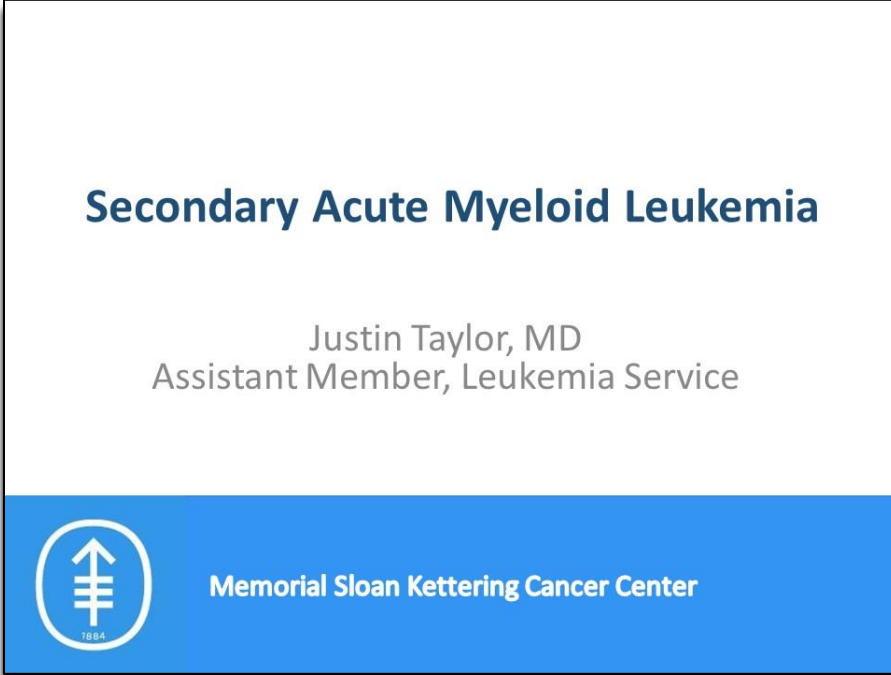


Understanding Secondary Acute Myeloid Leukemia (AML)

Mrs. Alicia Patten-Madera


Greetings and welcome to our program, “Understanding Secondary Acute Myeloid Leukemia”, also known as sAML. The Leukemia & Lymphoma Society exists to find cures and ensure access to treatment for blood cancer patients.

Our vision is a world without blood cancer. For more than 60 years, LLS has helped to pioneer innovation, such as targeted therapies and immunotherapies that have improved survival rates and quality of life for many blood cancer patients. We advocate for patients, survivors, and their families, helping them navigate their cancer treatments and ensuring that they have access to quality, affordable, and coordinated care.



Secondary Acute Myeloid Leukemia

Justin Taylor, MD
Assistant Member, Leukemia Service

 Memorial Sloan Kettering Cancer Center

Secondary Acute Myeloid Leukemia

We're fortunate to have as our presenter, Dr. Justin Taylor, Assistant Member at Memorial Sloan Kettering Cancer Center in New York, New York. Dr. Taylor is a medical oncologist and Assistant Member of the Memorial Sloan Kettering Cancer Center's leukemia service. He sees patients with a variety of leukemias and performs research on the cognitive role of genetic alterations in leukemia development. He performs laboratory-based research and translational clinical trial research to advance new therapies for patients with leukemia. Active areas of investigation in his lab include targeting specific types of mutations called spliceosome mutations and also targeting the nuclear export pathway.

Thank you, Dr. Taylor, for volunteering your time and sharing your knowledge with us. I am pleased to turn the program over to you.

Financial Relationships

No relevant financial relationship(s) exist



Financial Relationships

Justin Taylor, MD

Well, thank you, Alicia, and thanks to the LLS for having me here to speak about this important topic of secondary acute myeloid leukemia. And I'm going to be talking about some therapies that exist for this type of leukemia, but I have no financial relationship with any of the drug companies that I'll be mentioning.

Overview

- 1) What is secondary acute myeloid leukemia (AML)?
- 2) How is secondary AML diagnosed?
- 3) Current and emerging treatments for secondary AML
- 4) Future research directions

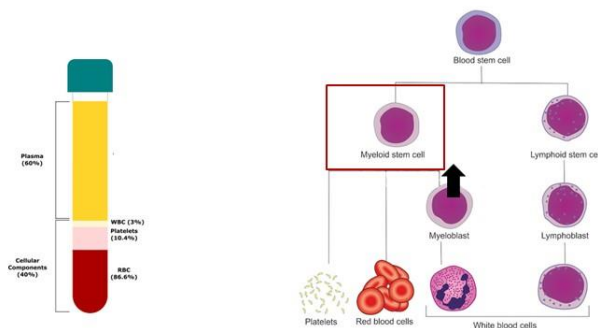


Overview

And so, the overview of the talk today: I'm going to just touch on these topics listed here. What is secondary acute myeloid leukemia? And how is that diagnosed? And then, finally, and a lot of the focus will be on some new and emerging treatments for secondary acute myeloid leukemia and possible future research in this area.

What Is Leukemia?

- Literally meaning “white blood,” leukemia is a cancer of the blood-forming tissues, including the bone marrow



What is Leukemia?

So, to start at a very basic level, just what do we mean when we say “leukemia,” so that everyone’s on the same page? Leukemia is a word that literally means white blood. It’s a cancer that forms from the white blood cells. And in the picture that I have shown on this slide, on the left-hand side, you can see that the blood consists of about 60% liquid form called plasma, and the rest of it is cells. A majority of those are the red blood cells, and then you also have the platelets. And the tiniest fraction there you can see in the middle is the white blood cells.

And then if you look at the picture on the right, this shows you how the white blood cells that are found in the blood actually form. And they form in the bone marrow. We’ll touch a bit on that later. That’s the inside of the bones. All of the blood within the bone marrow forms from a cell or a group of cells called the blood stem cells. That’s shown at the top of the picture. And then a blood stem cell can become any of those forms of blood cells that I talked about earlier: either the platelets, the red blood cells, or the white blood cells.

But to get to those different forms, they can take one of two pathways. They can become either a myeloid stem cell or a lymphoid stem cell. And I’ve drawn a red box around the myeloid stem cell because the myeloid leukemias that we’re talking about, acute myeloid leukemia, come from that type of stem cell. And specifically, where the arrow is pointing is the myeloblast. And the arrows pointing up to denote that you have an increase of those myeloblasts, and that is what is predominantly seen in acute myeloid leukemia as you have too many of these myeloid blasts. And so, the blood literally gets filled up with these white blood cells, and that’s where the term leukemia came from.

Secondary Acute Myeloid Leukemia

- Definition: Secondary acute myeloid leukemia (sAML) refers to a leukemic process either:
 - (A) Evolving from prior myelodysplasia (MDS), myeloproliferative disorder (MPN), or aplastic anemia with or without treatment; or
 - (B) Occurring after previous exposure to radiation or chemotherapy exposure for another cancer

Secondary Acute Myeloid Leukemia

And so when we say secondary acute myeloid leukemia, we're talking about a subtype of acute myeloid leukemia. And this refers to a process that either (a) comes from a prior blood disorder, like myelodysplasia, myeloproliferative disorder, or aplastic anemia, whether a patient has had treatment for those diseases or not. That's one type of secondary acute myeloid leukemia, and then the second type (b) is those that occur after previous exposure to radiation or chemotherapy for a different type of cancer—a nonblood cancer like a breast cancer or a lung cancer.

Primary versus Secondary AML

- Primary AML refers to leukemia arising *de novo* (or “anew”)
- The prognosis for primary and secondary AML are different with secondary AML having worse outcomes
- Because of the worse outcomes with secondary AML the treatments have recently changed and are different from primary AML



Primary versus Secondary AML

But secondary acute myeloid leukemia is actually an older term, and it's used mainly to separate it from primary acute myeloid leukemia. And that refers to leukemia that arises anew. There was no preceding diagnosis of any other type of cancer or blood disorder. And you might hear that referred to as “de novo leukemia”, which just means “arising anew.”

And the reason that we separate them is the prognosis or the outcome, whether you have primary or secondary leukemia, are different, with secondary leukemias having generally worse outcomes. And because of the worse outcomes, the treatments for secondary leukemia have recently changed and would be different from someone who was diagnosed with primary acute myeloid leukemia.

Changing Definitions

- Recognition that prior myelodysplastic syndromes may go undiagnosed led to development of a diagnostic classification called AML with myelodysplasia-related changes (AML-MRC)
- Chemotherapy and radiation can also induce myelodysplastic syndromes (MDS) with poor prognosis and high likelihood of transforming to AML, such that therapy-related MDS and AML are thought of similarly (t-MDS/t-AML)



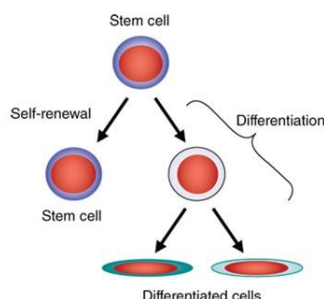
Changing Definitions

And so, as I mentioned, a secondary acute myeloid leukemia is almost becoming a more historical term because we have new changing definitions. This has been brought about by recognition that prior myelodysplastic syndrome or MDS can sometimes go undiagnosed for many years. And that led to the development of a new category of AML called AML with myelodysplasia-related changes or AML-MRC for short. And that is a type of secondary acute myeloid leukemia, but we prefer now to use this more specific term, AML-MRC, for those patients where the secondary AMLs come in from myelodysplasia. And then chemotherapy and radiation, I talked about causing therapy-related or secondary AML that's therapy related. And we now recognize that there's also a therapy-related MDS that can arise from these same types of treatments, and those two diagnoses are kind of lumped together now as therapy-related myeloid neoplasms.

So, the current thinking is secondary AML really exists in two forms, and we now have more specific terms for them: AML-MRC and therapy-related myeloid neoplasms.

A Deeper Understanding

- The origin of AML is considered to be due to acquisition of genetic mutations over time
- Each hematopoietic (blood) stem cell divides once every 40 weeks and incurs about 11 mutations each time
- If a mutation occurs in a leukemia-related gene it leads to a condition called clonal hematopoiesis



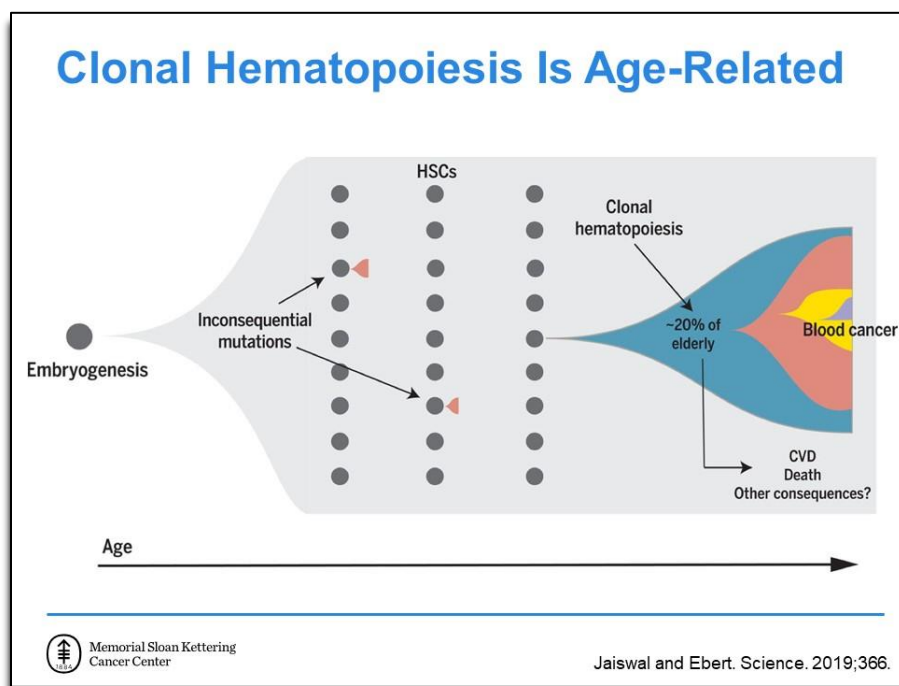
A Deeper Understanding

And if you'll permit me just to do a little bit deeper diving into our understanding of leukemia, before we get to the diagnosis and treatments. We're now understanding more and more about the origin of leukemia, and it's thought to be due to acquisition of genetic mutations over time.

So, I mentioned previously blood stem cells are the cells that form all of your blood. And they do that by dividing, meaning one cell becomes two. And in the graphic that I have there on this slide, you can see there's two fates for a blood stem cell. If it goes down one path, it can do what's called self-renewal, meaning make another blood stem cell that will be able to produce more blood. Or if it decides to differentiate, then it would become one of these more mature blood cells that I talked about.

So, that process happens for each of the stem cells, and a person does have many stem cells in their bone marrow. And they're dividing at different times, each time that one of these blood stem cells divides, it incurs approximately 11 mutations. This is because in order for one blood stem cell to become two cells, it has to double its DNA. This DNA is the genetic material of a cell, and when it does that it makes mistakes. And that happens on the order of about 11 mutations each time it divides.

If a mutation occurs in a leukemia-related gene, then it could lead to further problems. However, most of these mutations are occurring in areas of the DNA that have no real leukemia-related effect. But so, it's thought to be a process of almost luck. And if it's bad luck, it can fall within a leukemia-related gene. And if that happens, it leads to this condition that we've termed clonal hematopoiesis.



Clonal Hematopoiesis is Age-Related

So, I know that's a big word: clonal hematopoiesis. It doesn't really roll right off the tongue. But it refers to this phenomenon that can happen in healthy individuals as we age. So, what I'm depicting in this graph is, on the very left-hand side of the screen, from the time that you're born and form the blood stem cells, those are called HSCs in this graph for hematopoietic stem cells. You begin acquiring mutations each time one of these cells divides. And what's shown in the red with arrows pointing to them, these inconsequential mutations means that the mutations fall in parts of the DNA that don't have a consequence on further development of leukemia.

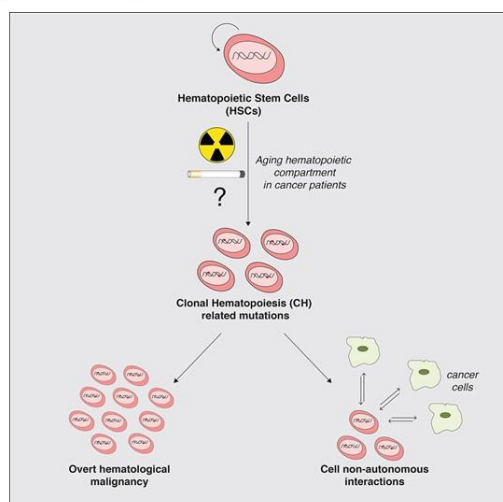
But on the right hand of the screen, and as you age, just with time, you have more of these mutations and a higher chance of one of these mutations occurring in a leukemia-related gene.

So, on the right, about 20% of elderly individuals if they're tested in their DNA of the blood, they would be detected to have this thing called clonal hematopoiesis that means one of the stem cells acquired a leukemia-related gene, and that can be detected upon testing.

And then you can see only a certain percentage of those individuals. It's about 1% per year of individuals that do develop this clonal hematopoiesis, can be at risk for developing a leukemia from that. And that's thought to be due to further acquisition or mutation. So, it's really a time-dependent thing.

Clonal Hematopoiesis and t-AML

- Clonal hematopoiesis is a risk-factor for therapy-related AML and is seen in a higher percentage of cancer patients compared to healthy individuals



Clonal Hematopoiesis and t-AML

But I wanted to bring clonal hematopoiesis up as it relates to therapy-related leukemia, one of the types of secondary AML, because clonal hematopoiesis has recently been identified as a risk factor for therapy-related AML. And it was observed here at Sloan Kettering that a higher percentage of cancer patients, compared to healthy individuals, it can occur up to 20% of elderly individuals. But in cancer patients it can be seen even higher than that.

And that's thought to be due to some of the exposures that cancer patients get exposed to through their treatment: either radiation or chemotherapy. And because some cancers are associated with smoking, there might be a higher incidence of smoking in cancer patients. Not all, but that was also a risk factor for developing clonal hematopoiesis. And basically, patients with other cancers, like breast cancer, lung cancer, that have clonal hematopoiesis are also at a higher risk of getting this therapy-related acute myeloid leukemia. And, you know, we're still studying this, so that's why there's two possibilities at the bottom of the slide there, that either the chemotherapy and radiation that the patients get select for those cells in the bone marrow that are already abnormal. Or, those cells that are abnormal in the bone marrow could be communicating with the cancer cells, and they could be helping each other. So, that's an active area of research.

Clonal Hematopoiesis and AML-MRC

- Certain mutations seen in clonal hematopoiesis are associated with primary or *de novo* leukemia, but others are associated with MDS or MPN
- For example, one study showed that the presence of one of a group of mutations called spliceosome gene mutations was >95% specific for secondary AML

Clonal Hematopoiesis and AML-MRC

But just as we understand more about how leukemia develops, that also informs our understanding of secondary leukemia.

And there is also an association between clonal hematopoiesis and this AML with myelodysplasia-related changes that I mentioned earlier. Certain mutations, seen in clonal hematopoiesis, are associated with primary leukemia, but others are associated with secondary leukemia because they're associated with these preceding disorders, like myelodysplastic syndromes or myeloproliferative disorders.

So, for example, there was a group at the Dana-Farber Cancer Center that showed that the presence of one of these group of mutations called spliceosome gene mutations, one of the genes that I study, they showed that if you found one of those mutations within a patient with acute myeloid leukemia, that predicted with 95% specificity that that patient had actually a secondary acute myeloid leukemia.

How Is Secondary AML Diagnosed?

- The symptoms of secondary AML are similar to primary AML although in AML-MRC the white blood cell counts tend to be low (as compared with high in primary AML)
- Symptoms are related to the failure of the normal blood production resulting in anemia (causes fatigue or shortness of breath) and thrombocytopenia (low platelets: causes bruising or bleeding). Infections can be seen because of lowered immune system



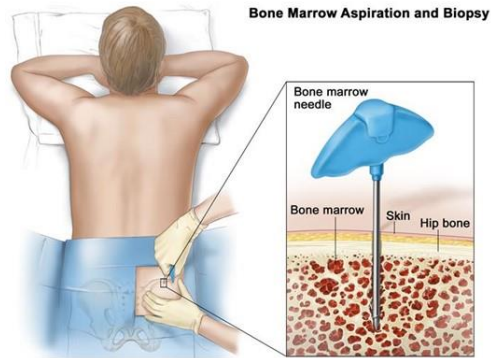
How is Secondary AML Diagnosed?

So, how do we do this in practice? How is secondary AML actually diagnosed? So, a patient would present with symptoms very similar to primary acute myeloid leukemia. So, usually this is detected by the patient, feeling a symptom of fatigue. That could be also seen as shortness of breath or bruising, bleeding, or an infection. Something brings them to medical attention, and then they get a blood test done.

And the blood counts are abnormal. So, in primary leukemia, I told you those white blood cells are very high, so that can be seen in secondary leukemia as well. Although in the AML with myelodysplasia-related changes, sometimes the white counts are very low at presentation. And then in all types of leukemia the patients can also present with anemia and thrombocytopenia, which means low platelets. And that is mostly what causes the symptoms. And then the immune system is also affected by leukemia, so infections are also more common.

Diagnosing Secondary AML

- Even though some evidence of secondary AML can be detected from a blood draw, the diagnosis requires a biopsy of the bone marrow



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Diagnosing Secondary AML

So, once the patient is brought to medical attention, and there's a suspicion for leukemia because of what's seen on the blood counts, then really the diagnosis is made by doing a biopsy of the bone marrow. So, I told you all of the blood is formed from the bone marrow, and that is where we need to make the diagnosis. Even though we can get a good sense from the peripheral blood and tests are being improved to be able to make some diagnosis from just a blood test, we still require this bone marrow biopsy the majority of times.

And so, a bone marrow biopsy is what's being shown in this slide here. It's done at the patient's bedside with the patient awake and some numbing medication that's administered to numb the area so that there's no pain associated with this. And then the needle in the inset there, it's showing the needle has to go through the skin, through the hip bone, into the middle part. And then a portion of the bone marrow is drawn up through the needle and taken to be examined by a pathologist.

Diagnosing Secondary AML

- Your doctor knowing whether you have a history of a previous blood disorder or any radiation or chemotherapy in the past is very important because that information alone can be sufficient to make the diagnosis if AML is seen on the biopsy
- The pathologist (the doctor who makes the diagnosis by examining the bone marrow under the microscope) can also identify whether dysplasia is present and at high enough levels that it can be categorized as AML-MRC



Diagnosing Secondary AML

But very key to making the diagnosis of secondary AML would be the hematologist or oncologist asking you and finding out whether you have a history of a previous blood disorder or have received any radiation or chemotherapy in the past for another type of cancer. And that information alone would be sufficient to make the diagnosis of secondary AML if AML is seen on the biopsy.

And so the pathologist is the doctor who looks at the bone marrow under the microscope. They can also identify certain features that might make them think that it would be a secondary AML, and those features are called dysplasia. And that's why the name is acute myeloid leukemia with myelodysplasia. It has to be at certain levels, and I'll get to that on the next slide.

Genetics Are Key to Diagnosis

- If there is no known history of previous blood disorder or radiation/chemotherapy exposure and no evidence of dysplasia of the bone marrow, the diagnosis of AML-MRC can still be made
- Genetic abnormalities associated with MDS can also be used to make the diagnosis of AML-MRC

Genetics Are Key to Diagnosis

But also the genetics are very key. I told you the spliceosome mutations are seen particularly in this disease. And then also the other genetic abnormalities that are associated with myelodysplastic syndrome can be used to make a diagnosis of AML-MRC, even in the absence of a known prior blood disorder or radiation and chemotherapy exposure.

Diagnostic Criteria for AML-MRC

- Must not have a mutation in NPM1 or biallelic CEBPA mutations
- $\geq 50\%$ of dysplasia in 2 or more cell lineages
- The presence of an MDS-related cytogenetic abnormality, except for del(9q), even in the absence of dysplasia

Diagnostic Criteria for AML-MRC

So, these are the criteria. There are certain genetic abnormalities that should not be present, and that's because those are typically associated with primary leukemia. And then if the pathologist sees greater than 50% of this dysplasia, they can also make this diagnosis. And then even if you don't have dysplasia or a history of prior blood disorder or chemotherapy and radiation, the presence of one of these MDS-related cytogenetic abnormalities can make the diagnosis.

Prognosis of Secondary AML

- In comparison to primary AML, secondary AMLs are usually considered adverse or poor risk
- The exception is cases of therapy-related AML with inversion of chromosome 16 or a translocation of chromosomes 15 and 17, which can have the same outcomes as primary AML with those genetic abnormalities
- Complex karyotype and those with TP53 mutations may have the worst outcome overall



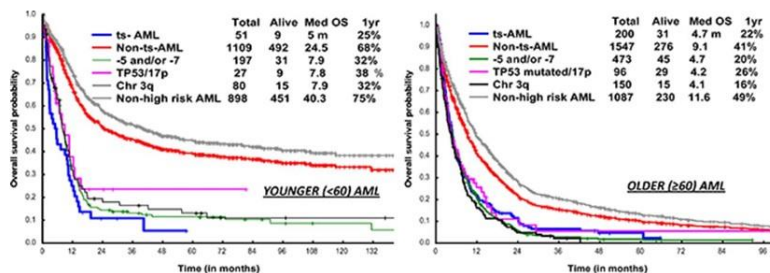
Prognosis of Secondary AML

And so, like I said before, in comparison to primary AML, secondary AMLs have a worse outcome. So, if you compared them to primary AMLs, they'd be considered a poor risk or adverse risk. And there are a few exceptions. I said not every case. So, certain chromosomal abnormalities, although these are rare in secondary AML, if seen, they can have the same outcome as a primary AML with those same genetic abnormalities. And those are listed there.

And then I'll mention this TP53 mutation and come back to it at the end. But there's lots of evidence and scientific rationale to believe that patients with TP53 mutations may have the worst outcome overall because they are very resistant to chemotherapy.

Treatment for Secondary AML

- Whether intensively treated or not, and regardless of age, patients with secondary AML have decreased survival compared to primary AML



Treatment for Secondary AML

And so, whether you get chemotherapy, which is called intensive treatment, or not, and regardless of whether patients are older or younger, the outcomes with secondary AML are worse than primary AML, meaning there is decreased survival. So, these plots that I'm showing on this slide on the left is younger patients less than 60 years old and older patients greater than 60 years old. That cutoff was arbitrarily chosen, but it does fit that you can see that the younger patients on the left side, the survival, which is shown on the vertical axis of this graph, so the higher up would be better survival. And so, if you focus on the red line or the gray line, those are nonsecondary AMLs. And the blue line is the therapy-related AML. And you can see the survival there is much less or much lower, and it's similar to other kind of adverse or poor-risk primary leukemias, which are the other lines.

And then the same thing on the right graph for the older patients. Even though overall the older patients don't do as well as the younger patients, the secondary AML patients still do worse. So, this was published in 2017 and was looking at data from before then. So, this was with our prior treatments.

A New Treatment for Secondary AML

- Prior to 2017 there existed no specific treatment for secondary AML
- Vyxeos[®], an intravenous drug containing two chemotherapies in an encapsulated formulation, was FDA-approved for secondary AML in August 2017
- Approval was based on a trial of patients with secondary AML receiving either Vyxeos[®] or the standard chemotherapies (uncombined)



A New Treatment for Secondary AML

And so, I mentioned there's a new treatment for secondary leukemia and really has changed the way that we treat secondary leukemia. As prior to 2017, they were treated similarly to primary leukemias. But then in August of 2017, this drug named Vyxeos[®] (daunorubicin and cytarabine) was FDA approved specifically for the treatment of secondary leukemia. And Vyxeos[®] is an intravenous or IV chemotherapy drug that contains two of the chemotherapies that were previously used for leukemia but in a different formulation: an encapsulated form called the liposome. And that was thought to make it a little bit safer to give and also a little bit more effective because it would go to the bone marrow a little bit more specifically and not damage other parts of the body as much. That was the thought.

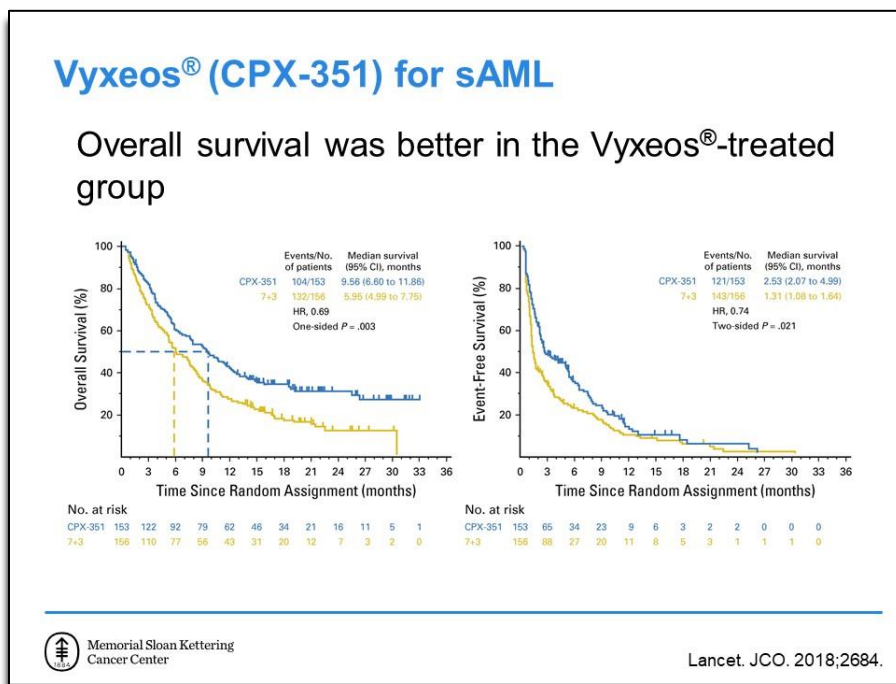
And it actually was approved based on a clinical trial done with patients, and specifically with secondary leukemia. And they got either Vyxeos[®] or the standard chemotherapy that was given before, which is the same two drugs that are within Vyxeos[®], but they're not combined and they're not in that special liposomal formulation.

Vyxeos® for Secondary AML

- Phase 3 randomized trial of 309 patients aged 60-75 years with newly diagnosed secondary AML
- Received induction therapy with Vyxeos® or daunorubicin and cytarabine separately (“7+3”)
- Primary goal of the study was to compare the overall survival based on treatment received

Vyxeos® for Secondary AML

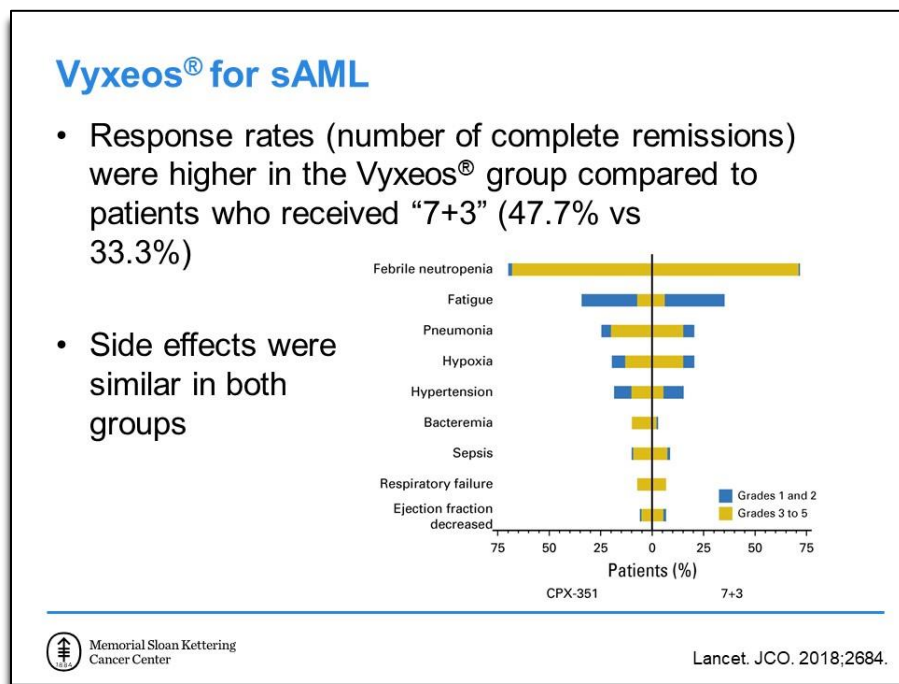
So, this was a Phase III trial, meaning it was a large trial, and it was randomized. So, they enrolled 309 patients, and they focused on the older patients: older than 60 years old but younger than 75. So, a very specific group of patients. And they had newly diagnosed secondary AML, so that was the patients that were treated. And as I mentioned, they got either one of the two treatments in a random fashion. And the primary goal of the study was to compare the overall survival based on the treatment received.



Vyxeos® (CPX-351) for sAML

So again, I'm showing the survival curve similar to those other graphs that we looked at where the vertical access is survival. On the left side is the overall survival, and the blue line is the Vyxeos®. It was called CPX-351 in the past, and that yellow line is the standard chemotherapy, which we refer to as "7+3." And you can see that the blue line is higher than the yellow line. And the median overall survival, meaning approximately 50% of the patients, if you look at that 50% survival mark, how long was the survival? And in the Vyxeos® treated arm, it was 9.5 months compared to the standard chemotherapy arm was only 6 months.

So, it did improve the overall survival compared to standard chemotherapy in these older patients who I showed you previously had the worst outcomes. So, that's why it was FDA approved for the treatment specifically of secondary AML. And it was the first FDA-approved therapy for this indication.



Vyxeos® for sAML

And so, the response rates or the remission rates, the number of complete remissions were also higher in the Vyxeos® group compared to the standard 7+3 treatment group: 48% approximately versus 33%. And so, that is a clinically meaningful outcome. Those patients got into remission, meaning their blood counts came back to normal, and there was no evidence of leukemia on their bone marrow biopsies.

And these side effects were similar in the groups, and the graph shown here shows that the bar plots to the left side of the line would be higher in Vyxeos® or CBX-351, and the bars on the right-hand side would be higher in the standard chemotherapy 7+3. And you can see that in most cases they're balanced.

What to Expect on Vyxeos®?

- Vyxeos® is given as a 90-minute infusion for 3 doses every other day, typically in the hospital
- Vyxeos® causes the blood counts to become very low, similarly to standard chemotherapy. The time to recovery of neutrophils and platelets is 1-2 weeks longer than with standard chemotherapy
- Vyxeos® was also associated with self-limited rash in ~50% of patients on the trial but not with “7+3”



What to Expect on Vyxeos®?

So, what can someone expect if they were going to be treated with Vyxeos? So, it's given as a 90-minute infusion, and it's given for three doses every other day. And typically, it's given inpatient in the hospital, not only those 3 days, but then further monitoring the hospital afterwards. But the drug is only given on 3 days. Similar to the standard chemotherapy, the standard chemotherapy is given over 7 days. The Vyxeos® also causes the blood counts to become low, and that's why patients typically would stay in the hospital.

But what was seen in this trial was even though the blood counts became low with both therapies, the time to recovery of the blood counts to become normal or high enough to leave the hospital was 1 to 2 weeks longer than with the standard chemotherapy. And that was mostly the neutrophils and the platelets that took longer to come back. And again, that was thought to be possibly related to the formulation. Again, the liposomal formulation was hypothesized to deliver the drug better to the bone marrow, and maybe that's where we saw the better effects. But also, that might be one of the reasons that we see the more prolonged time to recovery.

And then the, only thing that was noted was Vyxeos® was associated with a rash. Self-limited means it typically resolved without much treatment. So, it wasn't a severe reaction. But it did happen in about 50% of patients on the trial and did not occur with the 7+3. So, it may be that that's also related to the formulation.

What to Expect on Vyxeos®?

- After recovery of blood counts, a bone marrow biopsy is performed to assess for remission
- If in remission, patients on the trial received up to 2 cycles of consolidation (lower dose of Vyxeos® for just 2 doses) or could receive an allogeneic hematopoietic stem cell (“bone marrow”) transplant

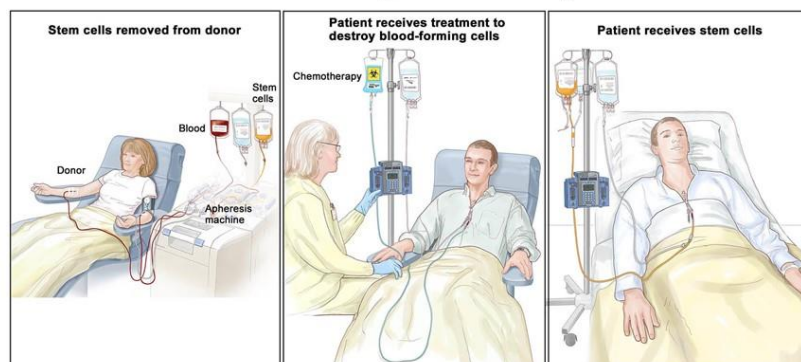
What to Expect on Vyxeos®?

So, that could be some of the expected side effects while in the hospital. But then once the blood counts do recover, a bone marrow biopsy would be performed again to look for remission. And this time it would be the same procedure as the diagnosis. But here they'd be looking for a recovery of the normal blood cells in making sure that there were no leukemia cells still seen there.

And if in remission, meaning no leukemia cells seen, the patients on the trial got up to two cycles of consolidation with Vyxeos®, which was just a lower dose of Vyxeos® for two doses instead of three. Or, the patients could receive an allogeneic stem cell transplant, often called a bone marrow transplant.

Hematopoietic Stem Cell Transplant

- Allogeneic means received from a donor. This typically is a sibling or unrelated individual who is found to have matching immune system markers



Hematopoietic Stem Cell Transplant

And let me just review bone marrow transplants, in case that's new to anybody. Hematopoietic stem cell transplant, often called the bone marrow transplant. Allogeneic, that word means that the cells are received from a donor, typically a sibling or an unrelated individual who is found to have the matching immune system markers, also called HLA markers.

And so, this here depicts what happens. The donor would come in to get the stem cells collected, and nowadays that is typically not done from the bone marrow. It's usually done from an apheresis machine shown there through the peripheral blood. And that's why we no longer use the term bone marrow transplant and call it the hematopoietic stem cell transplant.

So, the donor doesn't necessarily need to be in the same room or even the same state as the patient. The cells can be collected and shipped, and then the patient in the hospital would be receiving treatment. So, in the case of this trial, after they got Vyxeos® and were in a remission, they received other chemotherapy in order to prepare for the stem cell transplant. And that's typically given over a few days in the hospital. And then the patient receives the stem cells through peripheral blood. And those stem cells find their way to the bone marrow and begin making blood again in the patient. But these are now the donor-derived blood cells.

HSCT for Secondary AML

- A Swedish population registry trial showed that after 5 years there was <5% of intensively treated sAML patients alive who had not received an allogeneic HSCT
- Comparatively, receiving an allo-HSCT was associated with 20-30% being alive at 5 years
- This data could be confounded because patients who are sicker might not get HSCT

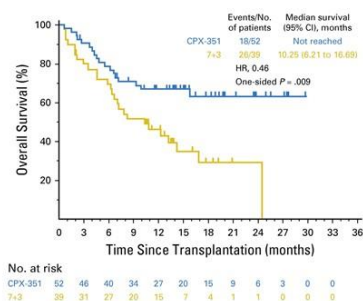
HSCT for Secondary AML

Stem cell transplant has been studied for secondary leukemia, but mostly from retrospective studies, meaning where they look back at the data. So, it hasn't been tested in a clinical trial.

And this study here, which was done in a Swedish population, it was a registered trial, meaning they looked at their whole population in Sweden. And they looked at all the patients who had secondary AML, and if they did not receive an allogeneic stem cell transplant at 5 years, less than 5% of those patients who got intensive chemotherapy were alive. Comparatively, those who did receive an allogeneic stem cell transplant, about 20% to 30% of those patients were alive at 5 years, suggesting that the allogeneic stem cell transplant has an effect on long-term survival in these patients. Although anytime there's a retrospective study like this where they're looking back at the data, these types of analyses can be confounded because patients who are maybe doing worse might not get the stem cell transplant. And patients that are doing worse, generally have poor outcomes compared to the patients that are healthy enough to get stem cell transplants, in a way. But this is the data that we have, that there is some role for stem cell transplant for secondary AML.

HSCT After Vyxeos®

- More patients treated with Vyxeos® received HSCT compared to standard chemotherapy (34% vs 25%) and had better outcomes after transplant



Memorial Sloan Kettering Cancer Center

Lancet. JCO. 2018;2684.

HSCT After Vyxeos®

And so in this study, they looked at the patients treated with Vyxeos® who received stem cell transplant compared to standard chemotherapy, and about 10% more patients were able to get stem cell transplant with Vyxeos®, likely because it induced more remissions -. But even when they looked at those patients that had transplant, whether they got Vyxeos® or standard chemotherapy, the patients treated with Vyxeos®, shown in the blue line again in this graph, did better than those with standard chemotherapy regardless of whether they got transplant.

So, even if both groups got transplant, the ones that previously received Vyxeos® to get into remission did better than the ones that received standard chemotherapy to get into remission.

Less Intensive Treatment Options

- Deaths after either Vyxeos® or chemotherapy within the first 60 days was 14% and 21%, respectively
- In some patients it might be better or the patient may decide to use a less intensive treatment
- The hypomethylating agents azacitidine and decitabine are a class of agents typically used in MDS and therefore have a rationale in sAML, though neither are FDA-approved for sAML



Less Intensive Treatment Options

So, the summary of that slide is that, if possible, the best treatment that we know of now is to give Vyxeos® followed by an allogeneic stem cell transplant. But there are some major toxicities that come along with this treatment. When they looked at just deaths after either Vyxeos® or chemotherapy within the first 60 days, so meaning while the patient might still be in the hospital or shortly after they left the hospital, it was lower with Vyxeos® compared to chemotherapy: 14% versus 21%. But those are still pretty high numbers of mortality.

So, in some patients, it might be better or, depending on the comorbidities of the patient, something that we call the performance status, or if the patient makes a decision that they would like to use a less intensive treatment to avoid that risk of mortality from getting chemotherapy or Vyxeos®, there are less intensive treatment options. So, a big class of drugs called the hypomethylating agents or HMAs for short, the main two that we use are called azacitidine (Vidaza®) and decitabine (Dacogen®). They are typically used in myelodysplastic syndromes and, therefore, there's a rationale for secondary leukemias that arise from those diseases. But neither of the drugs are FDA approved for secondary AML, but they are very commonly used.

Hypomethylating Agents (HMA) for sAML

- Compared to intensive chemotherapy, HMA therapy can take a longer time to induce remission
- Both azacitidine and decitabine are intravenous, though azacitidine can also be given subcutaneously
- Both HMAs cause the blood counts to fall, though not to the same degree as intensive chemotherapy



Hypomethylating Agents (HMA) for sAML

So, compared to intensive chemotherapy, these hypomethylating agents can take a longer time to induce remission. I didn't maybe explicitly say it, but with the chemotherapy or Vyxeos®, the remissions were typically seen after one induction cycle—so, around 30 days to a little bit longer. But with HMAs, the remissions can be seen after multiple cycles. And so, both of the drugs are given intravenously, although azacitidine can also be given subcutaneously, and they cause the blood counts to fall, similarly to chemotherapy, though not necessarily to the same degree. And then after about, again, 30 days, the blood counts come back to normal. That's considered one cycle. And then in the case of these drugs, hypomethylating agents, they're given again for multiple cycles until a remission is achieved. And again, that can take several cycles to achieve a remission as compared to chemotherapy or Vyxeos®, where you may see the remission after just the first cycle.

HMA Plus Venetoclax for sAML

- Venetoclax is an oral BCL2-targeted therapy recently approved for AML in older patients in combination with HMA or low-dose chemotherapy
- In the largest study of venetoclax with HMA (either azacitidine or decitabine), 25% of patients had secondary AML
- Similar to the entire cohort, 67% of patients with sAML had a complete remission with the median overall survival not reached at 15 months



HMA Plus Venetoclax for sAML

Now another exciting option for secondary AML is a drug called venetoclax (Venclexta®, Venclyxto®). This one is an oral pill that targets a protein called BCL2, and this was recently approved for AML in older patients in combination with hypomethylating agents or low-dose chemotherapy. So, they didn't specifically get approved for secondary AML, but they're used for AML in general and they are being commonly used. In the largest study of venetoclax with hypomethylating agent, either azacitidine or decitabine were used in this trial, approximately 25% of the patients had secondary AML. So, it wasn't a study specifically for this population, but they were allowed to be on the trial. And a quarter of the patients had secondary AML. And they had similar responses to the entire cohort; 67% of patients with secondary AML had a complete remission with HMA plus venetoclax and the median overall survival was not reached in this subgroup at 15 months of follow-up.

HMA+Ven versus Vyxeos®

- Cannot truly compare the two because the trials were very different. The Vyxeos® trial had 300 sAML patients and was randomized while the HMA+Ven trial had a subgroup of only 25 sAML patients
- Patients getting HMA+Ven were not allowed to have had prior therapy for MDS/MPN but that was allowed on the Vyxeos® trial.
- 60-day mortality was lower (8%) for HMA+Ven

HMA+Ven versus Vyxeos®

So, it's tempting to compare this to the Vyxeos® data, but you cannot truly compare the two because the trials were very different. The Vyxeos® trial was a large trial that was specifically done in secondary leukemia patients, and they had 300 patients and it was randomized. While the venetoclax and HMA trial, the secondary AML patients were only a subgroup of that. And it was only 25% of the patients in that study, which was approximately 36 patients, and they weren't randomized.

In the study of HMA plus venetoclax, the patients were not allowed to have had prior therapy for their MDS or MPN, but that was allowed on the Vyxeos® trial. So, the patients that went on the Vyxeos® trial had more prior treatments, which typically means that is a tougher group of patients to treat. So, even though you might look at the two results and say that the HMA plus did a little bit better than the Vyxeos®, it was really two entirely or different types of patients.

One thing that was seen though is that the 60-day mortality was lower for HMA plus venetoclax, so only 8% compared with 14% with Vyxeos® and 21% with chemotherapy. So, this might be a safer regimen to use in someone who has more medical comorbidities or maybe is a little bit more frail.

Targeted Therapies for sAML

- Recent drugs approved to target specific mutations in MDS or AML can also be used for sAML with those mutations
- IDH1 and IDH2 mutations are found in 5% and 20% of patients with sAML, respectively. Specific inhibitors called ivosidenib and enasidenib can selectively target the mutant proteins
- IDH inhibitor drugs are very well tolerated but can also take several months to have maximal effect

Targeted Therapies for sAML

And there's also been some advancement in other targeted therapies in MDS and AML that can be used for patients with secondary AML. Again, though they don't have the specific approval for that, they're commonly used. And a class of drug I want to talk about is called the IDH inhibitors. So, IDH1 and IDH2 mutations are found in 5% and 20% of patients with secondary AML, respectively. And there are specific inhibitors, one for IDH1 called ivosidenib (Tibsovo®) and one for IDH2 called enasidenib (Idhifa®), that can selectively target the mutant proteins.

And these drugs are very well tolerated because they're only affecting the cells that have this mutation, which are the leukemia cells, and don't have many effects on the rest of the body. But similarly to the hypomethylating agents, they can take several months to have their maximal effect. And so, again, it's only a select group of patients that are eligible to receive this therapy.

Emerging Therapies for sAML

- TP53 mutations are common and predict poor response to chemotherapy in sAML
- APR-246 is a first-in-class mutant TP53 stabilizing drug that is being developed in combination with azacitidine in MDS and AML with low blast count
- Of 45 patients, 53% had a complete response and the median survival was 11.6 months in preliminary findings

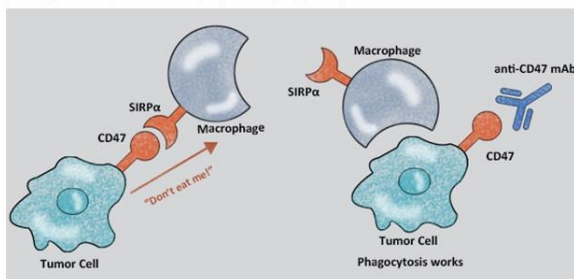
Emerging Therapies for sAML

And so, there's some emerging therapies for secondary AML for some of the more common mutations. I mentioned earlier TP53 mutations. These are quite common and predict a specifically poor prognosis in secondary AML because they confer resistance to chemotherapy. And so there's a drug being studied that's a first-in-class drug that stabilizes this mutated TP53, and it's being used in combination with azacitidine for patients with MDS and AML that has a low blast count. So, again, not typically seen in AML but more related to MDS, so it might be for these patients with AML-MRC that have myelodysplasia changes and have low blast counts.

This was a Phase II study where they treated 45 patients, and 53% had a complete response. So, all the patients that they treated had TP53 mutations so many of them were MDS and some with AML. And they saw, in this group of patients where you wouldn't expect a lot of responses to azacitidine alone, they saw 53% complete responses with azacitidine plus this new drug, APR-246. And the median survival was 11.6 months in these preliminary findings that were presented at the American Society of Hematology meeting in December of 2019.

Emerging Therapies for sAML (cont'd)

- Magrolimab is a CD47-blocking antibody. CD47 is a defense co-opted by cancer cells to tell the immune system “don’t eat me”
- 7 out of 9 patients with TP53 mutant AML responded in a phase 1 study

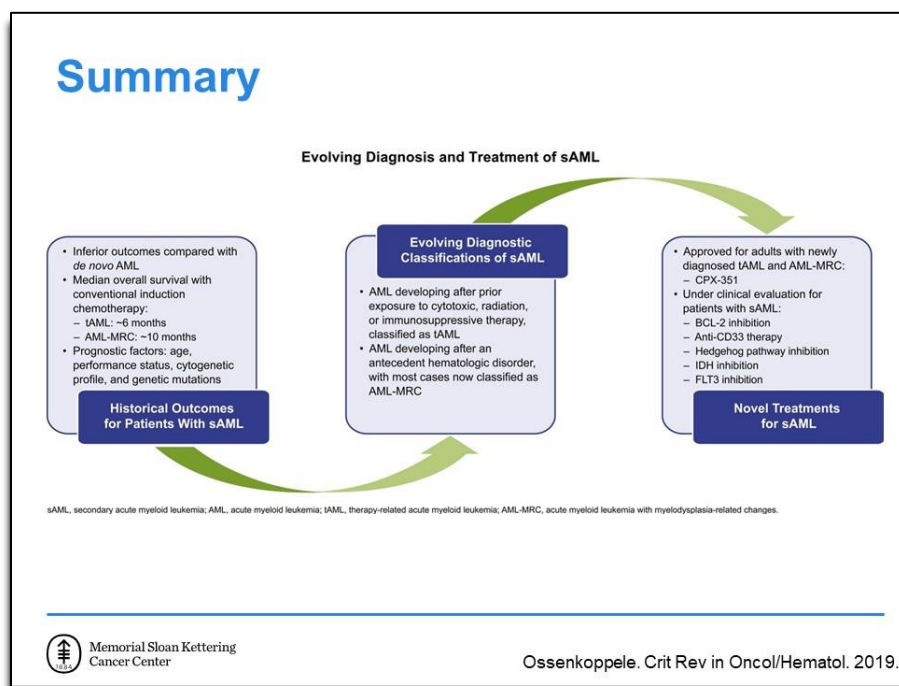


Emerging Therapies for sAML (cont'd)

Another presentation from that same meeting highlighted this drug called magrolimab, and magrolimab is a CD47-blocking antibody. And then CD47 is a kind of a naturally occurring molecule, but it's co-opted by cancer cells as a defense against the immune system.

Another one of the things we've learned in the last decade or so is that the immune system can be effective at fighting off cancers. However, cancers typically find a way to get around the immune system or evade it, and this is one of the mechanisms. So, there's been some immunotherapies for other types of cancer which have been very successful at targeting one of the ways that cancer cells evade the immune system. And this mechanism with CD47 could be applicable to many cancers as well but seems specifically relevant in blood cancers and in these patients with TP53-mutated AML.

So, this was a small study, a Phase I, and they only treated nine patients, but seven out of the nine patients with TP53 mutations responded to this drug as a single agent. So, this is still very early but potentially promising for patients with TP53 mutations, which make up a large proportion of secondary AML.

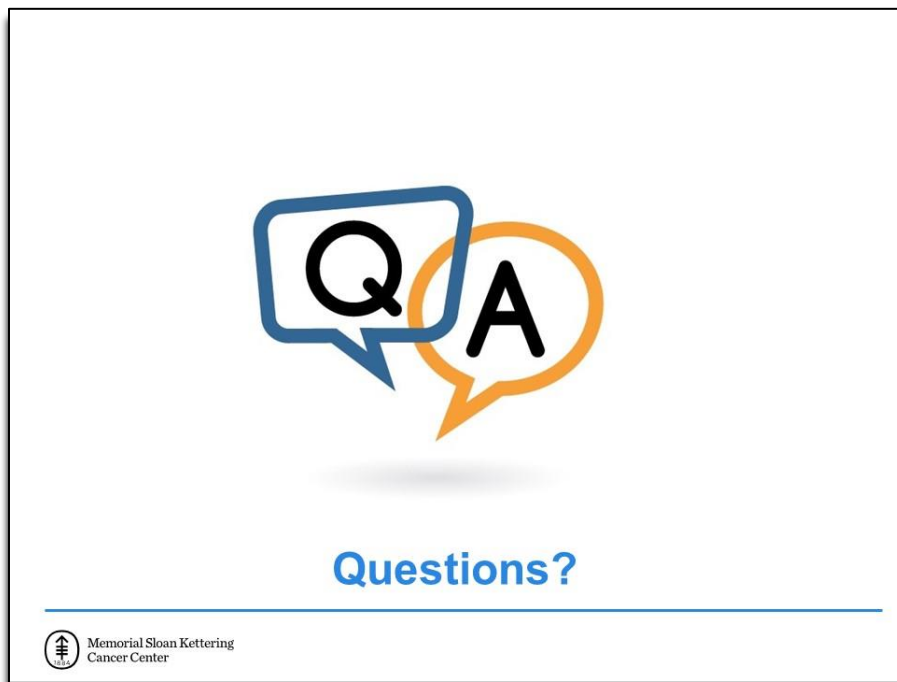


Summary

So, just to summarize, I got this nice slide from the review listed here. And they have it very similarly laid out to me where on the left I started off by telling you that historical outcomes for patients with secondary AML were poor compared to primary AML, with short, median overall survivals of around 6 months to 10 months, and certain factors related to outcome, like age, this thing we call performance status, comorbidities, and cytogenetic and genetic mutations.

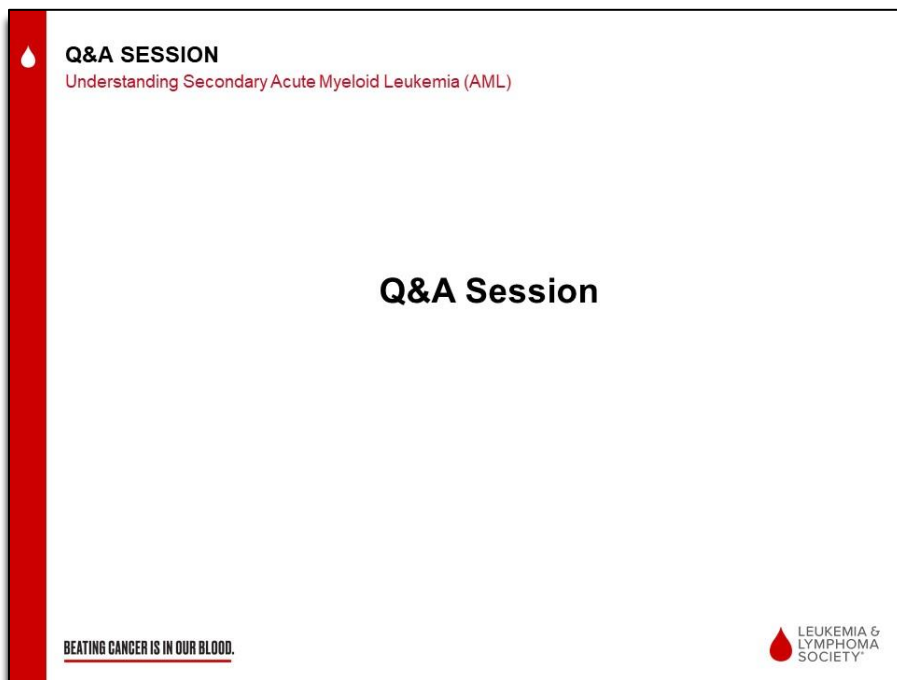
Then in the middle, we have this evolving diagnostic classification where we really break secondary AML down into two parts: either AML-MRC, which is secondary AML coming from a previously diagnosed blood disorder, or therapy-related myeloid neoplasms, which, include MDS and AML that's related to prior chemotherapy, radiation given for other types of cancers like prostate cancer, breast cancer, lung cancer. And we're beginning to understand more about exactly how and which patients are at risk for developing secondary AML.

And then on the very right, we have the new treatments for secondary AML with the first FDA-approved drug specifically for this group: Vyxeos® or CPX-351. And then we also have venetoclax, which targets BCL2 and can be used in combination with hypomethylating agents. So, low-dose chemotherapy for patients with leukemia, regardless of any mutations they have. And then there are specific drugs that target certain mutations, like the IDH mutations and IDH inhibitors. And then I mentioned some new things that are coming along the way directly targeting this TP53 mutations that are so commonly seen in secondary AML.



Questions?

So, that concludes the presentation, and I'm happy to stick around for any questions.



Q&A Session

Mrs. Alicia Patten-Madera

Thank you so much, Dr. Taylor, for providing us with this very important information. It is now time for the question-and-answer portion of our program. We have received some pre-submitted questions from patients and caregivers alike who have spoken to our Information Specialists. Our first question is, “There have been different views about transplant in secondary AML patients. Do physicians tend to consider transplant in the younger adults for secondary AML?”

Justin Taylor, MD

So the short answer is yes. And I think the person who asked the question brings up a good point that there has been some, maybe some controversy around stem cell transplant for secondary AML. As I showed in the slides, though, there’s a benefit to using allogeneic stem cell transplant in secondary AML. And so I would say for the younger patients, yes, that’s definitely an option and something that physicians like myself are using.

One of the things that comes up is that we’re learning that stem cell transplants work better in patients who have deeper remissions, meaning any test that we do looking for any measurable residual disease do not detect any remaining leukemia. And those type of deep remissions are harder to achieve in patients with secondary AML. And so, even though we still might recommend transplant, there may be a higher risk of relapse even after transplant in patients with secondary AML.

Mrs. Alicia Patten-Madera

Along the same lines of allogeneic transplant, our next question is, “If a patient goes through transplant, is graft-versus-host disease more prevalent in this population?”

Justin Taylor, MD

That’s a great question. That’s one of the main side effects or adverse effects from doing a stem cell transplant. So, in addition to the risk of relapse, graft-versus-host disease is another big concern. I’m not aware of any evidence that graft-versus-host disease would be higher in patients with secondary AML. It definitely still would be, you know, a concern and something to take into consideration when talking to a patient about undergoing a stem cell transplant is the risk of graft-versus-host disease.

Mrs. Alicia Patten-Madera

Thank you. Our next question is, “Is there anything that could have been done to prevent secondary AML, other than the obvious of not getting the treatment or having another cancer in the past?”

Justin Taylor, MD

Right. This is a very common question, and it sounds like this is pertaining to therapy-related AML where

Mrs. Alicia Patten-Madera

Yeah.

Justin Taylor, MD

Patients are developing leukemia after treatment for another cancer. And we don’t yet know enough to say if there’s any sort of prevention or intervention that can be done. The studies that I mentioned here were all, again, retrospective where we looked back at

Understanding Secondary Acute Myeloid Leukemia (AML) **Speaker: Justin Taylor, MD**

patients that had cancer and developed therapy-related leukemias, and we did see this higher amount of clonal hematopoiesis in those patients.

So, that's a correlation and suggests that patients that have clonal hematopoiesis are at a higher risk of developing a therapy-related leukemia if they get chemotherapy or radiation. But we don't yet know should we specifically avoid giving those patients chemotherapy. Say we detect clonal hematopoiesis in a patient with breast cancer before they've undergone treatment. should we choose nonchemotherapy options for those patients to avoid the risk of secondary AML?

Those kinds of studies are being done right now to try to answer that question, but we don't know if that would change the outcome. It's presumed it would, so it's more of a, nothing that you can do to prevent it. But maybe you might make a different choice about undergoing certain types of chemotherapy or certain types of treatment for the primary, like breast cancer, for example. But that's a great question.

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Mrs. Alicia Patten-Madera

Thank you, doctor. Our next question is, "What are your thoughts on complementary treatment for a patient with secondary AML?"

Justin Taylor, MD

That's another very common question and a legitimate question. I think a lot of patients are trying to figure out if there's anything that they can do or things that they can take that can help with the treatment. And my typical answer, first, I'd like to, hear what sort of complementary treatments they're considering 'cause there are some that we recommend regardless, like exercise, meditation. You know, those type of complementary things are generally helpful.

If they're talking about certain, you know, teas, extracts, complementary medicines, then it's good to know the specific one that they're talking about to make sure there's no interaction with chemotherapy and actually have the opposing effect to the chemotherapy or make the chemotherapy work less well. Some of them don't interact at all and would be fine to take, so it's just important to know exactly what the patient's considering taking and have a discussion with them about it.

Mrs. Alicia Patten-Madera

"What are other long-term side effects or late effects from treatment for a patient with secondary acute myeloid leukemia?"

Justin Taylor, MD

Yeah, you can develop secondary leukemias from the treatment of leukemia. Not very common because leukemias are rare compared to some of the more common cancers. But that would be one of the effects is risk for developing a therapy-related leukemia even after being cured of the first leukemia. It's so rare, it's usually not our focus.

There could be effects on the heart from chemotherapy. So, I mentioned that the chemotherapy we usually give consists of two medications. One of them is known to have effects on the heart, and we limit the amount of that medication that is given over a lifetime. Vyxeos® also contains that medication but at a lower dose and because of the liposomal formulation, may be protective of the heart. Although, as I showed, when they looked at the side effects, there wasn't a statistical difference in the cardiovascular effects with Vyxeos®, and we still limit the total amount of that drug that a patient can get in a lifetime, whether it's in Vyxeos® or not in Vyxeos®. So, there's cardiovascular effects that could be long term.

And typically, though, we don't see many of the neuropathies that you see with other types of chemotherapy. Those are numbness or tingling of the hands and fingers. It hasn't been so well studied, but there are effects on the cognitive function. Again, not so well studied so we don't know that they're specifically linked to any of these drugs, but some patients do report late cognitive effects.

And then, after transplant there are a whole host of later effects in terms of immune system, immune compromise from the process and graft-versus-host disease, which was brought up in another question.

Mrs. Alicia Patten-Madera

Our next question, "Is there a high incidence of relapse for secondary AML patients?"

Justin Taylor, MD

Yes, that's one of the reasons that there is a poor outcome is because of the risk of relapse. Even with the Vyxeos®, as I showed in the slides, it improved the overall survival. I didn't want to get into all the details, but if you look at the event-free survival, which included relapse or death, the difference between the Vyxeos® and the standard chemotherapy arm wasn't as great as in the overall survival so that means there were still relapses. Even though the patients ultimately lived longer with Vyxeos® compared to standard treatment, there were relapses in both arms. And so, I think that remains a big, big problem; those patients that went on to get the allogeneic stem cell transplant after receiving Vyxeos® did better.

So, I think if you can get to the allogeneic stem cell transplant, that would further reduce the risk of relapse, but it's not 100%. There can still be relapses even after allogeneic stem cell transplant., I think that's why some of this research into the newer treatments is especially important because even though we now have Vyxeos® approved, it's not curing everybody. And it's not preventing all the relapses, and so we're still needing other lines of therapy.

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Mrs. Alicia Patten-Madera

Our next question is, “What clinical trials are available for secondary AML patients?”

Justin Taylor, MD

Yeah, that's a good question. And I think one good source of information is www.clinicaltrials.gov. Many of the trials that are open to patients with leukemia are also taking patients with secondary leukemia. And if they are not, you can usually find out on that website. So, if you go to the website and you just type in acute myeloid leukemia as a search term, you're going to get back a long list of trials that are available. So, you might want to search secondary acute myeloid leukemia, but, again, that may narrow it. That may make you miss some of them, but if you can go through all the trials, you can find the ones that allow patients with secondary leukemia. And, most of them do. There are a few that aren't allowing patients with secondary leukemia, like if they're specifically trying to test something for primary leukemia, but most of them do. And not every clinical trial is open at every cancer center, so it's important to ask the doctor you're seeing what clinical trials they have available there and if there's something that they might think is particularly relevant to you that might be available somewhere else; or if you find something on clinicaltrials.gov you can find out which locations there available and your oncologist/hematologist can refer you to that specific center. As for the ones that I think are exciting, I listed the APR 246, that one is specifically for patients with TP53 mutations so that would be a conversation with your oncologist to find out if you had that

mutation or if you could be tested for that mutation and then the (CD47 antibody is not specifically for any particular mutation. I just highlighted that in that subgroup that they looked at with TP53 mutations, they had high rates of response. But they also tested that in other patients, regardless of mutation.

There is another trial that is testing a drug, again, that targets a specific type of mutation that patients might have, called 11q23 rearrangements. But, again, you would have to talk to your oncologist about whether you had this mutation and that trial was an option for you cause for patients without that mutation, the drug wouldn't work the same. So, it's, again, a conversation with your oncologist about your specific type of secondary leukemia. But I always encourage patients if they want to find more information to go to www.clinicaltrials.gov and can look for themselves and that helps start a conversation with their oncologist. And also I know The Leukemia & Lymphoma Society on their website has lots of information about how to select clinical trials.

Mrs. Alicia Patten-Madera

Thank you, doctor. Yes, we know that finding a clinical trial can be so overwhelming, so the LLS, we actually have a service that takes the burden off of patients and families where they can work one-on-one with an LLS clinical trial nurse navigator who will personally assist them through their entire clinical trial process. So, we try to take the burden off as easily as we can in such a challenging time. So, thank you for that information.

Our last question is, "What question should I ask, or should I be sure to ask my doctor about my diagnosis and treatment?"

Justin Taylor, MD

I would ask, like we were just talking about for clinical trials, if there are specific mutations that have been tested. Most places when they do the bone marrow biopsy will send a cytogenetic analysis, and they would find certain abnormalities. And more and more places now are also sending a mutational analysis in addition. So, I would just ask if a mutational analysis has been sent.

There's several companies that can be used: Foundation Medicine, Genoptix. Again, I have no relationship to these companies, so I'm not recommending any specific one of them, but if your doctor doesn't already have one that they use, there are several that your sample can be sent to. I do think that there are many treatments that are going to be coming soon that would require that molecular or genetic information to be known in order to get certain therapies.

It's not the standard treatment right now. Like I said, with Vyxeos[®], you don't have to have any specific molecular or genetic abnormality, but I always encourage patients to ask their doctor, what genetic abnormalities their cancer had and if those have been tested and if they should be tested.

Justin Taylor, MD

For the treatments, I would always ask them, "What are the other treatment options?" So, generally, we try to recommend what we think is the best treatment. But I think it's important for patients to also know what are the other treatment alternatives and so that patients can join the conversation about whether the treatment that we're recommending is the best for them and they can consider other options, including clinical trials.

Understanding Secondary Acute Myeloid Leukemia (AML)
Speaker: Justin Taylor, MD

I think even though we have approved agents for secondary AML, there's plenty of room for improvement still, and these clinical trials are exciting. And the only way that we're going to make those improvements, so I always have clinical trials as an option for all, patients.



Thank You

Mrs. Alicia Patten-Madera

That concludes the question-and-answer portion of our program. Thanks again, Dr. Taylor for sharing your time and knowledge with us. We appreciate your dedication and commitment to patients and caregivers throughout their cancer journey.

If you have additional questions, please call an LLS Information Specialist at 1-800-955-4572. Information Specialists are available to speak with you Monday through Friday, from 9 AM to 9 PM Eastern Time, or you could reach them by email at infocenter@LLS.org. Our Information Specialists can provide disease-specific information and support resources, including information about our personalized clinical trial assistance, nutrition consultations, financial assistance, online chats, and address other questions you may have.

On behalf of The Leukemia & Lymphoma Society, thank you for listening, and we wish you well.