also help define prognosis.

For instance, we know that abnormalities of the NPM1 gene and abnormalities of the CEBP-alpha gene (CEBPA), are associated with a more favorable prognosis in this disease. On the other hand, abnormalities such as the FLT3 internal tandem duplication, abnormalities of the MLL gene, or very important tumor suppressor gene, TP53, or abnormalities in c-KIT, can be associated with a tougher disease to treat.

### **Slide 11. 2016 WHO Classification**

And so taking that into consideration, the World Health Organization reconvened recently in 2016 and they've added a few additional types of leukemia to their categorization of AML with recurrent genetic abnormalities. So now you can see that they've added mutated NPM1 and biallelic mutations of CEBP-alpha as distinct categories of AML to our classification system.

So again it's an evolution of our classification from the way the cells look under the microscope to the genetic and molecular abnormalities that these leukemias harbor.

### **Slide 12. Risk Status Based on Cytogenetic and Molecular Abnormalities**

Why is this also important? Well, it's important because these abnormalities define how the disease behaves. So in one classification system done by the NCCN (National Comprehensive Cancer Network), you can see better risk abnormalities with chromosome abnormalities and certain genetic abnormalities. Also intermediate risk comprising about 50% of AML cases. And then high risk abnormalities where the certain gene abnormalities and chromosome abnormalities associated with that.

So this helps us prognosticate and it can also help us direct therapy.

So for instance, in patients who have better risk disease, they have a good chance of being cured with chemotherapy alone. And patients who have high risk disease, that form of leukemia is almost incurable with chemotherapy and so we try to move those individuals to allogeneic stem cell transplantation.

### **Slide 13. Mutational Complexity of AML**

You can see that this even really gets more complicated because it's not just these individual abnormalities, it's really about the pairings of abnormalities. So in this plot you can see that certain abnormalities like NPM1 mutations and abnormalities of FLT3 can go together.

---

## DR. JOSEPH JURCIC:

And really what we're looking at now is these pairings and how that can further refine our prognostication. And so I think we'll be seeing more of these studies going forward, more studies to confirm these results in initial testing.

### Slide 14. Using Old Drugs More Effectively: CPX-351

I want to address new issues in therapy. So I think this is an exciting time in AML. For years we've been struggling to define new treatments to advance the field. And now finally all of these molecular advances in molecular biology are really beginning to pay off. And we'll talk about how these abnormalities can influence targeted therapy going forward.

But sometimes in fact old tools can be used more effectively. And so a very interesting new drug that has been developed that's called CPX-351. So this particular agent consists of old drugs that we've used for decades – cytarabine and daunorubicin, basically the backbone of AML therapy – but they've been encapsulated in essentially a fat globulin. Something we call a liposome. And they are in a fixed molar ratio. So this ratio actually maximizes the synergy between these two agents to make them more effective and can minimize toxicity.

So there was a recent randomized study looking at CPX-351, comparing it to standard so-called 7 plus 3 chemotherapy with cytarabine and daunorubicin, conducted in higher risk patients who were older. And what this showed was superior overall survival, event-free survival, and remission rates for CPX-351. So this was very exciting results that were announced at the American Society of Clinical Oncology (ASCO) back in June. And it is likely that this agent will go on to be licensed for the treatment of this population and I think really become a new standard of care.

### Slide 15. Targeted Therapy for AML

There are a number of therapeutic targets that have been identified for AML and there's an active program in drug development for all of these targets. And I'm just going to highlight a few of them in our meeting today.

The first are so-called FLT3 inhibitors and targeting abnormalities in that gene that's important and controls proliferation of cells. Another protein called BCL-2 that controls cell death. IDH inhibitors. And then finally antibody-based therapies.

### Slide 16. Sorafenib + Chemotherapy for AML

So it's long been thought that if we take our standard tools of 7 plus 3 chemotherapies and add newer agents to it we may be able to improve outcomes. And taking a targeted therapy that doesn't necessarily have the same kinds of side effects as the other treatments and adding it to standard chemotherapy may be a reasonable strategy.

Well, this was one of the first trials to show that that notion in fact is a viable one. So this particular trial was conducted by a group in Germany and they took patients and gave them standard chemotherapy as well as chemotherapy with a targeted agent called sorafenib. Now this hits multiple gene abnormalities, among them FLT3, but many others as well. And there was an interesting result because those patients who received sorafenib in addition to chemotherapy had better outcomes. In this particular case had a longer event-free survival.

## DR. JOSEPH JURCIC:

That simply means that more patients were alive and in remission for a longer period of time with the addition of this oral agent to standard chemotherapy. And so this is really proof of concept that this is a viable way to move forward.

### Slide 17. FLT3 Mutations in AML

We talk about the FLT3 abnormalities because this actually has become now an important target for therapy. There are two different types of mutations in the gene FLT3 that can occur in AML. The more common one is the so-called internal tandem duplication. Seen in about 30% of people with acute myeloid leukemia. And as I indicated before, although remission rates tend to be about the same, the length of those remissions and the survival of patients with the FLT3 internal tandem duplication is less.

There's also a second mutation that can occur, seen less frequently, so-called point mutations, which actually can become an important point because this can be a mechanism of resistance to some of the earlier FLT3 inhibitors that have been developed.

### Slide 18. Midostaurin + Chemotherapy for Newly Diagnosed FLT3-Mutated AML

We present the results of one of the first studies looking at the combination of a FLT3 inhibitor with chemotherapy. And these results were presented by Rick Stone at the American Society of Hematology (ASH) meeting just about a year ago. This is an interesting study because it took patients who had FLT3 mutated AML. So was a molecularly defined population of patients.

So in this trial they took patients who had a molecularly defined abnormality, the FLT3 abnormality, and added a targeted agent, midostaurin, to standard chemotherapy. And they found not only improved event-free survival, but improved overall survival for the group receiving midostaurin. And so this is again an important paradigm-shifting trial, again showing that you can use molecularly defined populations with targeted agents and chemotherapy to improve the outcome in patients with acute myeloid leukemia.

### Slide 19. Next Generation of FLT3 Inhibitors in Development

We list some of the newer agents, some of the second generation FLT3 inhibitors that are under development now. And these tend to be a little bit so-called cleaner drugs. They don't hit so many other proteins, other genetic abnormalities, but are more defined towards the FLT3 abnormality. There's quizartinib, which has now entered so-called Phase III trials in patients with relapsed and refractory FLT3-mutated AML. Gilteritinib also in Phase III studies. And crenolanib, and it's sort of advanced Phase II studies, preparing to enter Phase III studies. All of them have demonstrated considerable activity in patients whose leukemia has returned after their initial treatment and all look promising for this patient population.

### Slide 20. Inhibiting BCL-2 in AML

So another interesting target is BCL-2. So BCL-2 is a protein that allows cancer cells to evade something called programmed cell death or apoptosis. There's a drug called venetoclax, which by the way is licensed for patients with high risk relapsed chronic lymphocytic leukemia (CLL), so a very different disease, but already on the market for that population. And this drug binds to BCL-2 and this frees certain apoptotic proteins that can lead to cell death.

## **DR. JOSEPH JURCIC:**

So this particular agent has also shown activity in patients with relapsed AML and it's been taken forward in older individuals who were previously untreated, in combination with hypomethylating agents, decitabine and azacitidine, as well as low dose cytarabine. And in all of these studies the addition of venetoclax has seemed to improve response rates compared to what would be expected over these other agents, and in some even seemed to improve overall survival rates. So it's a very exciting drug, well tolerated, and I think will actually become an important drug, not only for older individuals with AML, but perhaps even younger patients who are taking more intensive chemotherapy, and patients whose disease has returned after initial treatment.

## **Slide 21. Inhibiting IDH in AML**

So another target is IDH. So there are two enzymes, IDH1 and IDH2, that are important in the generation of energy for cells. So if there are any biochemists in the audience, you can see I've drawn the pathway, included that for you. But really the key feature here is that when this gene that encodes that enzyme, IDH, is mutated, it alters the genetic programming of these cells and allows these cells to remain immature and continue to grow, so that by blocking this abnormality you can essentially cause these cells to differentiate and die off.

## **Slide 22. IDH Inhibitors in Development**

I mention that there are actually multiple drugs now that are being developed to target both the IDH1 and IDH2 mutations. Or a combination of both. And these drugs are at various stages in development.

The one that's furthest along is called AG-221. It's an inhibitor of IDH2. And this has entered Phase III testing in older individuals with advanced AML who have progressed after a couple of different treatments beforehand.

## **Slide 23. Antibody-Based Therapy Strategies**

I wanted to discuss the antibody-based approaches and say a few words about immunotherapy.

So antibodies are proteins that our bodies normally make to fight off infection. But we can use this tool to generate antibodies that can recognize certain proteins on the surface of leukemic cells. So one target for therapy, CD33, this has been validated in multiple studies previously, so there's a new agent that's called SGN-33A that takes an anti-CD33 monoclonal antibody and uses it to deliver a drug, it's a type of drug called a pyrrolobenzodiazepine, directly to the leukemic cell. So this particular agent has produced remissions in relapsed and refractory patients with AML. It's been combined with azacitidine in newly diagnosed patients. And in fact has now entered Phase III testing in older individuals with untreated AML, in combination with the hypomethylating agent azacitidine.

Another approach is something called a bispecific monoclonal antibody. So this is an agent that's earlier in development and basically consists of pieces of monoclonal antibodies, one that binds to CD33, that attaches itself to the leukemia cell, and another that binds to a T-cell. So T-cells are part of the immune system that normally should be gobbling up viruses and bacteria. But here we can trick that cell into essentially attacking a cancer cell, attacking a leukemia cell. And so it engages the T-cell, brings it into apposition with the leukemic cell, and causes our own immune system to kill the leukemia cell. There's already an agent licensed in acute lymphoblastic leukemia that uses this principle.

# Update on Acute Myeloid Leukemia

September 29, 2016

**Speaker:** Joseph G. Jurcic, MD



**someday  
is today®**

---

## **DR. JOSEPH JURCIC:**

It's called blinatumomab. It targets a protein on the leukemic cell called CD19. This drug is already approved. And now similar drugs are being developed for acute myeloid leukemia.

And finally, another strategy is to take a monoclonal antibody, again in this particular instance that targets CD33, and deliver radiation directly to the leukemia cell. So there's a form of radiation known as an alpha particle emitter. Alpha particles are interesting in that they travel an extremely short path range. Only about one or two cell diameters. So that the radiation is extremely focused. And when you attach an alpha particle emitter, in this case actinium 225 to an anti-CD33 antibody, you can deliver those alpha particles directly to the leukemia cell, while sparing many normal tissues in the body. And so this is an interesting strategy that is currently entering Phase II testing in a national trial.

## **Slide 24. Role of Clinical Trials in AML**

We talk about the role of clinical trials. The last few slides have talked about new targets for therapy and all of these advances have been done through clinical trials. It is really the only way we can make more progress in this disease. These trials allow us to determine whether new treatments are safe, how effective they are, and whether a new treatment can work better than our current treatments. They can also help us find new ways to prevent and detect cancer. They can help us improve the quality of life for people before and after treatment. And by taking part in a clinical trial you can add to our knowledge about leukemia and hopefully improve things for future patients.

It can get very confusing when doctors talk about trials and ask for participation. They'll throw around these terms, Phase I, II and III. And so I just wanted to spend a moment to talk about what that means.

## **Slide 25. Drug Development**

So the purpose of a Phase I trial is really to look at a new drug and find out exactly what its side effects are and what the highest dose is that can be given safely or what the best dose is really, to take forward in subsequent trials. So after a drug that looks promising goes through Phase I testing, we now know the right dose to give, and we can enter Phase II testing. This is where we take a group of patients with similar diseases, say for instance FLT3-mutated AML, and give them all of the same treatment at the same dose, and we can determine how well that works. How many patients are going into remission, how long do they stay in remission, how long do they live after the treatment. So once we see a trial through Phase II testing or see a new drug through Phase II testing, we can then move towards Phase III testing, if it looks promising. So the idea here is we take the new agent which looks good, and compare it to our best available treatment. So that can be standard chemotherapy in many cases, and sometimes it is placebo, but most – in most trials with acute leukemia it is not. And then we compare how these two groups of patients, who are randomly assigned, do. And if the new treatment is better than our current standard, why then we have a new standard of care. And that's how drugs are developed and that's how we move the disease forward.

## **Slide 26. Risks and Benefits of Clinical Trials**

We see that there's many possible benefits to participating in clinical trials. These trials can provide access to a treatment that otherwise is not available, and of course when we are doing clinical trials we watch the participants extremely closely.



# Update on Acute Myeloid Leukemia

September 29, 2016

**Speaker:** Joseph G. Jurcic, MD



**someday  
is today®**

---

## **DR. JOSEPH JURCIC:**

We're always looking for new side effects and we're also looking for good things to happen as well, for rapid responses. If the new treatment is more effective than the standard treatment, you would be among the first to receive that treatment, and of course these trials really allow us to learn a lot about how cancer, about how leukemia behaves, and advance the field.

But as with anything in life, there are risks to this. A new treatment may not be better than the standard. New treatments can have unexpected side effects and in fact could be even worse than the standard treatment.

Because you're watched closely the down side of that is that you may have to see your physician more frequently. You may also need extra tests to determine how the drug is working in your system, how it's cleared from the system, or what effects it's having on certain targets.

And even if a new treatment does work for some patients, of course it doesn't necessarily work for all.

And finally, health insurance covers many clinical trials, but not always. And so I always advise patients to check with their insurance company to see what they would be responsible for paying for on these trials.

## **Slide 27. It Takes a Village to Treat AML**

I wanted to take a few moments to talk about the group effort that it really takes to treat leukemia, because it's not just the leukemia physician or transplant physician. It's many, many others. There are consulting physicians, infectious disease doctors, radiologists, radiation oncologists which we frequently use as part of conditioning for stem cell transplant. Other diagnostic services. We talked about the importance of chromosome and genetic testing, so there are doctors and technicians doing all of these tests, interpreting these results.

Finally, we know supportive care is so important in this disease, so blood banking. The nurses who are really the front line in treating this disease. Social work, physical and occupational therapy. Many, many others. So it really does take a village to treat AML.

## **Slide 28. Working Together Towards One Goal**

All of these people are really working towards one goal and that is making life as good as possible for the patient. We have the healthcare team, the immediate family, caregivers, the community, all working together to improve the future of patients with AML.

## **Slide 29. Conclusions**

Just to sum things up. AML is characterized by two things – increased growth and impaired maturation of early blood cells. Those are the hallmarks of the disease. And we've spent a lot of time talking about chromosome and molecular abnormalities. We can see how it can affect prognosis. It can also direct therapy. I've mentioned for better risk AML we use intensive chemotherapy and try to avoid transplant because of the better prognosis and less side effects with chemotherapy. In high risk AML we know that allogeneic stem cell transplantation currently is our best modality to try to achieve a long term remission. And in older patients this is certainly an area that requires a lot of intensive research. We know that lower intensity treatments serve as a backbone, but we're now seeing that outcomes can be improved by adding newer targeted agents to these treatments.

## Update on Acute Myeloid Leukemia

September 29, 2016

**Speaker:** Joseph G. Jurcic, MD



**someday  
is today®**

---

### **DR. JOSEPH JURCIC:**

Which brings me to the next point. We can see that these molecular abnormalities that can define prognosis can also serve as targets for therapy. This is true of the FLT3 abnormalities, of the IDH abnormalities. And so it's through these clinical trials that we can identify new drugs, bring them along, and this is how we make progress in this disease.

And finally partnership among patients, caregivers and healthcare team members is critical for the best outcomes of patients with AML.

So with that I'd like to turn it back over to Lizette for questions and answers. Thank you for your attention.

### **Slide 30. Q&A Session**

#### **LIZETTE FIGUEROA RIVERA:**

Thank you so much, Dr. Jurcic. It's time for the question and answer portion of our program. And we'll take the first question from our web audience.

Dr. Jurcic, Edward asks is CPX-351 available right now?

#### **DR. JOSEPH JURCIC:**

So it is currently not licensed. I believe that its application is before the Food and Drug Administration. And so it's certainly a promising drug. The results of the clinical trials look favorable and I would predict that it will become licensed, that it will be available, but it is not available at the moment.

#### **LIZETTE FIGUEROA RIVERA:**

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

#### **OPERATOR:**

Yes, and our next question comes from Abraham. Please state your question.

#### **ABRAHAM:**

Yes, Doctor. I am 77 years old and I have a broken twentieth chromosome, I've had heavy duty chemo for AML, and it pushed it into remission. I'm in remission now. I'm taking no medications for cancer whatsoever. I've been in remission for approximately a year. Is there anything I can do to help me stay in remission? Any medicines, any lifestyle changes? What can I do to keep me here?

#### **DR. JOSEPH JURCIC:**

It's a great question. So after patients go into remission we obviously want to do everything possible to help them stay in remission. One of the principles here is that we can kill many leukemia cells with this intensive chemotherapy. In fact to get into remission we have to kill about 99.9% of them. However, it's that 0.1% that's left behind, that if we don't address effectively, can start to regrow and cause relapse. And so that's really a key question.

## Update on Acute Myeloid Leukemia

September 29, 2016

**Speaker:** Joseph G. Jurcic, MD



**someday  
is today®**

---

### **DR. JOSEPH JURCIC:**

Now the fact is, after intensive chemotherapy people have looked at various strategies of so-called maintenance treatment. Most of these trials that have been done in AML have not proven effective and long term maintenance treatment with lower doses of chemotherapy in general has not been proven successful.

One of the things that we're looking at now would be maintenance with sort of less intensive therapies, oral treatments, newer agents that haven't been tried before. So that's one important strategy. Also strategies that can get the immune system to recognize and destroy these residual leukemia cells.

So this is a very active area of investigation. I think even though the trials with older chemotherapeutic drugs have not been so successful, I believe this is really something that needs to be looked at, now that we have more tools at our disposal.

And so at this point I can say that there's nothing really that's been proven to be useful in this particular setting, but it is an active area of investigation.

As far as what you can do with your lifestyle, there's nothing that I guess you can eat or drink or do or not do that's been proven to be helpful. I think maintaining a healthy lifestyle overall, eating a proper diet, and exercise is important for your overall health and well-being, but I can say that there's been nothing – no modifications you can do in your lifestyle that really have been shown to make a difference.

What we have to hope is that with the intensive chemotherapy that you've had, those residual leukemia cell have already been dealt with and we've killed enough of them so that the disease does not return.

### **LIZETTE FIGUEROA RIVERA:**

Thank you, Doctor.

And I have a question from the web audience. Margaret asks, I don't understand how CAR T-cell therapy can be used in a myeloid disease. Unlike non-Hodgkin lymphoma, for example, where a patient can live without B-cells for a time. It doesn't seem logical that a patient can live without myeloid cells. Can you shed some light on this?

### **DR. JOSEPH JURCIC:**

Absolutely. That's a great question. A lot of people are asking themselves exactly the question. People who do research in CAR T-cells are asking exactly that question.

Now the major – just to sort of generalize, to get everybody up to speed, because that's a pretty advanced question – the CAR T-cells, first of all, let me explain what a CAR T-cell is. So the principle here is that one takes their own T-cells from the body and then transfects them with a gene that encodes – what stands for a chimeric antigen receptor, that's what CAR stands for. So what this means is essentially it's kind of a hybrid molecule. It's part T-cell receptor that can stimulate the T-cells, to kill the targeted cell, and the sort of business end of this is a piece of a monoclonal antibody that recognizes a protein on the surface of the leukemia cell. So the major success that we've seen in CAR T-cells so far has been in acute lymphoblastic leukemia and those particular constructs target CD19, which is an antigen that's seen on B-cells. And so when you give these CAR T-cells they potently kill off leukemia cells and yes, they kill off normal B-cells, that are the things that make antibodies to fight infection.

## Update on Acute Myeloid Leukemia

September 29, 2016

**Speaker:** Joseph G. Jurcic, MD



**someday  
is today**<sup>®</sup>

---

### **DR. JOSEPH JURCIC:**

And so you're absolutely correct. In ALL, when a patient is in remission after receiving CAR T-cells, their antibody levels will be low, but you can simply replace them very easily with something called IVIG, intravenous immunoglobulin. So it's kind of an easy problem.

But if one were to target an antigen that's seen on myeloid cells, it gets a little more dicey. So the main CAR T-cells that have been looked at, at least in experimental systems, none of this is in patients yet, are CD33, and we've talked about the importance of that target, and another one called CD123. The problem with these particular antigens is that they're seen on normal myeloid progenitor cells. So if you kill all of the CD33 targeted cells or all of the CD33 positive cells or 123 positive cells in the body, you're not going to be able to make normal healthy cells. You won't make neutrophils. And you're right, it's really impossible to live long term without those cells.

So people are looking at a number of strategies to try to adapt CAR T-cell therapy to these targets. And there are various ways that you can allow those CAR T-cells to go in and do their job and kill the leukemia cells and then kill off the CAR T-cells. And there are various strategies that are being looked at to do exactly that. For this strategy to work, you've got to get the cell – you've got to have like these T-cells basically self-destruct at some point.

Another possibility would be go in and kill off all the progenitor cells as well as leukemia cells, but then follow that up with a stem cell transplant. And that may be another way to overcome this.

And of course the final way would be to try to find a target that is specific for the leukemia cells, but not kill off every normal myeloid precursor cell in the body. And of course people are looking for that sort of antigen. It's a big of a Holy Grail, but I think perhaps we're getting closer.

And so those are the strategies that are being looked at for applications of CAR T-cells in myeloid leukemia.

### **LIZETTE FIGUEROA RIVERA:**

Thank you so much, Doctor, for the explanation for the CAR T-cell therapy. And along that line we do have another question on the web from Diane that asks if you can please redefine and further explain what a monoclonal antibody is?

### **DR. JOSEPH JURCIC:**

So antibodies in general are proteins that are made by our body by B-cells. And normally we make these antibodies to fight off infections, viruses, bacteria, fungi. Okay, that's the normal function of the antibody.

Well, we know that there are certain proteins that are at least if not specific to the leukemia cells, that are found on leukemia cells preferentially, and we can make antibodies that target that one specific protein. And because it's targeting one protein that's why it's a monoclonal antibody, it's from a single clone, that binds to one specific protein.

And so generally the way these antibodies were made initially was by injecting leukemia cells into mice. The mice would react to human leukemia cells because of the foreign invader, if you will. And so the mice would make antibodies to fight off the leukemia cells that they were being injected with. And then a particular antibody that targeted a specific protein was isolated, those could be cloned and made in large numbers.

## Update on Acute Myeloid Leukemia

September 29, 2016

**Speaker:** Joseph G. Jurcic, MD



**someday  
is today®**

---

### **DR. JOSEPH JURCIC:**

We've since learned to make fully human antibodies so that mice can generate essentially a protein that's identical to a human, human antibody. And this is the backbone of this sort of antibody therapy that can be used – it actually has multiple applications. Some antibodies have potent effects on their own and can stimulate the immune system. A good example of that would be rituximab that's used to treat lymphomas as well as chronic lymphocytic leukemia. And actually can have benefit in acute lymphoblastic leukemia as well.

So in AML that sort of antibody that has enough potent immunologic effects on its own has not been found yet. But we can use these antibodies as delivery vehicles as well. And so we talked about how an antibody can be – you can attach a drug directly to an antibody. So you can envision this antibody circulating through the body, attaching itself to the leukemia cell, delivering this drug directly to the leukemia cell, sparing normal cells in the body from the toxic effects of this drug.

We can use it to deliver radiation directly to the leukemia cell with basically the same principle. Or you can take pieces of antibody, like we talked about the bispecific antibodies, where you can target two different types of cells. Target one cell, the leukemic cell. The second cell that is the effector cell, the cell that will kill the leukemia cell. And so that approach has been done in ALL successfully with a drug called blinatumomab and similar agents are now under development for AML.

I hope that clarifies things a bit.

### **LIZETTE FIGUEROA RIVERA:**

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

### **OPERATOR:**

Thank you. And our next question comes from William from Minnesota. Please state your question.

### **WILLIAM:**

Yes. I've been treated for myeloblastic leukemia since November First. I'm 82 years old. I've been in excellent physical condition my whole life and I still am, outside of the AML. I was on Vidaza® for a while, for about four months, and it didn't treat me too good with the side effects, so they switched me over to decitabine, Dacogen®. That not only treated me a lot better, but it also lowered my blasts in my bone marrow. Now the doctor, the oncologist told me there's venetoclax that's at our university in a clinical trial that I could take, but I would have to stop my decitabine and switch over to the venetoclax. And on your program today you mentioned that the decitabine, the venetoclax could be taken in conjunction with it. So which is correct?

### **DR. JOSEPH JURCIC:**

So the trial that I highlighted in the presentation today was for patients who were previously untreated. Again, older individuals who had not received any therapy for their AML. And as first treatment they were given venetoclax in combination with either Vidaza – azacitidine, decitabine, or low dose cytarabine. And so all of those strategies actually seem to work pretty well. But before that there was an earlier study, a pilot study, looking at venetoclax alone. And that also showed activity in people who had received other therapies and their disease had returned. And in that trial patients did respond to venetoclax as a single agent.

## Update on Acute Myeloid Leukemia

September 29, 2016

**Speaker:** Joseph G. Jurcic, MD



**someday  
is today®**

---

### **DR. JOSEPH JURCIC:**

So I'm not sure what study that your doctor has at the local hospital, but I can tell you there is precedent for giving venetoclax alone and for patients responding to it. So I think perhaps we're both right.

### **LIZETTE FIGUEROA RIVERA:**

Thank you, Doctor. And we do have a question from the web. Stephanie is asking about acute promyelocytic leukemia, APL, the relapse rates for APL?

### **DR. JOSEPH JURCIC:**

So I think acute promyelocytic leukemia has really been one of the great successes in AML. So just to explain to everybody what this is, it's a specific subtype of leukemia, of AML. It used to be called the M3 variety in the FAB classification. And now we think of it by its unique chromosomal abnormality. It results from a translocation between chromosome 15 and 17. On chromosome 15 there's a gene called PML that stands for promyelocytic leukemia. And on chromosome 17 there's a gene that encodes the retinoic acid receptor alpha. And so bringing these two genes together causes the cells to get stuck at an early stage called the promyelocyte stage, and that results in the disease.

So very interesting because I guess back in the 90s a group from China started giving Vitamin A or Vitamin A derivative, all-transretinoic acid to patients with acute promyelocytic leukemia, and reported high remission rates. Following that a group in France did it and then that was brought to the United States. I was at Memorial Sloan-Kettering as a fellow at the time and we saw these remarkable response rates by giving a derivative of Vitamin A. And of course it was later recognized that it all had to do with the fact that the gene that encodes the receptor for Vitamin A was involved in this.

And so then a number of studies were done, combining this with chemotherapy, producing very high response rates, high long term remission rates, high cure rates.

Then about a decade later the Chinese once again started giving a form of arsenic to patients. Arsenic trioxide. And this produced response in about 90% of patients. I was still at Memorial Sloan-Kettering at the time as faculty member and we started giving it to patients there and we saw exactly the same sorts of responses. And on the basis of about 50 patients that were treated in the United States, this drug was licensed for acute promyelocytic leukemia.

And we now know that the majority of patients with acute promyelocytic leukemia can be treated with these two agents, a derivative of Vitamin A, all-transretinoic acid, and arsenic trioxide, and it can produce responses in virtually everybody with long term survival in about 85% to 90%, even in some studies more than 90% of patients.

So it's still a tricky disease to treat because when patients present they can have a lot of problems with bleeding and so the first few weeks of therapy can be difficult. It's important that the disease be recognized and treated promptly, that patients receive transfusion support, proper supportive care. But if you make it through those first few weeks the response rate is extremely high, the long term survival rates are extremely high.

## Update on Acute Myeloid Leukemia

September 29, 2016

**Speaker:** Joseph G. Jurcic, MD



**someday  
is today®**

---

### **LIZETTE FIGUEROA RIVERA:**

Thank you, Doctor, for the explanation. And we are very happy to report that there are very positive prognoses for APL patients, thanks to all of the clinical trials and the advancement.

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

### **OPERATOR:**

Thank you. Our next question comes from James from Missouri. Please state your question.

### **JAMES:**

Yes. I would like the doctor to maybe speak a little about the long term survival rates for bone marrow transplant patients 70 and older, who is intermediate risk.

### **DR. JOSEPH JURCIC:**

So when I first started in this field we only did transplants up to about age 60 or so. Even that was pushing it. We thought that the rates of severe reactions, so-called graft-versus-host disease where the new immune system can attack normal cells in the body was simply too high and it was too dangerous for people over the age of 60. So with advances in the procedure, and again I'm not a transplant myself, but I can tell you that there have been tremendous advances in transplant biology, in supportive care.

We now know we can offer this procedure safely up to around age 75 in most centers. So it's opened up the possibility of transplant for far more patients.

Now with intermediate risk disease overall we know that we can improve the chance for younger individuals staying in remission by about 50% over what it would be if they just received chemotherapy alone. In older individuals it is tougher. There still is more toxicity with transplant than for younger individuals. But it has gotten safer and safer.

And so we know that long term cure rates for intermediate risk disease in older individuals is still not what we would like it to be. And I think it requires a careful discussion with your leukemia physician, with your transplant physician about the risks and benefits of this more difficult treatment than standard chemotherapy, and what would be right for you. Clearly if you can get through the treatment safely, the chance of relapsing after a transplant is less than after chemotherapy. I think the key here is that they need to be able to take you through the treatment safely and that really is a discussion on a case by case basis.

So other factors that can play a role in this would be other medical conditions that the person has, as well as the type of donor. So is the donor a matched sibling or is it a perfect match from an unrelated donor, or are we talking about a half-match or haploidentical transplant or a mismatched transplant from either a relative or an unrelated donor. So all of this can play a role in predicting potential side effects of the treatment. And so like everything, the devil is in the details here.

### **LIZETTE FIGUEROA RIVERA:**

Thank you, Doctor. And our last question comes from Arthur. Arthur asks, I'm approaching ten years since diagnosis and nine years since my last treatment. Can I expect the AML to return?

## Update on Acute Myeloid Leukemia

September 29, 2016

**Speaker:** Joseph G. Jurcic, MD



**someday  
is today®**

---

### **DR. JOSEPH JURCIC:**

AML, if it relapses, usually does so pretty quickly, within about two to three years after the last treatment. So it would be unusual to relapse this late in your course. That said, we still follow patients long term with this disease because we know other things can happen. Having gone through the sorts of chemotherapy, we want to make sure that there's no damage to other organs. And we also – every time we give chemotherapy, where we can run the risk of damaging normal stem cells in the body, and a second disease developing later. A myelodysplastic syndrome or even a second leukemia developing many years later. So remember we talked about the category of therapy related myeloid neoplasms, well, that can even happen to patients who have been treated for an AML. They can develop a second form of AML or myelodysplastic syndrome years later.

And so it's important to follow up with your physician and make sure that your blood counts are still stable and that everything else – that you're otherwise healthy. But I think the chance of relapsing from that original leukemia at this late date is extraordinarily unlikely.

### **LIZETTE FIGUEROA RIVERA:**

Thank you, Doctor, and thank you, Arthur, for your question, and thank you, everybody for your questions.

Again thank you so much, Dr. Jurcic, 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.

### **Slide 31. Support Resources**

If we weren't able to get to your question today, you can please call The Leukemia & Lymphoma Society's Information Specialists at 1-800-955-4572 from 9 AM to 9 PM Eastern Time or reach us by email at [infocenter@LLS.org](mailto:infocenter@LLS.org). Information Specialists are available to answer your questions about treatment, including clinical trials, or answer other questions you may have about support, including financial assistance for treatment.

Again, we would like to thank Celgene Corporation and Stemline Therapeutics, Inc. for their support of this program.

Dr. Jurcic, 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**