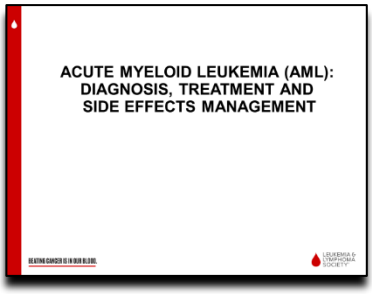
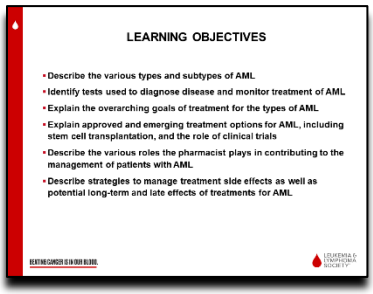



**Slide 1 - Acute Myeloid Leukemia (AML): Diagnosis, Treatment, and Side Effects Management**

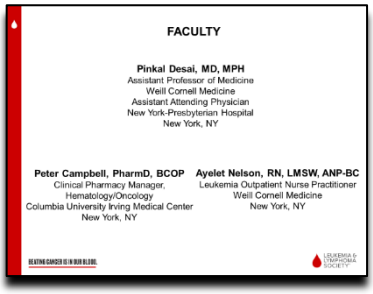
**Lauren Berger:** Hello, everyone. On behalf of The Leukemia & Lymphoma Society thank you for sharing your time with us for this continuing education program on acute myeloid leukemia: diagnosis, treatment, and side effects management.




**Slide 2 - Learning Objectives**

**The learning objectives for this program are listed on the slide:**

- Describe the various types and subtypes of acute myeloid leukemia (AML)
- Identify tests used to diagnose disease and monitor treatment of AML
- Explain the overarching goals of treatment for the types of AML
- Explain approved and emerging treatment options for AML, including stem cell transplantation, and the role of clinical trials
- Describe the various roles the pharmacist plays in contributing to the management of patients with AML
- Describe strategies to manage treatment side effects as well as potential long-term and late effects of treatments for AML

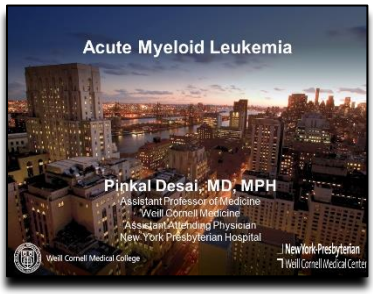



**Slide 3 - Faculty**

We 're fortunate to have as our presenters, Dr. Pinkal Desai, one of the nation's leading experts in acute myeloid leukemia and her colleagues, Dr. Peter Campbell, a clinical oncology pharmacist, and Nurse Practitioner Ayelet Nelson. We appreciate their dedication and their commitment to caring for patients living with blood cancers.

Dr. Desai is Assistant Professor of Medicine at Weill Cornell Medicine and Assistant Attending Physician at New York-Presbyterian Hospital, in New York. Dr. Campbell is Clinical Pharmacy Manager, Hematology/Oncology at Columbia University Irving Medical Center in New York. Ayelet Nelson is Leukemia Outpatient Nurse Practitioner at Weill Cornell Medicine in New York.

Our special thanks to Dr. Desai, Dr. Campbell and Nurse Practitioner Nelson for volunteering their time and expertise with us. Dr. Desai, I am now privileged to turn the program over to you.

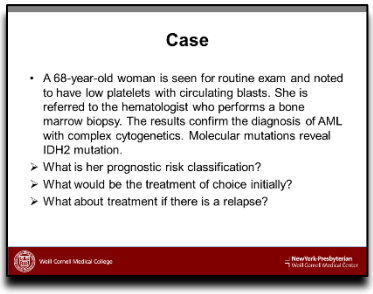



**Slide 4 - Acute Myeloid Leukemia**

**Dr. Desai:** I'm Pinkal Desai.

**Dr. Campbell:** And I'm Peter Campbell.

**Dr. Desai:** And we're going to talk today about management of acute myeloid leukemia.

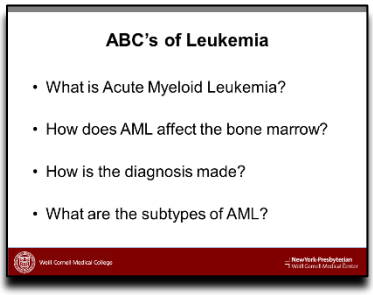



## Slide 5 - Case

I'm going to begin with a case that we're going to talk, which is a very typical presentation on an AML patient, then go over all of the literature, and we'll hope to answer all of these questions at the end of the presentation.

So, a 68-year-old woman is seen for a routine exam and was found to have low platelets and circulating blasts, or immature cells. She's referred to the hematologist who performs a bone marrow biopsy. The results confirm the diagnosis of AML with complex cytogenetics, and molecular mutations reveal an IDH2 mutation.

The questions that are relevant here are: What is her prognostic risk classification? Based on this history, what would be the treatment of choice initially? And how about if there is a relapse, what would be the best option for relapse?




## Slide 6 – ABC's of Leukemia

In order to go through all of these steps, we'll begin with what I call the ABCs of leukemia. The first question is, what is acute myeloid leukemia (AML)?

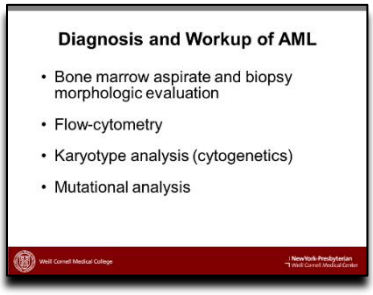
So, AML is a cancer of the bone marrow; the diagnosis is performed via a bone marrow biopsy. Sometimes on peripheral blood, but bone marrow biopsy is the standard of care in terms of diagnosis of AML. Patients have to have more than 20% blasts or immature cells in the blood or in the bone marrow biopsy to have a diagnosis of AML.

How does AML actually affect the bone marrow?

So, what happens normally in the differentiation of cells is that these blasts or immature cells are meant to become more mature cells and do their different functions in the body. When AML affects a patient, there is no differentiation and these blasts continue to proliferate and have a survival advantage, and they take up all the space in the bone marrow, so the other cells, the normal hematopoietic tissues, there is no place for these cells to actually perform their function. And, hence, the other counts start to go down.

We know that the bone marrow is actually a very finite space. It is present in most of our long bones, and it is in the middle of the bones, surrounded by pretty hard cortical bone. So as more and more space gets involved with leukemia, the more and more symptomatic a patient would become.

Like I said, the diagnosis is made by a bone marrow biopsy. There are several subtypes of AML which we are going to talk about.




## Slide 7 - Diagnosis and Workup of AML

When we do a bone marrow biopsy, we will usually perform an aspirate, which is the liquid part of the bone marrow procedure, and the actual biopsy, which is the solid part of the bone marrow biopsy.

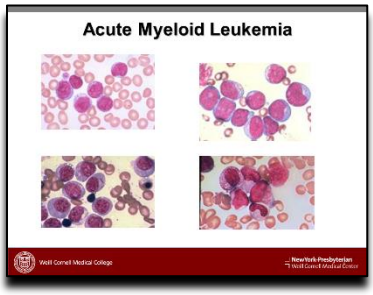
When we send this for evaluation, there are several tests that are done. One is morphologic evaluation. This is just looking at the microscope and seeing the percentage of blasts, and that would determine the 20% cut off for the diagnosis of AML. But morphologic evaluation is not the only thing. Actually, the modern diagnosis and workup of AML involves much more detailed analysis.

The first one would be flow cytometry. So, this is looking at the markers on these blasts and figuring out the various subtypes of AML which might be diagnosed based on flow cytometry. This is a much sensitive way of detecting AML than just morphologic evaluation.

The karyotype or cytogenetic analysis is an extremely important aspect of AML diagnosis because not only are certain cytogenetics pretty diagnostic of having AML, but it is also of prognostic importance in AML.

Mutational analysis is also another important aspect of it. This is looking at individual genes and how they are mutated. This is what we call the more personalized aspect of AML diagnosis and treatment because each individual's leukemia is different based on these mutational profiles of leukemia.

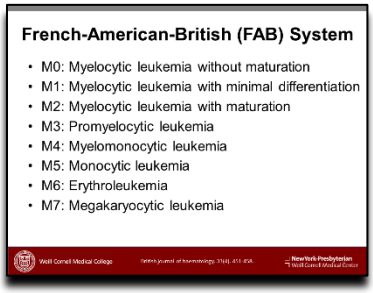
And what we do with this information is very important, in not just making a prognostic guidance as to how likely this leukemia is going to relapse or not, but it is also important in certain targeted treatments because the upfront and later management of leukemia might change depending on the presence of certain mutations. We're going to go through all of this in detail when we talk about treatment options for AML.




**Slide 8 - Acute Myeloid Leukemia**

This is how an AML blast looks like when we are looking at the morphologic evaluation. The blasts are typically large cells with a pretty large nucleus that is pink, and a very thin cytoplasm rim.

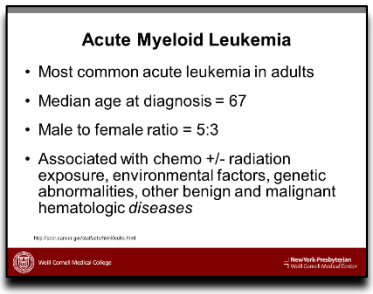
The nucleolus, which is present here in the center, can or cannot be present, but that doesn't have to be there for the diagnosis, but pretty much it is the presence of these blasts over 20% that clinches the diagnosis of AML.




**Slide 9 - French-American-British (FAB) System**

AML can have several subclassifications based on the French-American-British system of classifications. This is a morphologic classification. The only relevance of this classification is to define the MC or promyelocytic leukemia because the treatment of an MC AML is dramatically different than other forms of AML. So, the only relevance in this system is to make sure that the patient does or does not have promyelocytic leukemia.

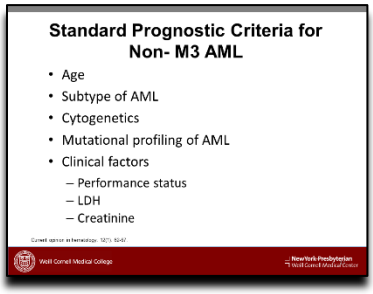
The other subclassifications from M0 to M2 and M4 to M7 are a little bit of historical significance at this point and we don't really take that into account in terms of treatment information.




**Slide 10 - Acute Myeloid Leukemia**

Now AML is the most common acute leukemia in adults. The median age at diagnosis is 67. More males are affected than females. Most of the AML's that happen are *de novo*, which means that there is no significant risk factor that has been identified. A very minor small amount of leukemias could be associated with previous chemotherapy or radiation exposure, environmental factors, certain genetic abnormalities, and prior other hematologic diseases like MDS or myeloproliferative disorders.

There is a very, very small percentage of patients that have familial AMLs but, usually, there is a pretty strong family history that has to be part of the workup of AML. But, generally, most of AML do not have a cause and it just happens as a *de novo* phenomena.




## Slide 11 - Standard Prognostic Criteria for Non-M3 AML

When we think about prognosis of AML, there are several factors that we look at in order to have a patient understand what's the risk of relapse or ultimate cure of this leukemia would be.

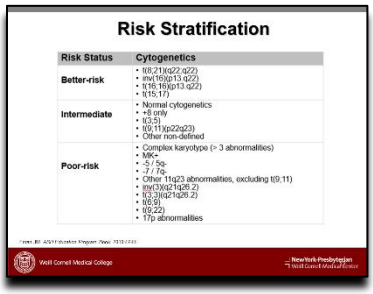
The first and the most important one is age. Younger patients with AML do well because they are able to handle treatments better. They are able to go to stem cell transplants, which is an important aspect of treatment of AML.

The subtype of AML, like I said previously, the M3 or the acute promyelocytic leukemia would have a very different prognosis, much better than compared to the other forms of AML.

Cytogenetics and mutational profiling are central to prognostication of AML.

There are certain clinical factors, in addition, that are important. Performance status, meaning how well a patient is at baseline, is very important. If somebody who is completely functional they, again, tend to handle treatments better relative to somebody who is, for example, wheelchair dependent.

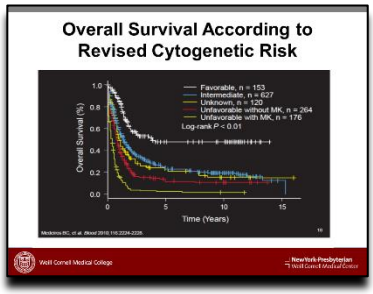
LDH and creatinine are more clinical factors which impact more volume or the aggressiveness of disease and also, to some extent, organ function, that is important when we have to give full-dose chemotherapies.




## Slide 12 - Risk Stratification

When we think of risk stratification, AML based on the cytogenetics or karyotype analysis, is divided into better-risk, intermediate, or poor-risk AML. Better-risk includes translocation 8;21, inversion 16, and translocation 15;17 which is, basically, APL.

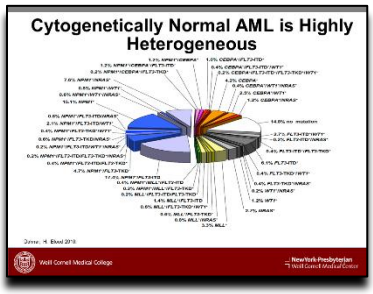
Poor-risk karyotype is any AML that has a complex cytogenetics, which would be more than 3 chromosomal abnormalities, having a monosomal karyotype specific mutation in these genes including a TP53 gene. The rest of all is intermediate-risk AML. And the biggest category within the intermediate-risk is patients with normal cytogenetics.




## Slide 13 - Overall Survival According to Revised Cytogenetic Risk

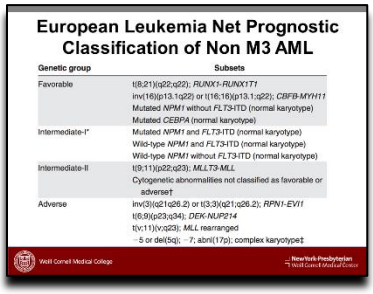
Now why are these cytogenetic risks important? Let's look at survival of patients with these individual abnormalities. Patients who have a favorable karyotype have a much better long-term survival compared to patients in these yellow and red, which are poor risk. As you see, there is a pretty significant drop in overall survival with poor risk cytogenetics. The middle one is the intermediate risk cytogenetics which, obviously, falls in the middle.

This is important because what we do long term in an AML patient is completely dependent on these risk classifications.



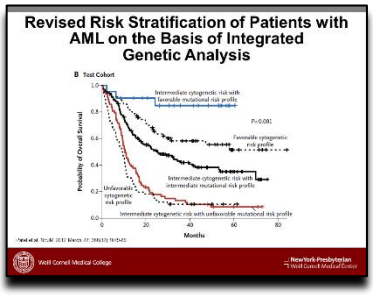

## Slide 14 - Cytogenetically Normal AML is Highly Heterogeneous

Now, with the advent of molecular stratification of AML, we now know that what we defined in the past as intermediate risk AML, or cytogenetically normal AML, is actually not one disease. As you look at this pie chart, it is made up of several subclassifications depending on the presence and absence of several genes, like CEBPA, FLT3, NPM1.



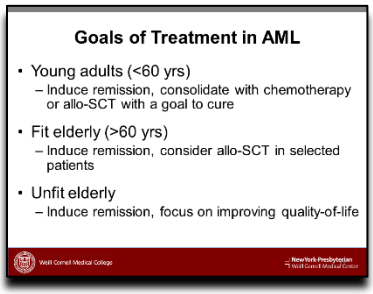

**Slide 15 - European Leukemia Net Prognostic Classification of Non-M3 AML**
And this has led to a new classification, which is the European Leukemia Net Prognostic classification, where we now classify AML into favorable, intermediate-1, -2, and at worst risk.

And what the biggest change here is the incorporation of molecular profiling into the prognostic classification. So, there are some patients with a normal karyotype that can, while they were initially categorized as intermediate, have now been recategorized as favorable, for example, the mutated CEBPA. This is very important, as this would be evidenced in the next slide, which looks at survival based on this integrated genetic analysis, or molecular analysis.




**Slide 16 - Revised Risk Stratification of Patients with AML on the Basis of Integrated Genetic Analysis**
You have people with the traditional favorable cytogenetic risk profile over here. When you divide the intermediate-risk, which is this, into intermediate cytogenetic risk but with favorable mutational profile, their survival is actually pretty good. And patients with intermediate cytogenetic risk but unfavorable mutational profile, pretty much follows the same risk classification as the unfavorable cytogenetic group.

And then, there are people who are truly intermediate, which means they have an intermediate cytogenetic risk and an intermediate mutational profile, and the survival of that group of patients is somewhere in the middle.




**Slide 17 - Goals of Treatment in AML[1]**
So now that we've established the risk classification, we go to the treatment of AML, and I'll come back to the risk classification as to how that will impact our treatments for these patients.

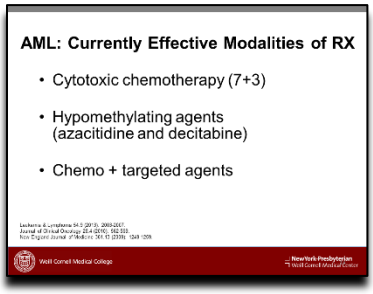
If a patient is a young adult, which is defined as under 60 years, the goal of treatment is to induce remission, consolidate with further chemotherapy or allogeneic stem cell transplant with a goal to cure.

In patients that are fit elderly, the goal remains the same: induce a remission and consider an allogeneic stem cell transplant in patients that are good enough to go through such a procedure.

In an unfit elderly patient, the goal is, obviously, still to induce remission, but you also focus on improving quality of life. It is absolutely important to these patients, if we are able to reduce the number of transfusions or reduce the number of infections, the survival in these patients is longer.

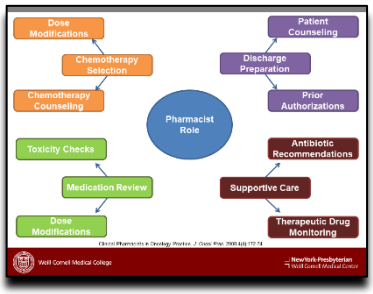
There have been multiple trials that have looked at treating patients who are unfit and elderly, and it has been seen over and over again that giving some kind of treatment for AML always leads to a better quality of life and better survival compared to somebody who is not treated for AML. And enrolling into clinical trials has been extremely, extremely important and helpful in order to get more newer drugs into these patients.

[1] Allogeneic stem cell transplant = Allogeneic bone marrow transplant (or stem cell transplant)- A treatment that uses healthy donor stem cells to restore a patient's marrow and blood cells. It uses high doses of chemotherapy and sometimes radiation to "turn off" a patient's immune system so that the donor cells are not rejected.




**Slide 18 - AML: Currently Effective Modalities of RX**

Currently, there are several effective modalities of treatment of AML. The big category is cytotoxic chemotherapies, traditionally known as 7 + 3, which we'll talk about later. This is the combination of cytarabine and an anthracycline. Also, hypomethylating agents, azacitidine and decitabine, as well as combinations of chemotherapy and targeted treatments. We're going to cover all of these in the presentation.




**Slide 19 - Pharmacist Role**

The first thing that we do once we have a diagnosis and we have a treatment plan, is find our pharmacist colleagues to help us figure out a plan and toxicity management.

**Dr. Campbell:** So, the pharmacists can play a big role in treating patients with acute myeloid leukemia, and this really starts with chemotherapy selection when working with the physician because a lot of these agents will require dose modifications based on different risk factors that the patients have, such as underlying organ function or comorbidities.

Also, it's an important role for the pharmacist to be involved in chemotherapy counseling when discussing these different treatment options with patients.

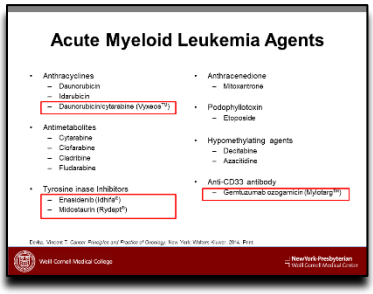
Once the patients have started treatment, medication review is something that is routinely done almost on a daily basis, and we conduct toxicity checks to see how the patients are tolerating chemotherapy, looking at their organ function, and then making dose modifications when necessary.

Another big role outside of chemotherapy that I'll briefly touch on is supportive care for these patients. So, patients with acute myeloid leukemia tend to face multiple challenges while they're undergoing induction chemotherapy, such as neutropenic fever or invasive fungal infections.

The pharmacist can play a big role in making antibiotic recommendations and then, alternatively, tailoring therapy specifically to the different cultures that come back, based on antimicrobial sensitivities.

And then, therapeutic drug monitoring is another area where we play a key role based on some of these drugs, such as aminoglycosides or vancomycin, needing therapeutic drug monitoring. Also, some of the antifungal agents that are used.

Now, once patients are ready to be discharged from the hospital, the pharmacists are also involved in patient counseling, as there are often a large number of medications that these patients will be discharged on, as well as assisting the medical team with any prior authorizations or drug acquisition issues that we encounter.

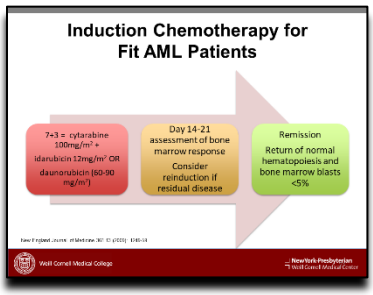



## Slide 20 - Acute Myeloid Leukemia Agents

So, in the treatment of acute myeloid leukemia, as Dr. Desai mentioned, there are several different treatment options, mainly with the backbone of therapy being cytotoxic chemotherapy. So, you can see that there are several drug classes that are listed here such as anthracyclines, for which daunorubicin or idarubicin tend to be commonly used, and there's a newer agent, which is a liposomal form. Antimetabolites such as cytarabine, clofarabine, cladribine, and fludarabine.

And then, in elderly patients, or those unfit for treatment, we tend to use less cytotoxic agents such as the hypomethylating agents, decitabine and azacitidine.

And I just wanted to point out, some of the newer agents that we'll specifically be touching on today, the liposomal daunorubicin and cytarabine or Vyxeos™, 2 of the new tyrosine kinase inhibitors, and then, an anti-CD33 monoclonal antibody, gemtuzumab, which is a therapy that has come back into clinical use.




## Slide 21 - Induction Chemotherapy for Fit AML Patients

**Dr. Desai:** So now we move on to what a typical fit AML patient would go through during treatment of AML. The standard induction chemotherapy that is widely used and has the most data on is 7 + 3, which is cytarabine given at 100 milligrams per meter squared in combination with either idarubicin, 12 milligrams per meter squared, or daunorubicin in dose ranges of 60-90 milligrams per meter squared. This is called 7 + 3 because the cytarabine goes for 7 days and the anthracycline goes for 3 days.

What is typical is patients are admitted in the hospital for a total of 4 weeks of admission in order to go through the treatment and tide them through the complications that happen after.

Once the 7 + 3 goes in, patients are usually followed with supportive care, treating for infections and also giving transfusions of platelets or blood, which are routinely administered to these patients. We also follow for organ toxicity and every other complication that may happen with chemotherapy.

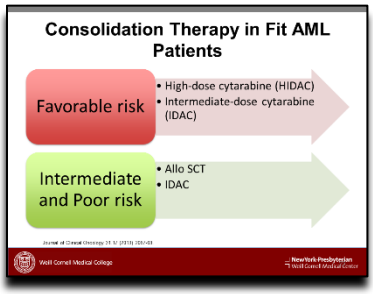
On day 14, sometimes day 14 to 21, there is usually a bone marrow biopsy that is performed to look at the status of the disease. The expected thing to find at this time is an ablated or an MP marrow, as in there is not much leukemia or any cells that are present at this point.

If there is a lot of disease, or if the bone marrow looks very cellular, then we consider a reinduction with either 7 + 3, or a 5 and 2, or some other chemotherapies in patients who are good enough to receive a second cycle of treatment.

If we determine that the patient is too sick, we generally do not risk a second chemotherapy cycle, but if they're fit enough, they would get a second cycle.

However, if the bone marrow is ablated or empty, then we would follow another 2 weeks in the hospital to await for count recovery.

At the end of 4 weeks, generally, if in remission, the blood counts would return to normal, that is the return of normal hematopoiesis, and we would do another bone marrow biopsy at that time. If the bone marrow blast is under 5% and hematopoiesis has returned to normal, the patient is determined to be in remission. At this point, they are discharged from the hospital and we plan for the next phase of treatment, which would be the consolidation treatment.



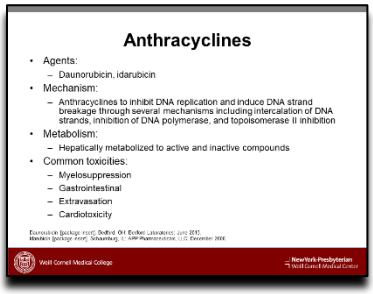

## Side 22 - Consolidation Therapy in Fit AML Patients

In patients who are fit AML patients, consolidation treatment will change depending on the risk profile of the leukemia. As we had an extensive discussion earlier with regards to what is favorable and what is intermediate and poor risk, this is where it comes into play.

If the patient has a favorable risk, which is translocation 8;21 or inversion 16, then the standard treatment would be cytarabine-based consolidation. This could be either high-dose or intermediate-dose, depending on the age and the cytogenetics.

However, if the patient has intermediate or poor risk, we would make a pretty good attempt at seeing if they're eligible for allogeneic stem cell transplant, and if a donor is available, they should be transplanted.

However, if they are not fit enough to go through a stem cell transplant, or if no donor is available, or the patient is unwilling to go through it, then an option is to give intermediate doses of cytarabine or other forms of chemotherapy as consolidation.




## Slide 23 - Anthracyclines[2]

**Dr. Campbell:** Now part of the backbone of this 7 + 3 therapy is, of course, anthracyclines. So, the 2 that we commonly use would be idarubicin or daunorubicin, and there is a dose range for daunorubicin, as was mentioned, from 60 to 90 milligrams per meter squared.

Now anthracyclines inhibit DNA replication and induce DNA strand breakage through a couple of different mechanisms, both by intercalating into the DNA strands and through the inhibition of DNA polymerase and topoisomerase 2.

In terms of metabolism, they do undergo hepatic metabolism to both active and inactive compounds. So, patients that have an underlying hepatic dysfunction, this does need to be taken into consideration.

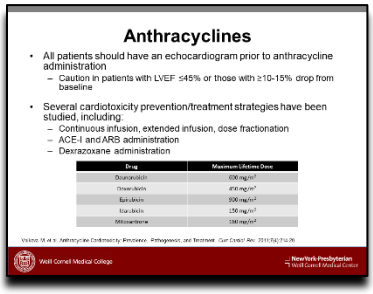
So, in terms of toxicities that we commonly see, myelosuppression is by far the biggest one that you'll see, although that will be the toxicity that all of these patients experience while undergoing cytotoxic chemotherapy.

Extravasation is something to be made aware of. Now, this is less commonly seen in the way that we give anthracyclines during the 7 + 3 regimen, as they're giving it via an IV push, while you have a practitioner, such as a nurse, at the bedside during administration. Extravasation tends to be more common when you're giving continuous infusions of these agents.

Probably the biggest thing that you'll see with anthracyclines is cardiotoxicity. Now cardiotoxicity can manifest in several different ways, both in an acute and a delayed manifestation. The mechanism of cardiotoxicity is multifactorial, so the anthracyclines are directly cardiotoxic to the cardiac myocytes, and they do undergo an oxidative stress over time.

So, the way that you'll see acute manifestations of cardiotoxicity is palpitations or arrhythmias that may occur. However, this acute presentation is not very common. What you more commonly see is a delayed presentation in which patients will experience an ejection fraction decrease over time.

[2] Myelosuppression= A condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets.




## Slide 24 - Anthracyclines

Because of this, all patients who are administered anthracyclines as part of any chemotherapy regimen should generally have an echocardiogram prior to administration, and you should take caution in administering these agents to patients that have a baseline ejection fraction less than 45%, or those that have greater than a 10 to 15% drop from baseline. So, this is particularly important in patients that have previously been treated for another malignancy such as breast cancer and have experienced an ejection fraction drop over time.

The other reason that this prior exposure is important is because the ejection fraction decrease that we see with anthracyclines tends to be due to a cumulative maximum lifetime dose exposure. So, in the bottom of the chart here, you can see that there's a table that lists all of the maximum lifetime doses.

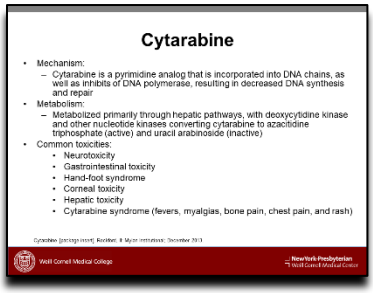
So, for example, with idarubicin, the point at which we start to be concerned for patients is when they reach a maximum of 150 milligrams per meter squared. And the closer that you get to these lifetime thresholds, the higher the incidence of cardiomyopathies is.

There are a couple of different treatment strategies that we can use to prevent cardiomyopathies in these patients, such as continuous infusion anthracycline administration. So, it's thought that if you administer the dose over a slower period of time, you get less of a peak effect and less damage to the cardiac myocytes.

You can also do something called "dose fractionation" where you take the total dose that you intend to administer and break it up over several days. Now this is not something that's commonly done in the treatment of acute myeloid leukemia, as these treatment regimens are pretty standard, but in other disease states you will see this.

ACE inhibitor or ARB administration is thought to be cardioprotective for these patients. So, if you have a patient that has an underlying cardiomyopathy, or experiences an ejection fraction decrease during treatment, you could start to administer an ACE or an ARB.

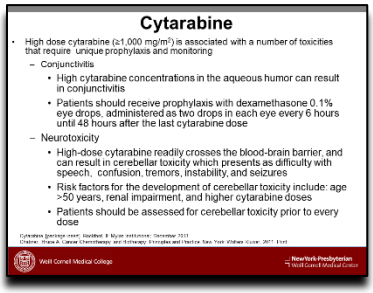
Another strategy that is less commonly employed in this setting is dexrazoxane administration. So, this is an antidote for anthracyclines commonly used during chemotherapy extravasation of anthracyclines. And in some disease settings, you will see this administered as a cardioprotective agent. However, again, not commonly done in the treatment of AML.




## Slide 25 - Cytarabine

Now the other agent that is the backbone of therapy in 7 + 3 and then, also, in the treatment of consolidation of AML, is cytarabine. So, this is a pyrimidine analog that gets incorporated into DNA chains as well as inhibits DNA polymerase. It's metabolized through hepatic pathways creating a couple of different active and inactive metabolites.

Now the toxicities that you'll see with cytarabine range pretty widely, and a lot of it will have to do with the doses that you're using. So, toxicities such as neurotoxicity tend to occur at high doses, as well as ocular toxicity. However, gastrointestinal toxicity such as diarrhea and vomiting can be seen even at lower doses.




## Slide 26 - Cytarabine

One thing to point out is specifically the administration of high dose cytarabine, as there are a couple of key toxicities that you can experience when administering this. Conjunctivitis occurs at high doses, and the high cytarabine concentrations in the aqueous humor can result in conjunctivitis. So, there's a couple of different treatment strategies that we can use to prevent this. Typically, what we will do, is use dexamethasone 0.1% eye drops administered as two drops in each eye every 6-8 hours until up to 48 hours after the last cytarabine dose.

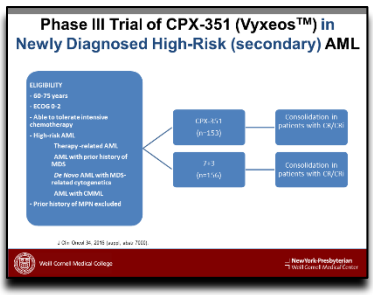
Now one thing to keep in mind that we commonly run into these days is drug shortages, and occasionally dexamethasone eye drops will not be available. When this occurs, using prednisolone eye drops or using liquid tears or artificial tears eye drops may be substituted as well.

The steroids are commonly used because it's thought that they can decrease the inflammation associated with conjunctivitis. However, there is data that does suggest that just flushing the eye routinely with artificial tears will help to prevent this as well.

The other key toxicity that we see with high dose cytarabine is neurotoxicity. So, because cytarabine readily crosses the blood brain barrier, you can see cerebellar toxicity which presents as difficulty with speech, confusion, tremors, or even seizures in extreme situations.

There are a couple of key risk factors that we think of when we're concerned about cytarabine neurotoxicities, and those include patients over 50 years old. So, if we think back a couple of slides, we use an intermediate dose cytarabine in certain patients that are of older age because of this risk factor. Those that have underlying renal impairments at the time of administration. And then, the higher the cytarabine dose, the higher the risk factor for neurotoxicity.

So, patients should be assessed for cerebellar toxicity prior to every dose of cytarabine that's administered. One of the most common ways that you'll see this done is to have them write their name prior to every dose. And what the nurse will look for, and the providers, is to see different hand movements or different patterns in the signature of the patient between each dose, which can signal cerebellar toxicity.



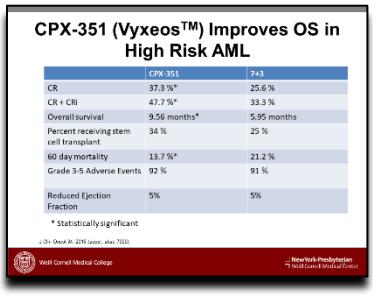

## Slide 27 - Phase III Trial of CPX-351 (Vyxeos™) in Newly Diagnosed High-Risk (secondary) AML

**Dr. Desai**: So, what we talked about so far is the backbone of induction and consolidation treatments for AML. Now, several other subgroups of AML and molecular subtypes have added treatment options and targeted treatments that are actually added to the 7 + 3 backbone in order to achieve greater responses and improve survival. We're going to now go through several of these options one after the other.

The first one is Vyxeos™ or CPX-351 (daunorubicin and cytarabine). This is now approved in the treatment of newly diagnosed high-risk or secondary AML. The original trial included patients 60 to 75 years old in good performance status, who were defined high-risk either because they had therapy-related AML, as in they had chemotherapy exposure for other cancers in the past, and then the AML was as a result of that chemotherapy.

Also, patients who have had previous history of myelodysplastic syndrome or MDS that then transformed to AML. Or patients with AML with a high-risk of cytogenetic risk, as we had talked about complex karyotype or monosomies, certain cytogenetics make patients high-risk. So, these patients were also included in this trial. Prior history of myeloproliferative disorders were, however, excluded in this trial.

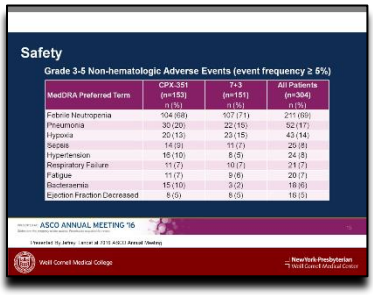
Patients were randomized to receiving Vyxeos™ or 7 + 3 (daunorubicin and cytarabine), which we discussed just recently. And after, in remission, they were consolidated again with Vyxeos™ (daunorubicin and cytarabine) in the Vyxeos™ (daunorubicin and cytarabine) arms, and the standard consolidation in the 7 + 3 arm.




**Slide 28 - CPX-351 (Vyxeos™) Improves OS in High-Risk AML**

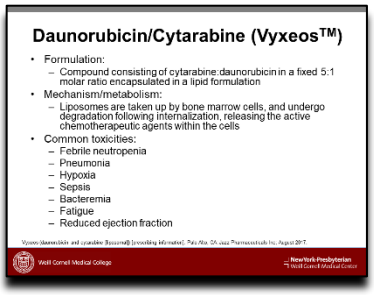
What was observed in the trial is that patients who received Vyxeos™ (daunorubicin and cytarabine) had a higher complete remission rate compared to patients with 7 + 3. This was statistically significant. There was also improved survival, which was also statistically significant. And a higher number of patients went into transplant in the Vyxeos™ (daunorubicin and cytarabine) arm. The 60-day mortality was also lower in the Vyxeos™ (daunorubicin and cytarabine) arm compared to 7 + 3 arm.

This led to the approval of Vyxeos™ (daunorubicin and cytarabine) in the subset of high-risk AML patients. The other AML patients who are not high-risk or don't have secondary AML, or younger patients, the standard of care is still 7 + 3.




**Slide 29 - Safety**

In terms of toxicity, it was pretty equally divided between Vyxeos™ (daunorubicin and cytarabine) and 7 + 3 in terms of the different kinds of toxicity: fever, pneumonia. That's the regular kind of complications that we see with induction chemotherapy in patients with AML.



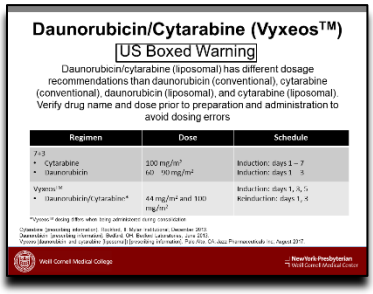

**Slide 30 - Daunorubicin/Cytarabine (Vyxeos™)**

**Dr. Campbell:** And just to elaborate a little further on Vyxeos™. Now the components of the drug are daunorubicin and cytarabine, which are similar to the agents that we use in standard 7 + 3. However, the difference here is that these two agents are combined in a fixed 5:1 molar ratio that's been encapsulated inside of a lipid formulation. And this lipid formulation is then selectively taken up by the bone marrow cells and undergoes degradation inside of the cells releasing the active chemotherapy within the malignant cells.

It was thought that this mechanism of action would have some effect on prolonging the effect of the agent and also decreasing the toxicity.

However, as we saw from the previous slide, a lot of the toxicities that we see with Vyxeos™ (daunorubicin and cytarabine) are very similar to those in patients undergoing standard 7 + 3 chemotherapy. Now, the common toxicities, again, are febrile neutropenia, infectious complications such as pneumonia, sepsis, and bacteremia. And then, we do see a small percentage of patients that have reduced ejection fraction; however, this is similar to patients who have standard daunorubicin and cytarabine.

One thing to note is the mechanism in which this is administered is different than that of standard 7 + 3, which is given as a continuous infusion over 7 days for cytarabine, and the anthracycline for 3 days. This is a fixed drug in a ratio given as one agent that is given every other day, so there are differences here.




## Slide 31 - Daunorubicin/Cytarabine (Vyxeos™)

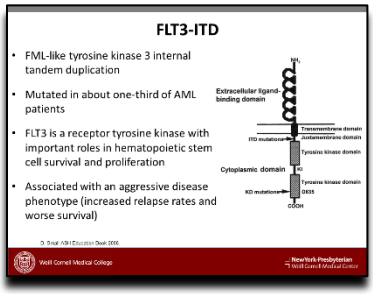
Now there is a black box warning for the daunorubicin and cytarabine liposomal formulation of Vyxeos™, and mainly it pertains to the fact that there are different dosing strategies for the 2 agents, and that they're not interchangeable and should not be confused.

So, as I just alluded to, the 7 + 3 regimen, as we discussed, the anthracycline is given as an IV push on days 1 through 3, and the cytarabine is given continuously on days 1 through 7.

Now Vyxeos™ (daunorubicin and cytarabine) is given in a fixed dosage form during induction on days 1, 3, and 5, and then patients that have residual disease that require reinduction, it is administered again on days 1 and 3.

So, it's important to note these differences and the pharmacists can play a key role in making sure that these 2 drugs are not interchanged with each other.

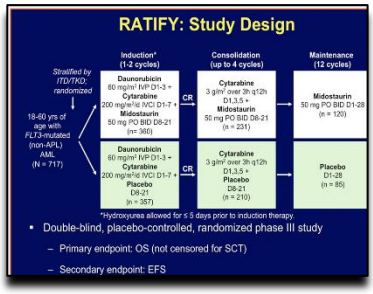
I just wanted to note that Vyxeos™ (daunorubicin and cytarabine) does have a different dosing strategy when it is administered during consolidation, later in therapy, if the patient responds.




## Slide 32 - FLT3-ITD

**Dr. Desai:** We now move on to the different molecularly defined subgroups of AML that are treated a bit differently than the standard 7 + 3.

The first one would be a FLT3 mutated AML. So FLT3, also known as FML-like tyrosine kinase 3 internal tandem duplication mutation. It's mutated in about one third of AML patients. And this is a very important mutation because not only does the FLT3 gene have an important role in hematopoietic stem cell survival and proliferation, understandably, the presence of this mutation is associated with a very aggressive disease phenotype that tends to relapse more and is associated with the worst overall survival.



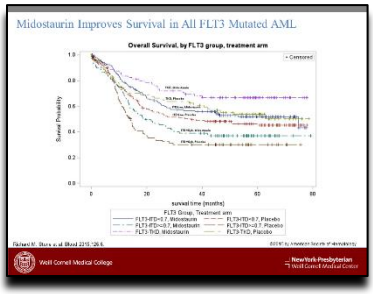

## Slide 33 - RATIFY: Study Design

What was developed in order to target this mutation was a tyrosine kinase inhibitor known as midostaurin. The trial RATIFY was a long trial that was conducted in various institutions in the US and abroad, where patients with FLT3 mutated AML, 18-60 years of age, were randomized to receive the 7 + 3, which is the standard, plus midostaurin from day 8-21. So, they would get the 7 + 3 for the first 7 days, and starting day 8, the midostaurin as an oral pill would begin at 50 milligrams twice a day, up to day 21.

After remission, consolidation would be with single agent cytarabine in combination with midostaurin again. And once the consolidation would finish, midostaurin was given as a maintenance for 12 cycles. Patients who were eligible for a stem cell transplant would go on to receive a stem cell transplant, but patients who would not get a transplant would get consolidation.

The control arm was standard 7 + 3 and placebo. So, this would be your standard 7 + 3 that we described in the past.

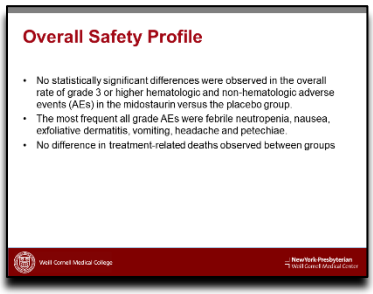
The primary endpoint was overall survival, and the secondary endpoint was just event-free survival. An event was defined as when the disease would come back.




## Slide 34 - Midostaurin Improves Survival in All FLT3-Mutated AML

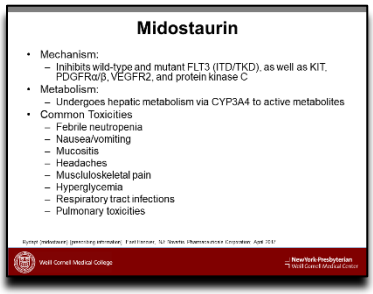
When you look at the overall survival by different groups, the top one is FLT3 tyrosine kinase domain mutation, or TKD, which is a different kind of a FLT3 mutation, and ITD, which is a second type of a FLT3 mutation. Regardless of the kind of FLT3 mutation, or the allele frequency, or the percentage of the leukemia cells that have the FLT3 mutation, all subgroups, patients who got midostaurin, which would be the top one, had a better survival compared to the placebo. Same thing for these curves and, similarly, for here.

So, this trial met its primary endpoint of increased overall survival with the use of midostaurin in FLT3 mutated AML, and midostaurin is now approved for induction and consolidation with AML 7+3 backbone but it is not approved for maintenance.




## Slide 35 - Overall Safety Profile

The overall safety profile was not much different between the 2 groups, 7 + 3 alone versus the 7 + 3 plus midostaurin. We saw similar grades of hematologic and nonhematologic adverse events. I will let Peter talk about the other midostaurin-related side effects now.




## Slide 36 - Midostaurin

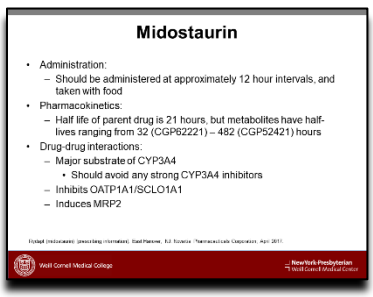
**Dr. Campbell:** So midostaurin is an exciting drug because it brings a FLT3 inhibitor to frontline therapy. So as Dr. Desai said, this inhibits both wild type and FLT3, as well as a couple of other tyrosine kinases such as KIT, PDGFR, alpha and beta, and then VEGFR as well.

In terms of metabolism, it undergoes hepatic metabolism via CYP3A4 to active metabolites, so drug-drug interactions are something that are of huge importance, and I'll touch on that in a second.

So, some of the common toxicities that we saw in the clinical trials are febrile neutropenia, nausea, vomiting, and mucositis. And then, also, headaches and respiratory tract infections are something that were more rarely seen.

And one thing that I want to point out here is that there were a number of patients that were seen in the midostaurin arm that experienced pulmonary toxicities.

Now, this was not necessarily directly related to the drug; however, it is hypothesized that this has something to do with the antiangiogenic properties of some of the off-site tyrosine kinase activity that midostaurin has.




## Slide 37 - Midostaurin

Now, when we're talking about these different toxicities, one thing that's very important is to think about drug-drug interactions that we have with midostaurin. Now, a lot of these patients who are undergoing treatment for AML are going to be at high risk for invasive fungal infections and, therefore, fungal prophylaxis is something that is routinely done in these patients.

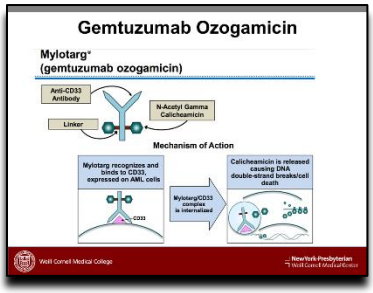
The difficulty that we experience with this is that the antifungal agents, voriconazole and posaconazole, are strong inhibitors of CYP3A4. So, therefore, we need to give some consideration to how we treat these patients, because if midostaurin is coadministered with either of these agents, it will greatly increase the active metabolites of this drug and the active drug itself.

Now, as you can see, the half-life of the parent drug is quite long, it's about 21 hours, but the metabolites' half-lives range anywhere from 32 up to 482 hours. So, especially when you're giving this with concomitant drugs that also inhibit the metabolism, this can be extended even further.

Now, one strategy that is employed is that patients, because they're generally admitted to the hospital during this time, we may hold the antifungal prophylaxis while administering, or in patients who have a diagnosed fungal infection, one treatment strategy that is employed is the use of amphotericin or liposomal amphotericin in order to avoid the drug-drug interactions.

So, this is a complex conversation that will occur with the medical team in the event that this happens, but the important take away point is to always be highly aware of any medications that are started due to these drug-drug interactions that will amplify the toxicities.

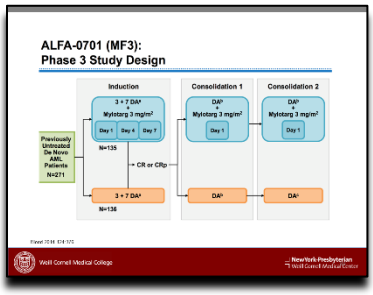
Now, in terms of administration, the drug is administered twice a day, and it's important that it is taken with food, and this can help to reduce some of the toxicities experienced with midostaurin.




## Slide 38 - Gemtuzumab Ozogamicin

**Dr. Desai:** The next drug category is gemtuzumab ozogamicin, or Mylotarg™, which is an anti-CD33 antibody linked to a chemotherapy agent calicheamicin. By itself, calicheamicin is extremely toxic and cannot be administered, but the concept of this drug is that the drug, Mylotarg™ (gemtuzumab ozogamicin) recognizes CD33, which is expressed in more than 90% of AML cells. It recognizes the CD33 molecule, binds to it, the complex is then internalized into the leukemia cells where calicheamicin is released, causing DNA strand breaks and cell death.

There is, however, some bystander effect when the cells are destroyed. There is some toxicity because of the leakage of calicheamicin to the surrounding cells, but this is a way to administer chemotherapy directly into the leukemia cells.

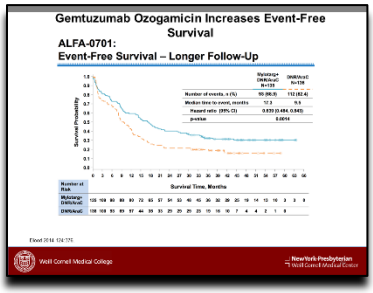



## Slide 39 - ALFA-0701 (MF3): Phase 3 Study Design

The history of Mylotarg™ or gemtuzumab is actually very interesting. It was initially approved for treatment of relapsed AML in the United States, and a trial that was ongoing in upfront AML with a much higher dose of Mylotarg™ (gemtuzumab ozogamicin) showed increased toxicity and, therefore, this was withdrawn from the market.

Thereafter, as more demand from the AML community went forward and multiple other trials showed increased efficacy at lower doses of Mylotarg™ (gemtuzumab ozogamicin), this was reintroduced back now, mostly because of this trial as well as a meta-analysis of other trials.

To go over this trial ALFA-0701, this was a Phase III trial of previously untreated *de novo* AML where Mylotarg™ (gemtuzumab ozogamicin) was administered with 7 + 3 at a dose of 3 milligrams per meter squared, which is the lower dose, on day 1, day 4, and day 7 of the 7 + 3 backbone. Patients were randomized to get 7 + 3 and Mylotarg™ (gemtuzumab ozogamicin) versus just 7 + 3 alone. In consolidation, 2 doses of Mylotarg™ (gemtuzumab ozogamicin) were given during consolidation 1 and 2, while the 7 + 3 control arm got the standard backbone of consolidation.

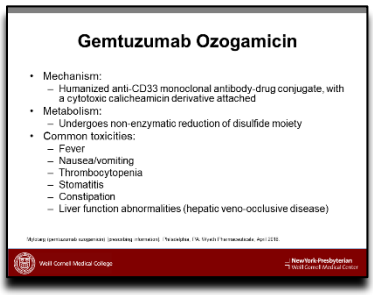



## Slide 40 - Gemtuzumab Ozogamicin Increases Event-Free Survival

What was observed in this trial, the primary endpoint of which was event-free survival, [was] that patients who got Mylotarg™ (gemtuzumab ozogamicin) had longer, even with longer follow up, better event-free survival compared to patients who did not get Mylotarg™ (gemtuzumab ozogamicin).

The other aspect of this trial, which was also interesting, is that when you look at cytogenetic subgroups of AML, the biggest subgroup where it impacted survival was actually the favorable risk or core binding factor, or 8:21 in inversion 16 AML. The effect of this drug in the adverse risk cytogenetic group was not much different than 7 + 3 alone.

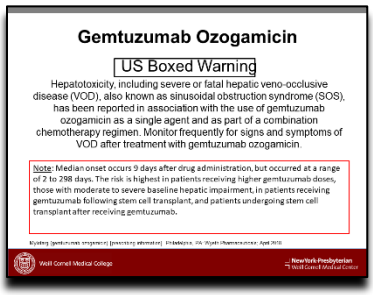
So, currently, Mylotarg™ (gemtuzumab ozogamicin) is approved by FDA for use in *de novo* AML and relapsed AML. In relapsed AML it is approved as a single agent, and in upfront in combination with the 7 + 3 arm.




## Slide 41 - Gemtuzumab Ozogamicin

**Dr. Campbell:** So, as was referenced, gemtuzumab is a humanized anti-CD33 monoclonal antibody but it's an antibody-drug conjugate, which means that it has the cytotoxic calicheamicin derivative attached to the anti-CD33 antibody, which helps to internalize this chemotherapy.

The metabolism is that it undergoes nonenzymatic reduction. And then, the common toxicities that we see, as we've sort of talked about, are fever, nausea and vomiting, thrombocytopenia, stomatitis was relatively frequently seen, as well as constipation. And then, one to really point out here, are liver function abnormalities that have been seen with this agent, especially hepatic veno-occlusive disease. And this is important because of the subsequent therapies that the patient may undergo.




## Slide 42 - Gemtuzumab Ozogamicin[3]

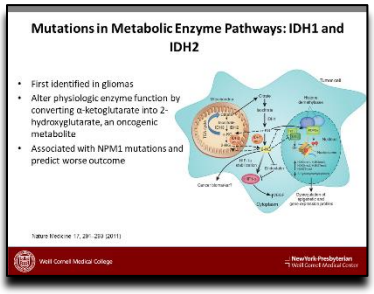
So, this is a US box warning for the drug, so hepatotoxicity, including severe or fatal VOD, also known as sinusoidal obstructive syndrome or SOS, has been reported with this drug.

So, the median onset typically is about 9 days after you start the drug, but it can really occur at any time and, in studies, has been seen as late as almost 300 days after drug administration.

Now the highest risk is seen in patients that receive higher doses, such as was referenced in previous clinical trials that were using higher doses of this agent, or those who have severe baseline hepatic impairments. So, patients that are being written for this drug, it's important for the pharmacist to undergo an in-depth review of the patient's labs, including their labs in the past, to see if they have any baseline hepatic dysfunction.

Now patients that receive this drug after a stem cell transplant, or those who plan to undergo a stem cell transplant in the future, may also be of concern because these are also risk factors for VOD. So, this is one of the agents that, while it has had treatment success, the conversation generally occurs about what the patient's risk factors for VOD are, what their underlying organ function is, and whether or not they're a good candidate for this treatment based on future therapy.

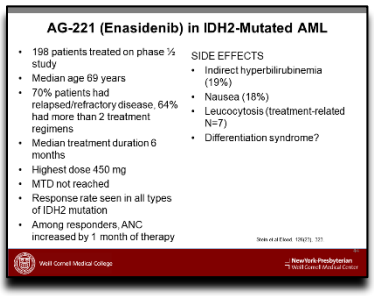
[3] VOD = Veno-occlusive disease (VOD) -A disease that may be a complication following high-dose chemotherapy and/or radiation, in which the blood vessels that carry blood through the liver, swell and become clogged. Source – www.LLS.org.




## Slide 43 - Mutations in Metabolic Enzyme Pathways: IDH1 and IDH2

**Dr. Desai:** Another drug that is of importance is drugs that target the IDH gene. So, there are mutations that are present in about 10-20% of AML patients that have a mutation in IDH-1 or IDH-2. IDH is enzyme isocitrate dehydrogenase in the Krebs cycle, which is the way glucose is incorporated into cellular metabolism. And what happens in patients who have the IDH-1 or -2 mutation is because of this mutation, the normal enzyme function which makes alpha ketoglutarate, instead of that, there's an oncogenic metabolite that is produced which is 2-hydroxyglutarate. This oncogenic metabolite is what causes the leukemia cells to proliferate and stop differentiating.

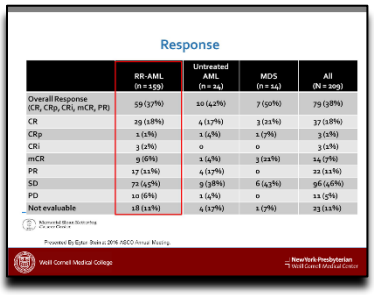
The presence of the IDH mutation predicts worse outcome generally compared to the absence of an IDH mutation when it's present with an NPM1 mutation, which is very commonly present in patients who have a normal cytogenetic AML.




## Slide 44 - AG-221 (Enasidenib) in IDH2-Mutated AML

In order to target this, enasidenib, or AG-221, was developed in IDH2-mutated AML. One hundred ninety-eight patients were treated on a Phase I/II study with a median age of 69 years. Seventy percent of these patients had relapsed or refractory disease and a lot of them had more than 2 treatment regimens before they enrolled onto the trial.

The highest dose on the trial was 450 milligrams. The responses were seen in all subtypes of an IDH2 mutation and, usually, the time to response of neutrophils was about 1 month on treatment.

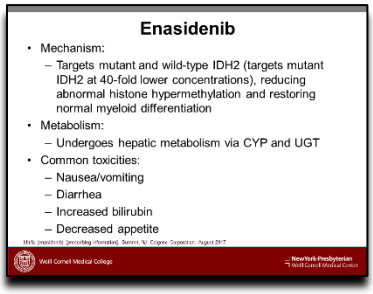



## Slide 45 - Response

What was seen in relapsed and refractory AML is an overall response rate of 37%. In untreated AML that was 42%, 50% in MDS, but an overall response rate of 38%. This in the setting of a relapsed AML or multiply treated AML is pretty significant, and based on this trial, the drug was approved for treatment of relapsed and refractory AML. It is not approved for upfront AML treatment.

What is very important on this drug clinically that we see is there is a differentiation syndrome that happens with these drugs where the patients who are taking the drug, and it can happen at any point, but early on in the first couple of months is more common. The white cell count can go up; it could be associated with mature neutrophilic leukocytosis or monocytosis, and there is usually an inflammatory signal associated with it where patients can experience fever, pleural effusions, or swelling in the legs, sometimes cardiac effusion. This is very important to recognize and be treated promptly with either steroid administration or Hydrea® (hydroxyurea), or both, in order to reduce the number of cells and reduce the inflammation.

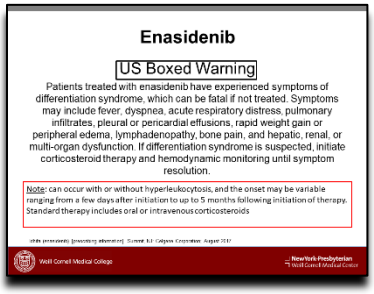
It's very important not to stop the drug if the, differentiation syndrome is treated promptly, because many people going through the differentiation syndrome are more likely to respond, so it's important that we continue the drug while treating the differentiation syndrome. However, if it is life-threatening, the drug has to be interrupted until this is resolved and then restarted again with close monitoring.




## Slide 46 - Enasidenib

**Dr. Campbell:** So, this agent works through a couple of different mechanisms, so it targets both mutant and wild type IDH2, although it targets the mutant IDH2 at about 40-fold lower drug concentrations. And, in addition to reducing the histone hypermethylation, it also restores normal myeloid differentiation, which is responsible for this differentiation syndrome that was just mentioned.

Now it extensively undergoes hepatic metabolism through both the CYP and UGT systems, which I'll touch base on in a second. It was overall well tolerated; nausea and vomiting and diarrhea were commonly seen. Also, increased indirect hyperbilirubinemia was seen; however, this usually goes down over time and patients can continue treatment through this indirect increase. And then, decreased appetite was also seen in clinical trials.



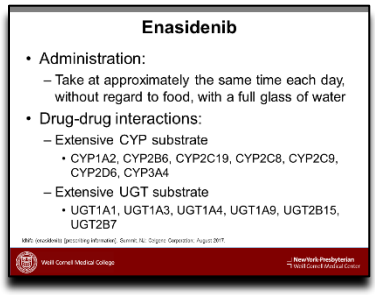

## Slide 47 - Enasidenib

Now, as Dr. Desai mentioned, there is a black box warning for differentiation syndrome. Now, the interesting thing with this agent that I'll just touch a little further on, is we typically think of, in the treatment of acute myeloid leukemia, using cytotoxic chemotherapy, which is typically going to kill the cells and make them undergo apoptosis.

Now what's different with this drug is that, in addition to having some cytotoxic effect, it also causes cells to undergo differentiation and maturation and, because of this, we run a risk having differentiation syndrome.

So, the symptoms include fever, acute respiratory distress, you can see pulmonary infiltrates on either a chest x-ray or a chest CT. And then rapid weight gain from the fluid going into the third spaces, so it's peripheral edema and lymphadenopathy.

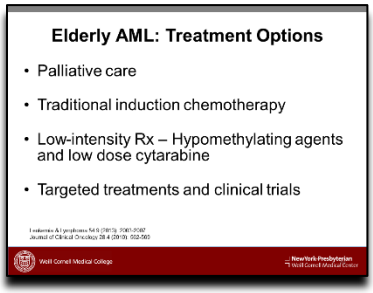
Now, this can occur with or without hyperleukocytosis and the onset can be variable, but as Dr. Desai mentioned, it typically occurs early on in treatment, and within the first 5 months of starting therapy. And then the therapy that is standard in these patients is to either administer oral or intravenous corticosteroids.




## Slide 48 - Enasidenib

So, in terms of administration, it's taken at approximately the same time each day, and there is no regard to food; however, it is recommended to take with a full glass of water.

The interesting thing with this agent is that if you were to look at the package insert or any drug reference for this agent, you'll see that it undergoes extensive metabolism through the CYP system and the UGT system. So, when you initially look at this, you would think that any drug-drug interactions would be severely limiting to the administration. However, the important thing to note is that although there are many different CYP enzymes that are responsible for metabolizing this agent, none of them are actually clinically significant. So, there are no known drug interactions which should be avoided with administration, which makes it very convenient to give this drug.




## Slide 49 - Elderly AML: Treatment Options

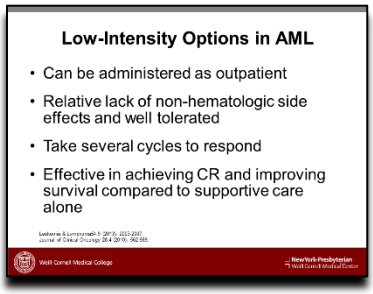
**Dr. Desai:** So, we talked so far about fit patients undergoing chemotherapy-based regimens with the exception of the IDH2 inhibitor. We will now discuss elderly AML or unfit patients. There are several treatment options, palliative care is one of them. But, like I had said before, that there have been many trials that have shown that treatment of AML always leads to a better quality of life and better survival, so there's always a push to either clinical trial enrollment or some kind of treatment in order for these patients to feel better.

In elderly AML patients who are fit, they can go through the traditional induction chemotherapy like we discussed, but the unfit elderly patients, the 2 backbones of treatment would be hypomethylating agents and low dose cytarabine, which is a low dose of chemotherapy, as we know. And, also, targeted treatments and clinical trial enrollment.

What is important to know in the low intensity treatment with both hypomethylating agents and the low dose cytarabine, they take several months to respond. So, it is very important to support these patients through this period of neutropenia and infections and cytopenias with transfusions.

Usually, a typical drug, either hypomethylating or low-dose cytarabine, will take at least 2 to 4 cycles before we can see a full effect in terms of remission.

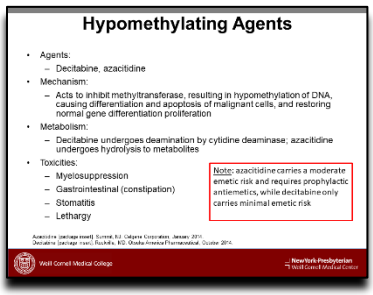
These are also lower-intensity treatments, so there is not a lot of organ toxicity that we see with these agents and, therefore, these can be administered outpatient if patients are willing to go through this in an outpatient basis rather than inpatient, particularly because it takes a long time for these drugs to work.




## Slide 50 - Low-Intensity Options in AML

Just summarizing what I had said before, that although administered outpatient with relative lack of nonhematologic side effects, they take several cycles to respond. They're also effective in achieving CR and improving survival compared to supportive care alone.

Many times, these drugs may not achieve CR, but there might be some degree of transfusion improvements that can happen in people who have partial responses, for example. This is very relevant to an elderly AML population because this does improve their overall quality of life.




## Slide 51 - Hypomethylating Agents[4]

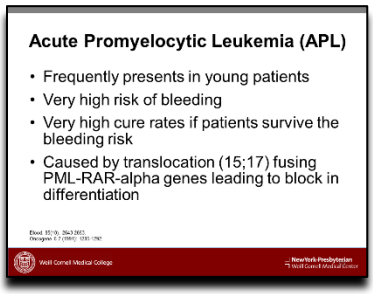
**Dr. Campbell:** So, the 2 agents that are hypomethylating agents that we use in this setting are decitabine and azacitidine. So, these act to inhibit methyltransferase which results in hypomethylation of the DNA. So, this causes differentiation and apoptosis of the malignant cells and, again, restores normal gene differentiation. So decitabine undergoes deamination by cytidine deaminase and azacitidine undergoes hydrolysis or metabolism.

Now, as was mentioned, these are relatively low-intensity agents; however, we do see myelosuppression, as is common with all of our different treatment options. And probably one of the most common toxicities that we see is the gastrointestinal complication of constipation.

Now one thing to note when reviewing orders for the hypomethylating agents is that they do carry a different emetogenic risk. So, while decitabine is a low emetogenic risk, and typically does not require any premedications, this confusion can be carried over to azacitidine, which is different in that it does carry a moderate emetic risk. So, prophylactics, antiemetics are required when administering azacitidine; however, they

[4] CR = Complete response

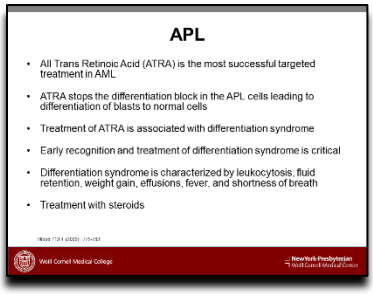
are not required typically when administering decitabine. However, there may be patients that are more sensitive to the drug and do require antiemetics with decitabine; however, that is not standardly done.




**Slide 52 - Acute Promyelocytic Leukemia (APL)**

**Dr. Desai:** I want to briefly touch upon acute promyelocytic leukemia, which is the M3 specific type of AML that is treated very, very differently than all we've talked about so far. APL frequently presents in younger patients and is associated with a very high risk of bleeding due to the nature of the blast itself. However, if the patient survives this initial period of bleeding risk and go in to remission, there is an extremely high cure rate with this AML, reaching about 98%.

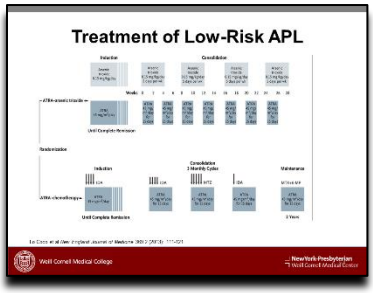
APL is caused by a translocation of 15, 17 chromosomes leading to fusion of the PML-RAR-alpha genes. And what this fusion causes is a block in differentiation that leads to APL.




**Slide 53 - APL**

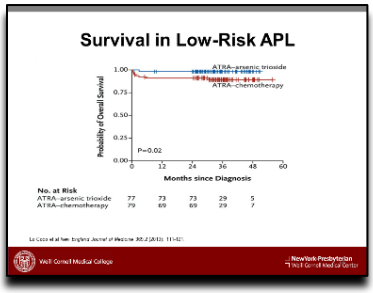
I would say that treatment of APL is probably the most successful targeted treatment in AML because ATRA, or all-trans retinoic acid, specifically stops the differentiation block in APL cells and leads to the differentiation of these blasts to normal cells.

Treatment of ATRA is associated with differentiation syndrome, which is kind of like what is observed with the IDH inhibitors but maybe more pronounced and perhaps more dangerous. Early recognition and treatment of this is very, very critical. It is associated usually with leukocytosis, fluid retention, weight gain, effusions, fever, and shortness of breath. The standard treatment is steroids; prompt administration of steroids usually resolves this syndrome, but in life-threatening cases, sometimes ATRA has to be interrupted.



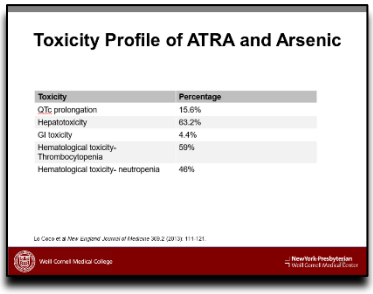

**Slide 54 - Treatment of Low-Risk APL**

The standard treatment of low-risk APL in the old days was chemotherapy with ATRA. There was a big trial that was performed in Europe that randomized patients to ATRA and arsenic, which is another agent that is very active, particularly in APL, and leads to apoptosis of APL cells. Patients in this arm were treated with a combination of ATRA orally and arsenic IV every day for 30 days, after which patients were usually in remission. And then, this was followed by consolidation for 4 cycles with the combination of ATRA and arsenic. Arsenic was given as 4 weeks on and 4 weeks off, while ATRA was given as 2 weeks on and 2 weeks off throughout these 4 consolidation cycles. The randomization arm was ATRA with standard chemotherapy.




**Slide 55 - Survival in Low-Risk APL**

And what was observed in this trial was that patients who got the ATRA and arsenic had better survival and lower toxicity compared to ATRA and chemotherapy. So, combination of ATRA and arsenic is now the standard treatment for low risk APL.



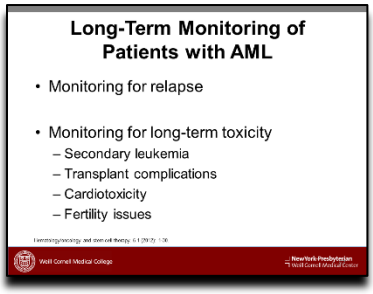

## Slide 56 - Toxicity Profile of ATRA and Arsenic

**Dr. Campbell:** Now in terms of the 2 agents that we commonly use, ATRA and arsenic, we do see an interesting toxicity profile. So, in terms of both ATRA and arsenic, you can see hepatotoxicity which, typically, we are able to treat through. However, at higher levels, such as greater than 5 times the upper limit of normal, we do occasionally have to withhold these agents temporarily. However, based on the good treatment outcomes, we do typically try to treat through if at all possible.

Now, the other toxicity that is very commonly seen with arsenic trioxide is QTc prolongation. So, in patients who are initiating arsenic trioxide, generally a baseline EKG is obtained and then, daily, throughout the initial phases of treatment, and as the patient progresses through induction, you can reduce the frequency of EKGs down to either 2 or 3 times a week in some cases.

Now one important role that the pharmacist can play in this setting is to make sure that the patient is on no other QT prolonging agents or agents that have the potential to do so, as the QTc prolongation seen with arsenic can be quite profound, and the additive effect can be quite dangerous.

The other toxicities that you do see include neutropenia. Now the differentiation syndrome that is seen, again, just to reiterate, is commonly treated with steroids. There have been studies that have looked at the use of prophylactic steroids for differentiation syndrome; however, there's no real consensus on what the best treatment approach is. However, this is something that can be considered in patients that are considered to be high risk, such as those with a white count at presentation over 10,000.




## Slide 57 - Long-Term Monitoring of Patients with AML

**Dr. Desai:** Once we have treated a patient with both induction and consolidation for all of AML, the big things that we have to follow through is monitoring for relapse. Some AML patients can have molecular monitoring like, for example, APL; others are generally monitored by just looking at blood counts and seeing if blood count abnormalities are present. If they are present, that would lead to a bone marrow biopsy to see if there is an actual relapse or not. But what is very important is monitoring for long-term toxicity.

Some patients who go through transplant can have secondary leukemia because of the chemotherapy regimens that are given as part of the transplant conditioning. So, whenever leukemia relapses, we always want to see if the native disease that has relapsed or a new leukemia. For the most part, the relapses are actually the original leukemia. The risk of secondary leukemia is low but something we have to look out for.

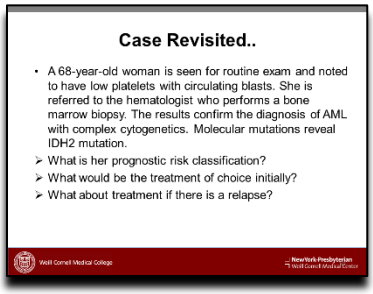
There are several transplant complications that have to be looked at in follow-up of patients; cardiotoxicity, as was mentioned in the past, is important, and if anybody who has shortness of breath or any cardiac symptoms, an echo is the standard. There is no monitoring strategy as such in order to repeat echo serially, but it is based mostly on symptoms.

Fertility issues are particularly relevant because young patients with AML may need to, or may want to be pregnant in the future, so what is standard many times in male patients is we would advise sperm banking before the treatment of leukemia begins. This is a little bit hard in female patients because, usually, oocyte preservation would require a surgical procedure, and many times AML presents as a medical emergency, so surgery in the presence of low counts and everything, are not practical.

But what we do advise is, after the induction is done, prior to transplant, fertility management is an important part. We do have a team of fertility experts that will see the patient to see if any kind of oocyte preservation or sperm banking is advised and is possible, given insurance coverage and everything else.


## Slide 58 - Financial Assistance Programs

So, another role that pharmacists can play is with financial assistance programs. So, because most of these agents do carry a significant cost, many drug companies do have financial assistance programs, as well as The Leukemia & Lymphoma Society also having several resources available to patients to help sort through the financial assistance.




## Slide 59 - Case Revisited..

**Dr. Desai:** So now that we have talked about everything in the management of AML, I would like to revisit our case. As we remember, this was a 68-year-old woman who was diagnosed with AML with complex cytogenetics, and the molecular mutation through an IDH2 mutation.

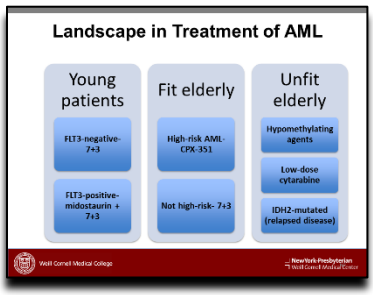
So, in terms of her prognostic risk classification, because of the presence of the complex cytogenetics, she would be classified as at worst risk or high risk for relapse.

The treatment, initially, could be 7 + 3 or Vyxeos™ (daunorubicin and cytarabine) but, as we know from the discussion of the previous trial, this was the subject population that was used with complex karyotype, and Vyxeos™ (daunorubicin and cytarabine) had a survival advantage over 7 + 3. So, in this case, the treatment of choice would be Vyxeos™ (daunorubicin and cytarabine) but, obviously, this has to be discussed in detail with the patient. And because this is a high-risk cytogenetics, after achieving a remission, the standard practice would be to go through a stem cell transplant.

If the patient goes through all of this and still experiences a relapse, for this patient, because there is a mutation in the IDH2 gene, what is approved and has probably the higher response rate would be an IDH2-directed drug which is enasidenib, which has been approved for relapsed IDH2-mutated AML. So that would be the treatment choice if there is a relapse.

Sometimes in the presence of a relapse that happens many, many years after the diagnosis of AML, for example, after 2 years, you can consider reinduction with chemotherapy also as a valid choice because those patients are also likely to go into remission with chemotherapy.

But if the relapse happens in a very short time from achieving a previous remission, for example, 6 months after achieving a remission, then chemotherapy is not likely to put these people into remission and more targeted treatments and clinical trials would be the way to go in order to get a higher chance of achieving a CR.




## Slide 60 - Landscape in Treatment of AML

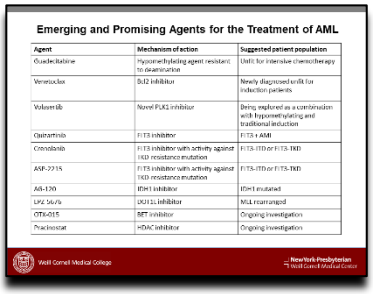
The current landscape in the treatment of AML can be summarized on this slide. For young patients that are FLT3-negative, 7 + 3 is the standard of treatment, and in FLT3-positive patients, midostaurin plus 7 + 3 is the standard of care.

Certain patients, for example, the favorable risk, are good candidates for Mylotarg™ (gemtuzumab ozogamicin) in combination with 7 + 3 because, not only is the drug active particularly in that subgroup but, also, these patients are less likely to go through stem cell transplant, so the hepatic veno-occlusive side effects that we see with Mylotarg™ (gemtuzumab ozogamicin) are less likely to be relevant in this population.

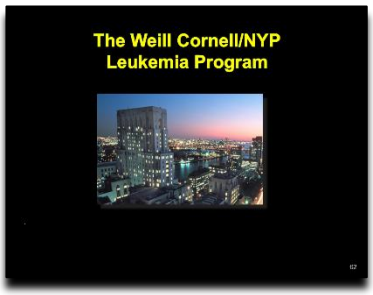
In a fit elderly population, high-risk AML, as evidenced by previous exposure to chemotherapy or previous diagnosis of MDS, if those patients have AML, Vyxeos™ (gemtuzumab ozogamicin) or CPX-351 would be the drug of choice. And if the patients are not high-risk, then 7 + 3 would still be the standard of care.

In unfit elderly, hypomethylating agents or low dose cytarabine would be the standard of care.

And in relapsed diseases, if there is an IDH mutation, the IDH2 inhibitor drug enasidenib would be the standard of care. You could also be treated with Mylotarg™ (gemtuzumab ozogamicin) as a single agent as long as they're able to handle the side effects of cytopenias that can be associated with the drug.

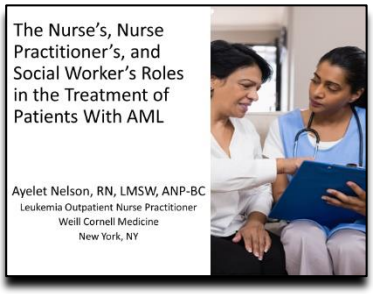



**Slide 61 - Emerging and Promising Agents for the Treatment of AML**
And, obviously, the most important message here is that there are several clinical trials ongoing with so many different targeted treatments, both in the upfront and the relapse setting, and clinical trial enrollment in these various trials are extremely important because the reason we have all these approvals recently is absolutely due to the enrollment of patients on these clinical trials, and more and more are needed because a lot of work in AML is still not done, and we are not anywhere close to the survival we would want a patient to have. And these new drugs are key to getting to a better response rate, particularly in older patients where the responses are not as good as younger patients.

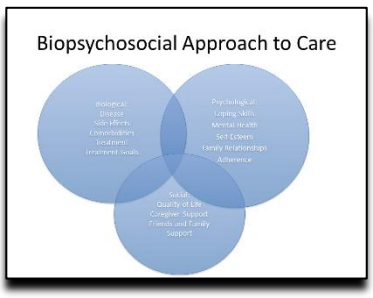



**Slide 62 - The Weill Cornell/NYP Leukemia Program**
Thank you for listening to this talk. We would like to thank you for your attention.

**Lauren Berger:** Thank you, Dr. Desai & Dr. Campbell, for your very clear and informative presentation, I am now pleased to turn the program over to Ms. Nelson.



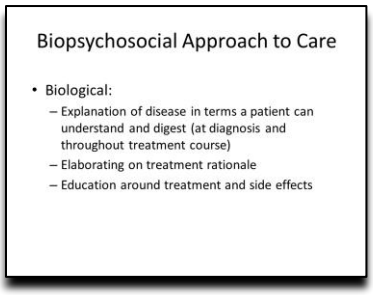

**Slide 63 – The Nurse's, Nurse Practitioner's, and Social Worker's Roles in the Treatment of Patients With AML**
**Ayelet Nelson, RN, LMSW, ANP-BC:** Hi, my name is Ayelet Nelson, and I'm here to talk today about the role of the nurse, nurse practitioner, and social worker in the treatment of patients with acute myeloid leukemia.




**Slide 64 – Biopsychosocial Approach to Care**
What I've done is really approached the way we care for patients from the biopsychosocial approach, which takes in three aspects of care—the biological, the psychological, as well as the social. The biological is what we think about when we think about a doctor's visit. We talk about the disease, the side effects, the comorbidities of the patient coming into the treatment, treatment itself, and treatment goals. What is our goal here?

We also talk about the psychological effects, and this is really a nursing role, a social work role, and we talk about how they're coping with their diagnosis. What was their mental health before and now? How is their self-esteem? What are their family relationships, and how adherent are they to the medication or treatment regimen?

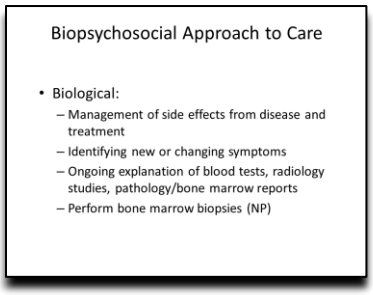
We also take into account the social aspect of care. So what does their quality of life look like? What is their caregiver support like? What is their friend and family support like? And all of this comes into our approach for taking care of these very complicated patients.




**Slide 65 – Biopsychosocial Approach to Care**

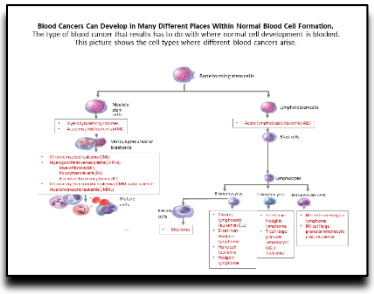
I'm going to start by going through the biological. So when we talk about the biological, a huge role for the nurse practitioner and the nurse is education. So really explaining the disease to the patient in terms they can understand, both after a diagnosis and throughout the treatment course. It's important to remember that patients need to be educated throughout the process and not to assume that they would get it at any particular point.

Elaborating on the treatment rationale, are we going for cure? Are we going for stabilization? How does this treatment work? All of this is an important piece of the conversation. We also talk about the treatment and its side effects, how it works, what to expect.



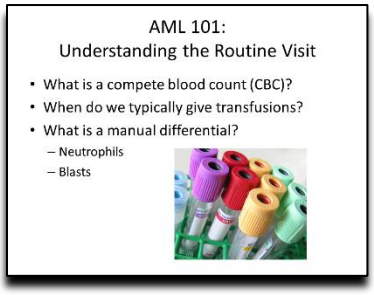

**Slide 66 – Biopsychosocial Approach to Care**

We talk about managing the side effects from both the disease and the treatment; identifying new or changing symptoms, the "when to call" as we tell our patients. And we also have an ongoing explanation of blood tests, radiology studies, pathology, and bone marrow reports, which we're going to talk more about later in this presentation. As a nurse practitioner, I also perform bone marrow biopsies, and we're going to review that briefly, later on.




**Slide 67 – [Image] Blood Cancers Can Develop in Many Different Places Within Normal Blood Cell Formation**

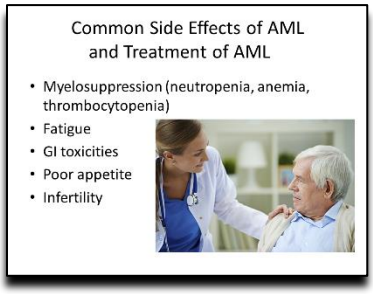
The first thing we do when we have a patient with a new diagnosis of AML is I typically draw a bone. It looks like a dog bone; I have no artistic talent. And I show them sort of how a stem cell can become either part of the myeloid factory or the lymphoid factory of the bone marrow. And we break down what makes up these factories and how we determine that their diagnosis was acute myeloid leukemia, explaining to them at each stage that the myeloid factory makes some of the white cells, the red cells, the platelets. Acute means it came on all of a sudden, from the myeloid factory, and leukemia meaning a cancer of the white cells. And this sort of helps to break down some of the terminology the patient's going to hear and make them familiar with this new vocabulary.




**Slide 68 – AML 101: Understanding the Routine Visit**

We also make sure patients understand the typical components of a complete blood count (CBC), so the white cells, the hemoglobin, the platelets, as well as a brief understanding of the manual differential because this helps patients to understand where they are in treatment and be a partner in their care. So when they see a hemoglobin of 6, they know they'll need a transfusion. So we explain to them what the transfusion guidelines are. In our clinic, we transfuse for less than 8 for hemoglobin and less than 20 for platelets, typically. But, again, it's a case by case basis. Younger patients and older patients may have different parameters.

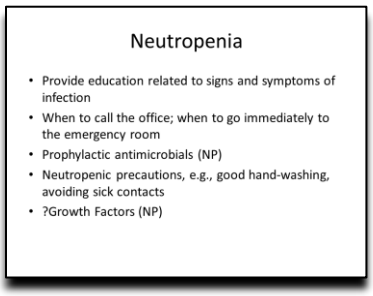
We also explain to them what a neutrophil is and how important that is for the immune system and when they would need prevention or watching for certain symptoms, more specifically, as well as what blasts are so that they can help to trend how their treatment is going in a very concrete way.




**Slide 69 – Common Side Effects of AML and Treatment of AML**

Common side effects of AML and the treatment of AML, unfortunately, overlap, so this has to be explained to patients, that both the leukemia and sometimes the treatment can have the same symptoms. And you have to explain to them the rationale of treatment very carefully so that they understand why we're doing this and what to expect.

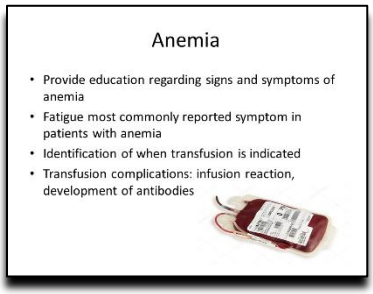
So myelosuppression, including neutropenia, anemia, and thrombocytopenia; fatigue; GI toxicities; poor appetite; and infertility are all things we address when talking about side effects.




**Side 70 – Neutropenia**

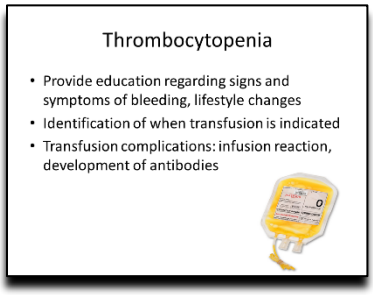
Neutropenia, the role of the nurse and the nurse practitioner is often to explain what the signs and symptoms of infection are, the "when to call the office". So when you have a fever greater than 100.4, if you're just feeling terrible, if something changes, if you're short of breath, all of these are things to call or go to the emergency room about. And we break this down very carefully for the patients.

We also explain to them when their neutrophils drop, because now they have that word neutrophils. They'll be started on prophylactic antimicrobials. And as a nurse practitioner, we prescribe those. So we prescribe an antibacterial, an antifungal, and an antiviral for prophylaxis. Additionally, we talk about good hand-washing and avoiding sick contacts. And, occasionally, we use growth factors; but that's a topic for another time.




**Slide 71 – Anemia**

Anemia, we provide education regarding signs and symptoms of anemia. Fatigue, obviously, is the most common symptom, as well as increasing dyspnea on exertion or shortness of breath. We do not treat for fatigue. So if the patient has a hemoglobin of 9 but feels fatigued, that doesn't mean they're getting a transfusion. Our charge nurse likes to tell us, "Your patient is addicted to hemoglobin," and we really try and set parameters as to when a transfusion is indicated. Fatigue is both a common side effect of the treatment as well as anemia, so it's important to differentiate where that is coming from. Additionally, we talk about transfusion complications, including infusion reaction and development of antibodies.

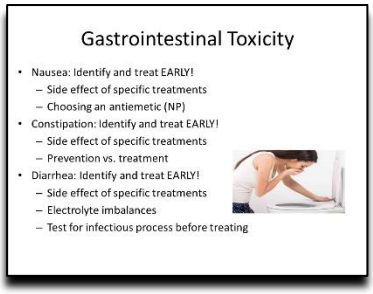



**Slide 72 – Thrombocytopenia**

Thrombocytopenia, or low platelets, we talk about the signs and symptoms of bleeding and lifestyle changes, including not using a straight razor, for example. We also identify when a transfusion is indicated, when your platelets are less than 20 -is what we do in our clinic, as well as if there's any signs or symptoms of bleeding. We also again review transfusion complications, including infusion reactions and development of antibodies.


**Slide 73 – Fatigue**

Fatigue is one of the most difficult side effects to treat. I can't give you a pill to make you more awake and more excited about your day. And as we talked about earlier, blood is not always the answer. We do encourage light walking, but we do say, as opposed to the average adult when you're running and you feel like stopping and you're supposed to push through, you should listen to your body. And if you feel like stopping because you're tired or out of breath, you should listen to your body and sit. But light exercise is a way to combat the fatigue associated with treatment.

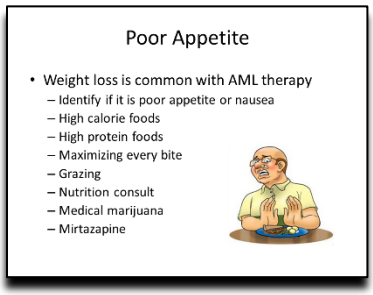



**Slide 74 – Gastrointestinal Toxicity**

Gastrointestinal toxicity. As you'll see on this slide, everywhere it says, "Tell us EARLY!." And so that's true for everything, but specifically gastrointestinal toxicity. If we identify the nausea before it gets out of hand, it's easier to treat. There are various antiemetics on the market that come in various forms, so we can really treat to the patient and make sure that we're adequately addressing their nausea. And we're often successful with that.

Constipation, you don't want a patient coming in and telling you that they have not gone to the bathroom in five days. You really want to stay on top of it. Mention it at every visit. Make sure that they're not constipated. Again, prevention is easier than treating.

Diarrhea, we don't treat for diarrhea unless we know that there's no infectious process. So it's important for them to tell us early so we can test to make sure that there's no *C. diff* or other infection that is ongoing, and we can then tailor a treatment to that. And we also can address electrolyte imbalances before they become problematic.




**Slide 75 – Poor Appetite**

Poor appetite and weight loss are very common with AML therapy. It's important to identify if it's nausea as the causation or if it's poor appetite. We, obviously, encourage high calorie foods, high protein foods, maximizing every bite, leaving a bowl of candy or nuts in front of a patient who's sitting on the couch throughout the day, because you're tempted to eat if the food is there.

We also have a dietitian who works on our service whom we consult on many, many patients. And now medical marijuana has become legal in many states, and that is an option for patients, as well as on occasion we prescribe mirtazapine, which does have the effect of increasing appetite in the right person.


**Slide 76 – Infertility**

Infertility is something that is difficult to address because, for women especially, there's not a wonderful solution at diagnosis. For men, it's easy and very important to address before treatment. The cryopreservation of semen can be done before treatment is started. For women, this is often addressed at diagnosis and too much for a patient to even digest at that point. But it's important to bring it up, and it's important to revisit it.

It's also appropriate for the patient to mourn the loss of their fertility in the immediate future but be aware of possibilities after treatment for fertility options. So a referral to a reproductive endocrinologist, even though it seems out of whack with everything going on with an initial diagnosis, it's an important part of the nurse practitioner or nurse relationship to bring this up and make sure patients have a way to vocalize their feelings about this and address any possibility of fertility in the future.

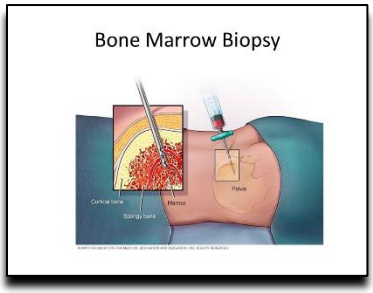

**Slide 77 – Treatment Goals**

Treatment goals. It's important to clarify the goals of treatment. Patients often don't understand why they're continuing to get treatment if they're in remission, especially older patients. So it's important to talk about stabilization versus cure. What is your goal? How is the patient doing? What is their disease status? Are there new treatments coming out? What does their quality of life look like? Making sure there are no new clinical trials that a patient could be eligible for. And it's also important for the nurse practitioner to address end-of-life questions that the patient may have, nurse or nurse practitioner, I should say.

It's important to be honest with my patients. My patients always comment that they know I'll always be honest. I don't sugarcoat things. I think it also offers the opportunity for the patients to feel comfortable asking questions and having that conversation. And, truthfully, patients are often more willing to have this conversation with nurses, nurse practitioners, and social workers because they know us on a first name basis. Some of that hierarchy is removed, and they feel comfortable having this conversation to determine next steps and answer their questions in a real way.

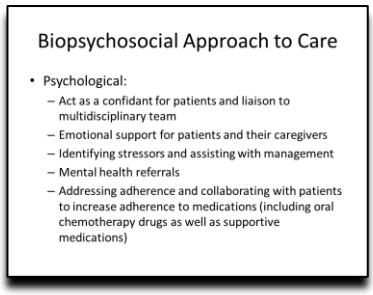

**Slide 78 – Micromanagement: Ongoing Goals of Therapy**

One of the big things for nurse practitioners is micromanagement. So the macro discussions of the treatment is something that happens typically with the physicians in the room. You're having a bigger discussion about next steps. But the micromanagement, including the maintenance of the counts, the transfusions, the toxicities, the quality of life, that is all going on in the conversation with the nurses and nurse practitioners and it's important to address that on an ongoing basis so the patients know that you're thinking about them and thinking about where their treatment is going.



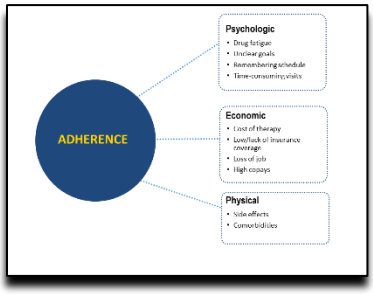

**Slide 79 – Bone Marrow Biopsy**

Nurse practitioners also have the role of performing bone marrow biopsies in our institution and in many institutions across the country. I'm not going to go through what the process is like. I'll just say that as a nurse practitioner, it's really important to communicate what to expect. And if done right, it's not a terribly painful procedure. And it's important to help patients express their fears and anxiety about the procedure before it happens and have that space where it's safe to say that they're scared. And throughout the procedure make sure that they're comfortable.



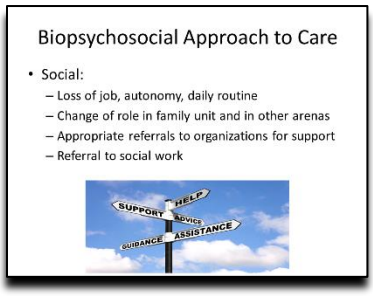

**Slide 80 – Biopsychosocial Approach to Care**

The psychological piece of the biopsychosocial model is that we act as a confidant for patients which has been explained throughout the biological as well. We provide emotional support for patients and their caregivers. This is done by the entire team of nurse practitioners, nurses, social workers, as well as physicians. We identify stressors and assist with management, we offer mental health referrals, and we address and collaborate with them to increase adherence to medications. A lot of the new oral chemotherapy drugs, as was discussed earlier in this presentation, you need to adhere to a certain schedule. And we can talk to patients about what roadblocks exist or why they're not compliant or how we can increase compliance so that they get the most out of their treatment. In addition to supportive medication, is there a hesitancy to take medication or are they just forgetting? How can we improve that so that the patient's quality of life and experience with the treatment is improved?



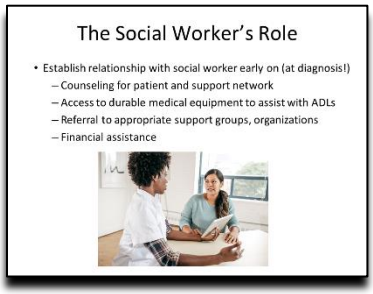

**Slide 81 – [Image on Adherence]**
This is a short, quick slide on adherence. There are many factors that go into adherence. I'm not going to spend too much time on this, but obviously, patients get tired of taking their meds, get tired of coming to visits. There's the cost of therapy. There's the lack of insurance. There's the loss of their job.

I had one patient recently who told me he doesn't come to visits because he often goes to his job late. So we were able to fix his schedule so that he could get to his job on time, and it didn't affect his take-home pay, which was why he wasn't adherent to our schedule. It's also important that we identify the side effects and make sure the patients aren't having side effects that they're not telling us about, which is changing their adherence to the medication.

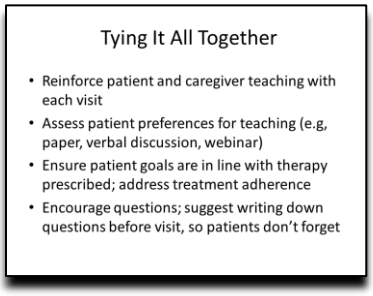



**Slide 82 – Biopsychosocial Approach to Care**
The social aspect of the biopsychosocial model is the loss of personhood. So you are now a patient. You have a new role, both in your family life and your outside life, in all aspects of your life. And it's important to address that and note its importance.

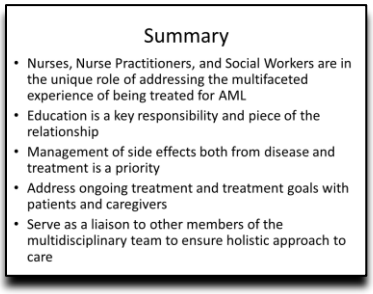
So there are appropriate referrals to organizations for support, referral to social work, which we're going to talk about on the next slide more specifically. But making sure that you address that there is a loss outside of having this diagnosis that encompasses a lot of aspects of their day-to-day routine.




**Slide 83 – The Social Worker's Role**
The social worker's role is one of the very, very important roles in the treatment of a patient with AML. We refer to a social worker at diagnosis so that they're a face that they know, a person that they can count on. They often are helpful in addressing the patient's needs at diagnosis, normalizing their feelings, and helping to reframe how they're viewing their life at this point. They offer counseling for both the patient and the support network. They help to do very concrete things like access to durable medical equipment, to assist with everyday living, and they offer referrals to appropriate support organizations and financial assistance.

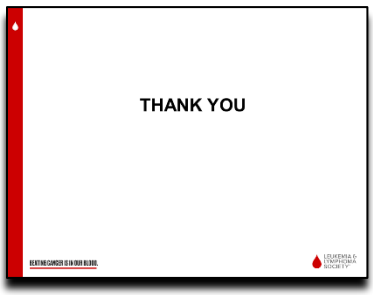



**Slide 84 – Tying It All Together**
In conclusion, we reinforce patient and caregiver teaching with each visit. We make sure that we're teaching the patient in a way that works for them. We ensure the patients' goals are in line with the therapy prescribed and treatment adherence when addressing with the patient what their quality of life looks like, are they happy with the treatment, how are they doing as often as they want. We also encourage questions and create that relationship where they're not afraid to ask those questions to us.




**Slide 85 – Summary**
So, in summary, nurses, nurse practitioners, and social workers are in the unique role of addressing the multifaceted experience of being treated for AML. Education is a key responsibility and a piece of their relationship that cannot be overlooked. Education should occur all the time. It's an ongoing process, and it's never done. Making sure that the management of side effects from both the disease and the treatment is a priority and addressed, as well as addressing ongoing treatment and treatment goals with patients and caregivers and serving as a liaison to other members of the multidisciplinary team to ensure this holistic approach to care.

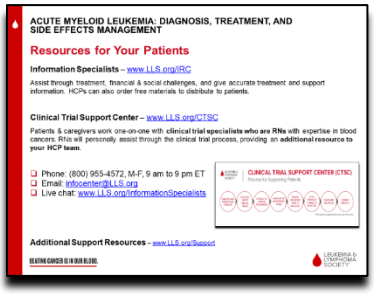
Thank you so much.




**Slide 86: Thank You**
**Lauren Berger:** Thank you, Dr. Desai, Dr. Campbell and Ms. Nelson for your very clear and informative presentations.


**Slide 87: CE and Research**
I am now pleased to share resources for you and your patients. Visit The Leukemia & Lymphoma Society website to access web based and in-person programs offering free CME & CE credit, as well as information on Research.

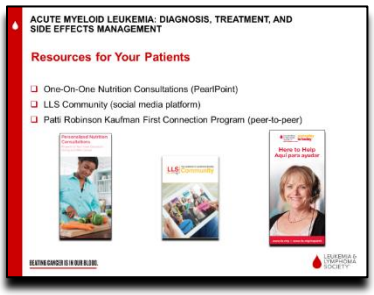

**Slide 88: Resources for Patients**
LLS also offers AML and other blood cancer disease specific information including booklets, telephone/web education programs, videos and podcasts for patients and their caregivers, and also an interest to healthcare professionals. You can order booklets from LLS to give to your patients, or they can access these education resources directly from LLS.




**Slide 89: Resources for Patients**

LLS Information Specialists, who are oncology social workers, nurses and health educators, provide patients and their caregivers with personalized assistance for managing treatment decisions and side-effects, as well as for dealing with financial and psychosocial challenges.

Our Registered nurses with expertise in blood cancers work one-on-one with patients, via telephone, to find an appropriate clinical trial, and to assist through the clinical trial process. They also help patients with questions to ask their own healthcare team.




**Slide 90: Nutrition Consultation, LLS Community**

Patients can also receive one-on-one consultation from a certified dietician to guide them in eating well and working toward a healthy life style during and after cancer treatment. The Leukemia & Community also offers an online social network for blood cancer patients and their caregivers. And this provides an important resource for connection and information.

All of these specialists, as well as booklets and on-line programs can serve as additional resources to your healthcare care team. To refer your patients, please use the contact information on this slide.

Thank you for joining us for this education program.