AML – Emerging Treatment Strategies

TRANSCRIPT

Wendy Stock, MD
July 19, 2012

WELCOME AND INTRODUCTION

Clare Karten, MS

[Slide 1] On behalf of The Leukemia & Lymphoma Society (LLS), a warm welcome to all of you and a special thank you to Dr. Wendy Stock for sharing her time and expertise with us today.

We have over 700 people participating in today's program from across the United States and from Barbados, Canada, Colombia, India, the United Kingdom and Uruguay.

You should have received or downloaded materials for the program. Dr. Stock has prepared slides that she will explain during her presentation. If you don't have a copy of the slides already, you can view or print them from our website at www.lls.org/programs.

Following Dr. Stock's presentation, we'll take questions from the telephone and Web audiences. We're also audiotaping and transcribing today's program for posting on our website at www.lls.org/leukemiaeducation so you will have the opportunity to read or listen to the program again at your convenience.

Before I turn the program over to Dr. Stock, I would like to introduce The Leukemia & Lymphoma Society's President and CEO, John Walter.

John Walter

Thank you, Clare. I'd like to add my welcome to the patients, caregivers, survivors and healthcare professionals participating on this call today. We are fortunate to have Dr. Wendy Stock with us, an expert in the medical management of acute and chronic leukemia and myelodysplastic syndromes. We appreciate her dedication to supporting the LLS mission through her research and clinical practice. Dr. Stock, thank you for taking the time out of your busy schedule to provide us with information about emerging treatment strategies for acute myeloid leukemia (AML).

LLS is committed to bringing you the most up-to-date information about acute leukemia and other blood cancers. We know it is important for you to stay current so that you can work with your healthcare team to determine the best options for the best outcomes. Our vision is that one day a great majority of people who have been diagnosed with a blood cancer will be cured or they will manage their disease with good quality of life.

Since 1954, the LLS has invested more than $814 million in research programs specifically targeting blood cancers. We will continue to invest in research for cures and improving access to care and in services that improve the quality of life for patients, survivors and families. This program is one step on the road of your journey to managing your life after a diagnosis of AML. Thank you, and I'll turn the program back over to Clare.

Clare Karten, MS

[Slide 2] Thank you, John. It is now my pleasure to introduce Dr. Wendy Stock, Professor of Medicine, Section of Hematology/Oncology and Director of the Leukemia Program at The University of Chicago Medicine. Dr. Stock, we are so privileged to have you with us today, and I now turn the program over to you.

PRESENTATION

Wendy Stock, MD

Thank you, so much, Clare. It's a great honor for me to be on the call today, and I hope to provide all of you over the next few minutes with a bit of information on the background about the characteristics of acute myeloid leukemia and then talk about some emerging treatment strategies for particular subsets of patients with AML.

[Slide 3] As you can see from the next slide, AML is a disease that increases with age. And you can see that the peak age or the median age of most patients with AML is actually in the late '60s to early '70s. And yet the disease affects all age groups, particularly beginning with young adult years. So, it's a common disease to all age groups.

[Slide 4] It is a disease that arises from a single transformed hematopoietic stem cell. Thus, we call it a clonal disease because we believe that the disease arises initially from a single or maybe a couple of transformed cells. These cells are characterized by a block in normal blood cell maturation that gives them a growth advantage and the inability to mature into a normal adult blood cell.

It's a very heterogeneous group of diseases. Even though they're all called acute myeloid leukemia, there are many, many subsets. We're learning about more subsets of disease with increasing ability to interrogate the genome. The disease has been characterized by recurring abnormalities of chromosomes within the leukemic stem cell, as well as new molecular genetic abnormalities that have been defined in the last 10 years or so.

[Slide 5] The clinical features of acute leukemias, both acute myeloid and acute lymphoblastic leukemia include a presentation with fatigue, easy bruising and paleness. Patients often have fevers when they present because their blood counts are abnormally distributed and they don't have normal infections fighting cells.

As I mentioned previously, this results from the maturation arrest in blood cell development and results in the inability to form normal, mature adult blood cells and leads to anemia. Because of impaired red blood cell development, thrombocytopenia – which means low platelets due to impaired megakaryocyte development – which give rise to platelets and neutropenia in the case of AML due to the absence of normal granulocytes, which are normal adult white blood cells.

[Slide 6] The goals of treatment for acute leukemia are, of course, hopefully curing the disease; and we do that by eradicating the malignant clone. This is typically done by using a combination of chemotherapeutic drugs, and those drugs are chosen based on the semi-selective killing of rapidly dividing leukemia stem cells.

New strategies have also been developed that specifically target molecular genetic abnormalities that are unique genetic abnormalities that are unique to the leukemia cell population. The goal is to restore normal blood cell growth and development, also known as hematopoiesis.

[Slide 7] The diagnostic workup for leukemia is crucial, and it's important to get this done properly and in a center that can do the complete work-up to make the right diagnosis at the very beginning of treatment. This involves examination of the peripheral blood smear, a bone marrow examination from which we do many, many important tests, including a test called immunophenotyping that helps to characterize the subset of disease; and it identifies proteins on the cell surface that are present in AML and in other leukemias. And it helps us make the diagnosis.

Cytogenetics and FISH, which is an acronym for fluorescence in situ hybridization, identifies specific chromosome rearrangements, and/or deletions that are frequently present in specific subsets of AML. Now we have additional, more sophisticated molecular diagnostic techniques to identify unique mutations that help us even further to characterize these diseases. Some of the ones that we use currently in our diagnostic and therapeutic decision-making include the presence of a *PML-RAR* (promyelocytic leukemia-retinoic acid receptor), or alpha fusion gene, which is the characteristic of acute promyelocytic leukemia, a subset of acute myeloid leukemia or the presence of a *FLT3* mutation, *NPM1* mutation, and *CEBPA*. These are all molecular genetic mutations that occur uniquely in the leukemia cell and help us prognosticate an increasingly develop therapies directed toward those subsets.

In recent years, we have now identified a number of fascinating new mutations that often occur in leukemias; and they're listed on the slide, including *IDH1*, *IDH2*, *TET2*, *DNMT3A* and *WT1* and many others as well, which are soon to be incorporated into diagnostic panels to help us refine our diagnostic ability and hopefully to begin to develop subset-specific therapy.

Patients who might be considered for transplant should also have HLA (human leukocyte antigen) typing right at the time of diagnosis. HLA typing is a way of beginning to immunologically type the patient, which we need for proper selection of a donor for a stem cell transplant, and it should be done before treatment is initiated.

[Slide 8] As I mentioned, the diagnostic work-up is crucial, and it involves examination of the peripheral blood, which you can see in the upper left-hand corner of the slide. The bone marrow aspirate, which helps give us an idea of the appearance of the malignant cells and helps our pathologists characterize the type of AML, and a bone marrow biopsy, which gives us a feeling of the architecture of the bone marrow, whether it's full of leukemia, whether there are only a small percentage of leukemia cells within the marrow; and these are crucial parts of the diagnostic work-up.

[Slide 9] As I also mentioned, doing cytogenetics, which is done in a very well trained laboratory where they look at the chromosomes within the leukemia cells to identify the rearrangements that may be present within the leukemia population. On this slide there is an example of a normal chromosome 15 and a normal chromosome 17, as well as chromosomes called derivative or der(15) and der(17), which represent a translocated chromosome. You can see in the right-hand part of this little cartoon what pieces of chromosome 15 and 17 are rearranged so that part of 15 and part of 17 become fused. This fusion creates a new gene; 15 is called *PML-RARA* because the gene on chromosome 15 is a PML gene, right at the point of the fusion. The gene on chromosome 17 is the *RARA* gene, which is also part of the fusion on chromosome 17. When these two chromosome pieces come together, a new gene is formed, that gene is responsible for the development of acute promyelocytic leukemia.

You can also see in the upper right-hand picture, which is difficult to see, another technique, FISH, as I mentioned earlier, that we use to identify fusion genes because the two different signals, a red and a green signal in the case of representing chromosomes 15 and 17, get fused together; and you see a fusion signal that in this picture you can sort of see as a red/green signal or sometimes as a yellow signal since red and green together make yellow. All used to identify the leukemia.

[Slide 10] In addition, prior to initiation of treatment, we do a number of ancillary tests, including usually a MUGA (multigated acquisition) scan or an echocardiogram, which is to measure cardiac function, since some of the drugs that we use are toxic to the heart. We want to make sure that patients are going to be able to tolerate the drugs that we hope to deliver to treat the leukemia. Most patients get an indwelling tunneled catheter of some sort, often a HICKMAN or a triple lumen catheter. Sometimes a PICC (peripherally inserted central catheter) line, which is placed in the arm, but again is a tunneled catheter centrally placed; and, occasionally, an even bigger bore catheter if patients are going to have their own stem cells collected at later time points for potential autologous stem cell transplant or donation of their own stem cells.

Often centers advise a pre-treatment CAT (computed axial tomography) scan of the sinuses, a high resolution CAT scan of the chest to make sure that there's no occult or not obvious or even obvious infection prior to the time of treatment.

Dental examination is important. We give Provera® (medroxyprogesterone) to prevent heavy menstrual cycles since patients are at risk for bleeding due to low platelets during the treatment. And we discuss fertility issues, particularly for younger adults who are planning on having an allogeneic stem cell transplant in the future.

[Slide 11] As I mentioned, supportive care during the treatment is also crucial. At diagnosis we do a number of laboratory tests to make sure that we're safe in proceeding with chemotherapy. We often give blood and platelet transfusions, even before we start treatment and during the course of many of the weeks of treatment for AML. Typically, we try to maintain the hemoglobin level of approximately 8 grams or higher and the platelet count at 10,000 or higher.

Hematopoietic growth factors can be used in the setting of infection, but they are not typically used during treatment just off the cuff. They're used when people have infectious complications, but not typically as standard of care for this leukemia.

[Slide 12] Infections are a big problem. As I mentioned, the white blood cell count is abnormal, and people don't have normal infections fighting cells. So often centers will give prophylactic or preventative antibiotics to try to prevent infection: antibacterial drugs, antifungal drugs and antiviral drugs are often given to prevent infection. Not all centers use these empirically. Some do. And then all centers will use antibiotics and broaden the spectrum when patients develop fever. Some of the drugs that are used typically for treatment of bacterial and fungal infections are listed here on this slide.

[Slide 13] Most people want to know how did I get this disease, and that is an excellent and confounding question. In most cases, we really don't know why people get acute myeloid leukemia, although recent evidence suggests that there may be certain genes that predispose patients to the development of leukemia. We are just beginning to learn about that, and that may not be in the majority of patients.

We do know that certain risk factors do exist. There are some genetic disorders that predispose towards the development of leukemia. Often these leukemias manifest during childhood. They include Down syndrome and neurofibromatosis and some much less common among already rare disorders, including Klinefelter's syndrome and Shwachman syndrome, etc.

Certain physical and chemical exposures are linked to the development of leukemia, though the actual strength of the link is always in question. People always ask whether certain exposures may have given them a risk for the development of leukemia. We don't typically know that that's a fact, although there is a fairly strong link between the development of leukemia and exposure to certain toxins, particularly benzene. Radiation exposure clearly is an increased risk for the development of leukemia, and perhaps the most threatening of all is the exposure to chemotherapy for the treatment of other cancers. As we get more and more successful at curing people of other diseases, one of the risks is the unfortunate and very frustrating and sad complication of a subsequent development of a second malignancy, that being acute myeloid leukemia.

We are trying our very, very best to understand why certain people who are successfully treated for other malignancies develop second malignancies. This is not clear. It's a very small percentage of people, but this is something that we are actively investigating.

[Slide 14] How do we treat leukemia? In the case of AML, the most active traditional chemotherapy drugs are cytarabine, which is a purine analog and an anthracycline; usually daunorubicin or idarubicin; another anthracycline-like drug is called mitoxantrone and other agents that have strong activity in AML include the drug etoposide.

These drugs are usually given in combination. The most common initial treatment is a combination that many of you may be familiar with. It's known as, "7+3," that's because seven days of cytarabine are given with three days of an anthracycline, daunorubicin or idarubicin most typically.

The first month of therapy is called, "induction therapy," and the goal is to achieve what we call a complete remission. What do we mean by that? We mean that the leukemia is no longer evident when we do a repeat bone marrow examination. We can't see the leukemia cells in the bone marrow, and the blood counts recover to normal levels.

We know, however, that although we don't see the leukemia anymore with the microscope, leukemia still is present below the level of visual detection. In order to cure leukemia, we know that some form of post-remission chemotherapy is necessary. What type of chemotherapy that is depends on many, many factors. There are multiple options. [Slide 15] Often additional courses of chemotherapy are required, as I mentioned, for eradication of the disease, sometimes three or four additional months of treatment. Those are typically called, "consolidation therapy months," for consolidating or strengthening the remission.

This approach, consolidation chemotherapy, may cure good-risk patients with leukemia. We're going to talk about that in a little bit. Other patients may benefit from a stem cell transplant in first remission. Most commonly, people are receiving allogeneic transplants from a donor; and I'm going to talk a bit about that later in the talk. This may and has been shown to improve the outcome of some higher risk patients with the disease.

As I mentioned, the detection of chromosomal abnormalities is crucial for us, not only to help us understand the diagnosis, but also to help us prognosticate for the patient, that is to help predict what their outcome is going to be and help us define the treatment plan.

[Slide 16] Increasingly, we have, as I mentioned, specific therapeutic strategies for different cytogenetic or molecular genetic subsets. The first group of patients that I'm going to look at here are those very good-risk patients, and you can see this is an older slide now. It's more than 10 years old, and our survival rates have improved further for certain good-risk subsets. I'm going to talk about one of those subsets in a minute, but you can see that the best risk subsets have more than a 70% cure rate, compared to patients with a normal cytogenetic who have about, in this slide, a 42% overall survival, which is actually improving as we have improved our treatments in the last decade.

[Slide 17] I'd like to talk for a few minutes about how we can incorporate the insights of cytogenetics and molecular genetics into treatment and give you three brief examples. One is for the good-risk subset, one is for the intermediate-risk subset defined by cytogenetics and molecular genetics and the last for the higher risk or more difficult-to-treat leukemias.

[Slide 18] The first subset that I'd like to talk about is acute promyelocytic leukemia. As I mentioned at the beginning, it is crucial to make the proper diagnosis of leukemia at the time of diagnosis so that the proper therapy can be implemented. In this case, treatment is now directed truly at the molecular

abnormality that causes this leukemia and that is that *PML-RARA* fusion gene that I showed you a few minutes ago.

This fusion gene creates an abnormal signaling pathway in the leukemia cell through a retinoic acid receptor, which is actually vitamin A. But this signaling pathway is crucial to normal blood cell development, and because of the presence of this abnormal fusion gene, the signaling goes awry and the cells don't mature in a proper fashion.

What was found approximately a decade ago was that certain drugs will push these leukemia cells into normal maturation just by giving, in fact, a form of vitamin A, the all-trans retinoic acid form of vitamin A. This has been incorporated into treatment with standard AML chemotherapy and now results in a cure in the vast majority of patients with AML. We have recently found another drug that pushes these cells to mature, that is arsenic trioxide, which has now been added to frontline chemotherapy and significantly further improves outcome. In some countries, arsenic trioxide has been used as the only therapy for this disease, sole therapy, and results in prolonged remissions in good-risk patients with this disease.

[Slide 19] So, as I mentioned, this disease is unique. It has a unique appearance, it has a unique fusion gene and it has a unique therapy. This is a picture of myeloblasts in acute promyelocytic leukemia, and the arrows are pointing at a conglomeration of granules that form these rod-like structures that are called, "Auer rods." Auer rods are the characteristic finding in acute promyelocytic leukemia. They can also be found in other leukemias, but they're the hallmark really of acute promyelocytic leukemia.

And as I mentioned, when you treat this disease, even just with a vitamin, the all-trans form of retinoic acid, you can push the leukemia cells into maturation; and then they just mature and die and the normal blood cells can recover.

[Slide 20] You could see in this picture what happens when you treat cells with differentiating agents, including ATRA, the all-trans retinoic acid and arsenic trioxide. On the upper left-hand corner you see some promyelocytes, the abnormal APL, leukemia cells. In the bottom left, after a few days of treatment with the differentiating agents, you could see that the cells go from being these blasts, etc., in the upper left-hand corner to beginning to mature in the upper right-hand corner to mature granulocytes which are present in the lower corner.

This happens over a period of weeks. It's quite fascinating. You can watch this just by taking a sample of the patient's blood every day and watching the effect of these remarkable agents.

[Slide 21] With this kind of treatment, when you combine these differentiating agents with chemotherapy, you can see this very impressive survival curve from a very large North American study that was published about two years ago. You can see now that more than 80% of patients are cured. Particularly beneficial in this study was the addition of arsenic trioxide to the ATRA and chemotherapy, and that's represented by the very best survival curve on the top there of your slide.

Thus, we are now able, if we make the proper diagnosis, to cure the vast majority of patients with this disease.

[Slide 22] As I mentioned, there are some very interesting studies now that suggest that maybe we don't even need chemotherapy at all. We could just use these targeted agents. We don't know that for sure. This is a small study, actually from India, where patients were treated only with arsenic trioxide, no all-trans retinoic acid, no chemotherapy. In the upper panel on the left, in panel A, you could see the survival there for good-risk patients; and good risk is defined in a number of ways, but mostly by the presenting white blood cell count at the time of diagnosis.

For those very good-risk patients, you didn't need to treat them with any form of chemotherapy, only arsenic trioxide. So, this is quite remarkable that understanding the disease biology has allowed us to develop truly targeted therapies that will hopefully minimize toxicity and significantly have been shown to improve outcome. That is one of our best risk groups of leukemia, and it just illustrates again that making the proper diagnosis up front is very, very important.

[Slide 23] I'm now going to talk to you about the majority subset of disease and talk to you about one group within this majority group. These are patients who when you look at the chromosomes of the leukemia, they don't have any abnormality. But as I mentioned, we now have sophisticated genetic, molecular genetic techniques to identify mutations that may be present, even without an obvious chromosomal rearrangement.

They are often found in patients who have, as I mentioned, a normal karyotype, no cytogenetic abnormality, represented on this slide by the star, with about half of patients being long-term survivors with the disease.

[Slide 24] But now we know that within this group of patients, it's a very heterogeneous group. Some patients do extremely well. Some patients don't do very well with chemotherapy. And what we've learned is that one subset of these patients with normal karyotypes often have a mutation in a gene called *FLT3*. This happens in up to 25% of patients with acute myeloid leukemia. Most of them have a normal karyotype. So, in this case it's also important at the time of diagnosis to send off for this particular molecular genetic mutation that occurs in up to 30% of adults. About 25% is the current estimate.

It occurs in all age groups, and as I had mentioned, it's most common in patients with a normal karyotype. That is they don't have a cytogenetic abnormality, but within the leukemia cells there is this mutation that you can't detect just by looking at the chromosomes.

The remission rates for patients with acute myeloid leukemia with a *FLT3* mutation are really quite high, but the problem is, in these patients, that we have found that relapses tend to occur quite quickly, even given standard post-remission therapy. And this is all relatively new in the last five years, this information.

[Slide 25] We now know that there are other genetic abnormalities that occur in patients with normal karyotypes, some of which, as I mentioned earlier, end up being very sensitive to standard chemotherapy, and patients do very well. Whereas, I just mentioned this other significant subset, those with *FLT3* mutations, may not do so well with standard chemotherapy.

Among the ones that may do well with standard chemotherapy who have a normal karyotype are those with an *NPM1* mutation or a *CEBPA* biallelic mutation as we call it. You could see from this slide, which is a bit difficult to understand, but you can see that this slide is trying to show you outcomes of patients with these different genetics who have transplants or don't have transplant.

The yellow represents patients who were transplanted. The blue represents patients who were not transplanted. Basically what I wanted to show you here was that patients who have *NPM1* and *CEBPA* mutations do about the same with or without transplants, and they do quite well actually. Whereas, people with *FLT3* mutations, you can see if they were transplanted, they may do better with transplants, represented by that yellow survival curve, than if they weren't transplanted in first remission.

[Slide 26] We're also trying to develop therapies specifically targeted at this particular mutation; and, in fact, this mutation results in abnormal expression of this *FLT3* gene, which happens to be a protein enzyme called a tyrosine kinase. Tyrosine kinase inhibitors or TKIs are successful at inhibiting many mutations that are present in many different kinds of cancers that have kinase mutations, including the *FLT3*. Multiple tyrosine kinase inhibitors or TKIs have been tested and demonstrate even single-agent activity, similar to what I showed you for arsenic, with target inhibition in patients with *FLT3* leukemias. It's not as effective as arsenic though, but some of the drugs that have shown single-agent activity include a drug that's used typically for kidney cancer and other solid tumor or solid organ tumor malignancies called sorafenib, a new agent called, "midostaurin" and a very new drug that has gotten a name – AC220 or quizartinib is its current newly minted name.

In a recently completed international trial, which is listed here, we tried to test the benefit of adding, just like we did in APL, the targeted agent, in this case the tyrosine kinase inhibitor midostaurin to chemotherapy for younger adults with newly diagnosed AML who had a *FLT3* mutation. This was a huge international study. It was completed a few months ago, and the trial results are pending. Our hope is that the addition of a targeted agent to standard chemotherapy will further improve the outcome of patients with *FLT3*-mutated AML, and we await these results with hopeful optimism I would say.

[Slide 27] The current *FLT3* inhibitor trials that are ongoing in the United States include a frontline trial in older adults with *FLT3* mutation, combining chemotherapy with another one of the tyrosine kinase inhibitors that targets *FLT3*, sorafenib. The most active of these drugs, AC220, is still being tested in the relapsed setting; and it's currently in an expanded phase II study with two different doses for patients with relapsed AML who have a *FLT3* mutation.

This drug has quite a bit of activity. [Slide 28] This next slide just shows you a little bit of how these drugs are initially developed. In this case, AC220 was tested in an animal model, a mouse model of myeloid leukemia with a *FLT3* mutation. You can see in panel A that untreated cells have a huge amount of *FLT3* activity. The "% phospho-*FLT3*" [y-axis title on Slide 28] means that the enzyme is very, very active. After two hours of treatment with AC220, the activity of this enzyme is shot way down, but 24 hours later the activity comes back and that suggests that you need to keep treating the patients with this, or in this case the animals, with constant exposure to the drug.

Basically what the other charts on this slide are showing you is that AC220 may be more effective than another tyrosine kinase inhibitor at maintaining, called sunitinib, at maintaining suppression of the malignant clone by inhibiting *FLT3*, and you can see that with dose escalation of AC220. At a higher dose, the animals that were treated with the higher dose at 10 mg/kg, actually, as a single agent, were able to survive much longer with their leukemia than those that received lower doses, which suggests significant activity of this drug. And this is how often the early phases of development of a drug are done.

[Slide 29] Currently, the recommendation for those patients with *FLT3*-mutant AML are, as I mentioned, it's crucial to screen for the mutation at the time of diagnosis because if you don't look for it, you're not going to know it's there. Because I showed you that transplant improves outcome for these patients in first remission, HLA typing should be done at diagnosis. We encourage, if there is an available trial, to enroll on a frontline clinical trial that incorporates *FLT3* into treatment with chemotherapy as frontline therapy, to consider allogeneic stem cell transplant in first remission if that's an option, and to try to enroll in new trials for relapsed disease with novel agents such as AC220 or quizartinib, which hopefully soon will be moved onto the frontline setting if the studies of the initial activity can be confirmed.

[Slide 30] Here again you can see the potential benefit with good survival of patients with *FLT3*-mutated AML who were transplanted in first remission.

[Slide 31] The final example that I'd like to give you encompasses a very large subset of patients with adverse cytogenetics. Those are the patients who have chromosome abnormalities that we know don't do well with our standard chemotherapy approach, and they're represented here on this slide. They include patients with deletion of the long arm of chromosome 5, the long arm of chromosome 7 or loss of chromosome 7, the loss of the long arm of chromosome 3 or patients with multiple chromosomal abnormalities, which we call a complex karyotype. These patients we know don't do well with standard chemotherapy, and we worked very hard in the last number of years to try to develop new strategies for these patients.

[Slide 32] The biology and age often coincide in AML, and typically the worst risk, cytogenetics and older age, are strongly associated. So, older adults often have these abnormalities that make the disease relatively resistant to chemotherapy. These types of leukemia often occur in people who have a preceding myelodysplastic syndrome or myeloproliferative disease. As I just told you, standard

cytotoxic chemotherapy, for example the 7+3 approach and post-remission chemotherapy, has not been very effective at curing patients.

[Slide 33] But we do have some very interesting new developments. In addition to the DNA, there are multiple levels of regulation of genes that we are learning about. One of the levels of regulation has to do with certain structures of the DNA that we call the epigenome. The epigenome, which includes histones which modify the structure of the DNA, and a lot of other small molecules that we've learned about, including microRNAs, which regulate myeloid development. There's evidence that abnormal methylation, which is the addition of a methyl group to critical regions of genes, silences genes that may be essential for normal blood cell development.

Multiple studies suggest that use of drugs that regulate the epigenome, that change methylation or change histone structure may be effective. These include drugs that are approved for myelodysplastic syndromes as well, including 5-azacitidine or Vidaza®, deoxycytidine or often known as Dacogen® and a histone deacetylase inhibitor that has been approved for treatment of certain lymphomas called vorinostat.

[Slide 34] On the next slide, I want to show you something that was a very interesting and important study that was spearheaded by Dr. Fenaux and colleagues. It was an international study to look at the outcome of adults with a low blast percentage in their bone marrow at the time of presentation, which is not uncommon in older adults with AML whose disease arises from a prior myelodysplastic syndrome. Using the drug 5-azacitidine versus a treatment strategy that was chosen by the investigator, this is a very complicated slide. But basically what was done in this trial is that patients were randomized to either getting azacitidine or a treatment strategy that their physician thought was the best alternative treatment strategy for them. In some cases, it was just transfusion support. In some cases, it was the use of low doses of cytarabine, the drug that we use in the 7+3 regimen, and in others, it was standard chemotherapy like the 7+3 regimen.

So in this trial, the doctor and the patient were allowed to choose, if they didn't get azacitidine, what they would have gotten. And what they found was that the use of azacitidine versus any of the other three choices significantly improved overall survival. And so for the first time here, we see that using a nontraditional approach to treatment improved outcome for these very high-risk patients. [Slide 35] You can see that on this slide. There was a significant improvement for the patients who received azacitidine, which is the blue line over the patients who got a conventional care regimen, either chemotherapy, very aggressive chemotherapy, low-dose chemotherapy or just blood transfusion and platelet support.

[Slide 36] We've taken this a step further and wondering whether if we give the drug that we're trying to change the epigenetic profile in the leukemia cells for longer periods of time, do we do even better? And there was an interesting study that was done and published a couple of years ago by the group from Ohio State University where decitabine was given for 10 days at a dose of 20 mg/m^2 to older adults with untreated AML. You could see that the median age of these patients was actually older, 74 years.

Remission was achieved in 50% of patients with this low-dose chemotherapy after three cycles. And, interestingly, both normal- and poor-risk cytogenetic patients responded. So, we're hopeful that this approach may actually improve the ability to tolerate treatment as well as the outcome of older adults. We know that this isn't the be all and end all and there are some ongoing trials using this strategy as well as a couple other interesting new strategies for high-risk and/or older patients with AML.

[Slide 37] There's a recently activated trial sort of following up on the data that I just showed to you of older adults who will be randomized to receive that 10 days of decitabine versus decitabine plus bortezomib (Velcade®), another drug that may further enhance the decitabine activity by regulating another epigenomic area called mirrors or microRNAs.

There is a trial in the Eastern Cooperative Oncology Group (ECOG) where another purine nucleoside that has demonstrated activity in older adults with AML, clofarabine, is being given with or without chemotherapy. There's also an interesting trial that has been recently completely, I believe, in the Southwest Oncology Group (SWOG), where they've used azacitidine plus a monoclonal antibody, Mylotarg® (gemtuzumab ozogamicin), to treat patients with AML.

[Slide 38] Allogeneic transplant can result in prolonged survival in patients who are over the age of 60, and this is important because I've shown you that standard chemotherapy alone cannot cure these patients. We have new strategies to utilize allogeneic transplant as a method of treatment for even older adults by using what we call reduced intensity conditioning regimen.

You can see here on this slide a recently published paper looking at long-term outcomes in adults over the age of 60 using one of these reduced intensity, or as they're also called, nonmyeloablative conditioning regimens to allow an allogeneic transplant to happen. Why do we want to do an allogeneic transplant? Because with an allogeneic transplant, you are actually receiving stem cells from a donor, and when you receive these stem cells, you know for sure they're not going to have leukemia in them You also know that they're not going to have any kind of leukemia or immune strategy that would hopefully allow the stem cells to eradicate any residual leukemia.

[Slide 39] So, in conclusion, standard chemotherapy may benefit only limited numbers of older adults with AML. It's critical to identify good-risk as well as bad-risk patients. We would strongly encourage enrollment on a clinical trial. Many are currently available. It's important to HLA type at diagnosis because transplant has the potential for cure, even in older patients, and maybe refer patients for transplant in first remission.

[Slide 40] Finally, AML treatment increasingly is dependent on the underlying biology of the disease. It's crucial to obtain the proper diagnostic work-up. Biologically targeted agents provide potential for significant improvements in outcome. Allogeneic transplant in first remission should be recommended for all high-risk groups, including older adults who may be eligible, and clinical trial enrollment is the path to cure.

And with that, I'd like to thank you all very much. I'll stop now to take questions

QUESTION-AND-ANSWER SESSION

Clare Karten, MS

[Slide 41] Dr. Stock, thank you so much for your clear and informative presentation. It is now time for questions and answers. For everyone's benefit, please keep your questions general, without many personal details so Dr. Stock can provide us with general answers.

Let's take our first question from our Web participants. Our participant writes, "My mother has AML, arising out of MDS (myelodysplastic syndrome). She has just achieved a second remission. She has not had molecular diagnosis yet. Is there a role for molecular diagnosis in her case as a guide to maintenance therapy, to keep her in remission?"

Wendy Stock, MD

That's a really good question. The good problem is that her disease is again in remission; and so it's unlikely that you would be able to identify the abnormality at this point. If there are cells that are present from the diagnostic sample or when she relapsed, then it might be possible to obtain that sample and do some of the molecular testing.

In general, if she's in second remission now, it might be appropriate to do some sort of maintenance therapy to maintain the remission; and she may have discussed that with her physician. Depending on her age, she could be a candidate for an allogeneic transplant. I don't know her age and I don't know if there are other comorbid conditions. For example, severe kidney disease or something that would prevent that.

And then there may be a trial that's available for people who are in remission for specific post-remission therapy. Many centers, for example, are testing novel vaccines or other strategies that might be available to her. So, it's a really good question. The good news is that she's back in remission, so you don't have a sample necessarily to test, unless the relapse sample was banked.

Clare Karten, MS

Thank you so much for that question and for your answer, Dr. Stock, and we'll take our next question from our telephone participants.

Operator

Thank you. Our next question comes from Marianne calling from Virginia. Please state your question.

Marianne from Virginia

Hi, Dr. Stock. Would you be able to comment at all on your recommendations for second transplant for those of us in high-risk groups such as *FLT3* who relapsed after a first allogeneic bone marrow transplant.

Wendy Stock, MD

That's another very, very good question. I think that in general, that might be a good approach, particularly if some sort of *FLT3*-targeted agent could be added to get you back into remission. And, in fact, there are some interesting data that have been published that are now using the tyrosine kinase inhibitors (TKIs) such as sorafenib or other TKIs in the post-transplant setting very early on to try to prevent relapse of the disease again.

So, it's certainly a reasonable consideration, particularly if, perhaps, some tyrosine kinase inhibitors could be incorporated to get you back into remission and then post-transplant as well. The other option is to do an early donor lymphocyte infusion, if that's a possibility when you're back in remission if you've had no graft-versus-host-disease to begin with.

So, there are other options that could be considered as well as a different kind of preparative regimen for the transplant that may have better anti-leukemia activity. So, it's certainly a reasonable consideration if you are in good shape and able to tolerate the rigors of a second transplant.

I wouldn't recommend it, however, if the disease was not in second remission. I think that that's the most important piece, is that you try to get back into a remission again prior to going forward with the transplant.

Clare Karten, MS

Thank you, Marianne, for that very good question, and thank you, Dr. Stock. We'll take our next question from the Web and continuing with talking about stem cell transplant. Talking about upper age limit, our participant asks, "Would a 74-year-old woman in otherwise good health ever be a candidate for a stem cell transplant?"

Wendy Stock, MD

The answer is, yes, although there are very limited data. You saw from one of my slides there are patients over the age of 70 who have been transplanted. The type of transplant regimen and the performance status as well as the overall condition of that person would be crucial, but certainly people have had transplants at that age. A matched sibling transplant would probably be the safest, a matched sibling donor. I think the alternative donor transplant has not been very much tested; not even sibling transplants have been very much tested in adults over the age of 70, but I still think it's

worthwhile to at least visit a transplant referral center and be evaluated if that's an interest of the patient.

Clare Karten, MS

Thank you, Dr. Stock, and we'll take our next question from the phone audience.

Operator

Thank you. Our next question comes from Steven calling from Michigan. Please state your question.

Steven from Michigan

Good afternoon. Thank you very much. I'm a recent transplant person from the Mayo Clinic. I had double cord transplant. They were unable to find a match for me, or my siblings didn't match, so I had a double cord blood transplant. I'm 63 years old, and I'm wondering what the research is showing in terms of the results now of using stem cells from the umbilical cords and what kind of research is being done and the success rate of that. I have acute myeloid leukemia, and I also have the chromosome problem.

Wendy Stock, MD

I think the fact that you've already engrafted with a double cord is excellent. One of the big challenges to the cord is the long time to engraftment, and that's probably why they gave you a double cord.

Steven from Michigan

I'm a double cord, and it's been very interesting because I was a larger man. Of course, I've lost a lot of weight through this; but it'll be six months that have passed going back for my check-up. But it's a slower process I understand when you do double cord than you do with the standard.

Wendy Stock, MD

That's correct. It takes longer to recover both immunologically to prevent infections as well as just the normal blood counts. But the data actually from the University of Minnesota, who has the largest experience with cords and double cords, are actually quite exciting in terms of outcomes. They even suggest from their data, which is really the only data like this that exists, that the cord blood patients who have good engraftment have excellent disease-free survival. So, I think it's a very promising strategy for people who can have cords that are fairly well matched and who engraft relatively well. That's still the biggest challenge to the cords, of course, and the fact that you're six months–

Steven from Michigan

Right, the platelet recovery in the red blood cells seems slower than the normal process, but–

Wendy Stock, MD

It's inevitably slower, but the fact that it's happening is a good thing; and the anti-leukemic effect of that double cord seems to be quite promising. So, I think it's a very exciting area of research and of options because it allows a lot more people who would not have been able to be transplanted to potentially receive a transplant.

Clare Karten, MS

Thank you, Steven, for your question, and thank you, Dr. Stock, for your excellent answer. Going back to our Web audience and continuing with our research-oriented questions, our participant writes, "Do you have any information about the Celator Trial, CPX-351? If so, could you discuss that?"

Wendy Stock, MD

Yes. CPX-351 is a very, very interesting idea. It's reformulation of a very old idea, which is, as I mentioned to you, cytarabine and daunorubicin are the two most active drugs, daunorubicin or idarubicin. But in this case, daunorubicin are the most active drugs for treatment of AML. And what CPX is, it's a little structure, kind of like a little fat globule actually, that incorporates a ratio of cytarabine and daunorubicin, just into this little globule. They have found that an optimal ratio, they've developed an optimal ratio of these two drugs to be put in this lysosome; they've tested it as a different way of giving chemotherapy, of hopefully a more effective way that will allow the chemotherapy to be released a little bit more slowly and for a more prolonged period of time.

The results from the trial have been recently presented at the American Society of Clinical Oncology (Annual) Meeting, and the drug seems to be quite, it's combination. It's really cytarabine and daunorubicin in this fat globular or liposome. The data suggest that the response rate in patients with relapsed disease is very high, higher than many other drugs that have been used in the relapsed setting. The most interesting piece of it is that it seems to be particularly effective for the poor-risk cytogenetic group.

So, I think it's quite promising. They're moving forward now with a frontline study comparing CPX to standard chemotherapy in high-risk AML. So, it's another interesting combination that I didn't have a chance to mention on the call.

Clare Karten, MS

[Slide 42] Thank you. Thank you very much, Dr. Stock. We'll take our next question from the phone audience.

Operator

Thank you. Our next question comes from Paul calling from Ohio. Please state your question.

Paul from Ohio

Dr. Stock, the patient's a 61-year-old woman. The original diagnosis was AML, and she's been through induction with cytarabine and idarubicin. That was successful, a first consolidation with cytarabine and idarubicin. But in the meantime, the diagnosis has been modified to MDS evolved into AML. What gets treated now, the AML or the MDS?

Wendy Stock, MD

The AML is what gets treated. And so what we know is just that those patients who have AML that evolved from MDS (myelodysplastic syndrome), or patients who present with AML with dysplastic features –dysplasia just means abnormal appearing or abnormally formed blood cells – and some people don't have a prior MDS but they have AML with dysplastic features. Those diseases tend to be more resistant.

But the patient is now in remission, which is great. And now the post-remission strategy has to be dictated by what might be the optimal treatment for that particular patient, that is in terms of tolerability. A transplant would certainly be a reasonable option if the patient was in good shape. Alternatively, since they're in remission, some form of post-remission therapy would be essential to try to maintain remission.

Typically in my practice, if the patient is eligible for a transplant, if they've had an antecedent myelodysplastic syndrome, I would advise a transplant in first remission, simply because that would be the best chance for curing the disease.

Clare Karten, MS

Thank you, Dr. Stock. We'll take one more question from our Web audience. "I am in remission for AML for 16 months now. What is the risk of the disease becoming active again?"

Wendy Stock, MD

Ah, that's a very good question. I would have to say that typically the majority of relapses from AML occur within the first two years after completing treatment. After that, the relapse rate becomes exceedingly smaller. But there's still a risk of relapse, and it particularly depends on the type of leukemia, that is the molecular or cytogenetic subset. Some AMLs we know tend to have later relapses, but once patients are out about 24 months, the risk of relapse becomes quite small, fortunately. But still not zero, and that's a great question. It's a question my patients often ask me,

and I always say that the risk is small, but it's not absent. So, they're getting to the point where it's getting to be much less likely that a relapse would happen, but it's still possible.

CLOSING REMARKS

Clare Karten, MS

Well, thank you for your answer to a question that's on so many of our minds, and thank you all for your questions. Our program has come to a close, so please help me thank Dr. Stock. We are so grateful you have donated your time today. We hope that many of your questions were answered and the information we provided will assist you in your next steps. If we weren't able to get to your question or if we can provide additional information or support, please call an LLS information specialist at (800) 955-4572. Our specialists can provide you with information about AML research and clinical trials.

On behalf of The Leukemia & Lymphoma Society, thank you all for sharing your time with us. Goodbye and we wish you well.